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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/502,685	07/27/2004	Nayna Govind	100629-US-PCT

CONFIRMATION NO. 7568

44992
ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

POWER OF ATTORNEY NOTICE

OC000000069488892

Date Mailed: 07/10/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/24/2014.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/rnturner myles/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/502,685	07/27/2004	Nayna Govind	056291-5543

CONFIRMATION NO. 7568

9629
MORGAN LEWIS & BOCKIUS LLP (WA)
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

POA ACCEPTANCE LETTER

OC000000069488980

Date Mailed: 07/10/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/24/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/rmturner myles/

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PTO/SB/81A (12-08)
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PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,759,328
Issue Date	July 20, 2010
First Named Inventor	Nayna Govind
Title	Composition for Inhalation
Attorney Docket Number	056291-5543

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 09629

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Inventor or Patent Owner

Signature	Meaghan Richmond	Date	June 24, 2014
Name	Meaghan L. Richmond	Telephone	+1.781.839.4054
Title and Company	Patent Attorney, AstraZeneca AB		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Govind et al.

Application No./Patent No.: 7,759,328 Filed/Issue Date: July 20, 2010

Titled: Composition For Inhalation

AstraZeneca AB , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3 ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 015506, Frame 0145, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From. _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3 73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Meaghan L. Richmond
Signature

June 24, 2014
Date

Meaghan L. Richmond; Reg. No. 61402
Printed or Typed Name

Patent Attorney, AstraZeneca
Title

Electronic Acknowledgement Receipt

EFS ID:	19398477
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	44992
Filer:	Gregory Thomas Lowen
Filer Authorized By:	
Attorney Docket Number:	100629-US-PCT
Receipt Date:	24-JUN-2014
Filing Date:	27-JUL-2004
Time Stamp:	18:07:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	5543POA.pdf	90895 c203714b2ad0da0ceced73249d2d759a705 1ef7a	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73.	5543Statement.pdf	82299 c96a77f15fec303a9447238bda8b119a1cf797c3	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	173194

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/502,685	07/27/2004	Nayna Govind	100629-US-PCT

CONFIRMATION NO. 7568

44992
ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

POA ACCEPTANCE LETTER

OC000000068876526

Date Mailed: 06/09/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/28/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/rmturner myles/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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10/502,685	07/27/2004	Nayna Govind	

CONFIRMATION NO. 7568

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1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

Date Mailed: 06/09/2014

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/rmturner myles/

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PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,759,328
Issue Date	20 July 2010
First Named Inventor	Nayna GOVIND
Title	COMPOSITION FOR INHALATION
Attorney Docket Number	100629-US-PCT

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 44992

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature	/Meaghan L. Richmond/	Date	May 28, 2014
Name	Meaghan L. Richmond	Telephone	+1.781.839.4054
Title and Company	Patent Attorney; AstraZeneca AB		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012 OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Govind et al.

Application No./Patent No.: 7,759,328 Filed/Issue Date: 20 July 2010

Titled: COMPOSITION FOR INHALATION

AstraZeneca AB , a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 015506, Frame 0145, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

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Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Meaghan L. Richmond/ May 28, 2014

Signature Date

Meaghan L. Richmond; Reg no. 61402 Patent Attorney, AstraZeneca

Printed or Typed Name Title

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	19150674
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	9629
Filer:	Meaghan Lynn Richmond/Jami Baumer
Filer Authorized By:	Meaghan Lynn Richmond
Attorney Docket Number:	
Receipt Date:	28-MAY-2014
Filing Date:	27-JUL-2004
Time Stamp:	17:09:34
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	PowerSB81A.pdf	747089 593d1044740d3da3781f752d8f79020d27f996899	no	2

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73.	StatementSB96.pdf	422936 406991ac06767e02c3f8cc4a61b88a218115e636	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	1170025

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/502,685	07/27/2004	Nayna Govind	

CONFIRMATION NO. 7568

POA ACCEPTANCE LETTER

9629
MORGAN LEWIS & BOCKIUS LLP (WA)
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

OC000000066911893

Date Mailed: 03/03/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/12/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/trwoodson/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/502,685	07/27/2004	Nayna Govind	06275-410US1

CONFIRMATION NO. 7568

26164
FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

POWER OF ATTORNEY NOTICE

OC000000066911886

Date Mailed: 03/03/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/12/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/trwoodson/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office: U.S DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 09629

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 09629

OR

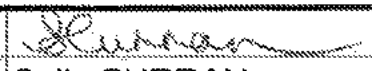
☐	Firm or Individual Name			
	Address			
	City		State	Zip
	Country			
	Telephone		Email	

Assignee Name and Address: AstraZeneca AB
S-151 85 Södertälje
Sweden

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	08 JANUARY 2014
Name	Sally CURRAN	Telephone	+44 1695 518538
Title	Senior Patent Director, Signed for and on behalf of AstraZeneca AB (publ)		

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	18175246
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Todd B. Buck
Filer Authorized By:	
Attorney Docket Number:	06275-410US1
Receipt Date:	12-FEB-2014
Filing Date:	27-JUL-2004
Time Stamp:	11:42:03
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73.	056291-5543.pdf	119284 7c761aa2ce77d2b5670558503384d07a4651 7d507	no	3

Warnings:	
Information:	

2	Power of Attorney	056291-5548-POA.pdf	104779 9adc78d49c72e80985cf88c2274b1e325b5b83a	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	224063

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office;U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of1995, no persons arerequired to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: AstraZeneca AB

Application No./Patent No.: 7,759,328 Filed/Issue Date: 20-Jul-2010

Titled: Composition for Inhalation

AstraZeneca AB, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: Govind et al. To: AstraZeneca AB

      The document was recorded in the United States Patent and Trademark Office at

      Reel 015506, Frame 0145, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Todd B. Buck/	February 11, 2014
Signature	Date
Todd B. Buck	48,574
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that yoube given certain informationin connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, pleasebe advised that: (1) the general authority forthe collection of thisinformation is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and(3) the principal purpose forwhich the information isused by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent applicationor patent. If you do not furnish the requested information,the U.S. Patent and Trademark Office may not be able to process and/or examineyour submission,which may result in termination of proceedings or abandonment of the applicationor expiration of the patent.

The informationprovided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the informationin order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an InternationalApplication filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, arecord may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from thissystem of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,759,328 B2
APPLICATION NO. : 10/502685
DATED : July 20, 2010
INVENTOR(S) : Nayna Govind and Maria Marlow

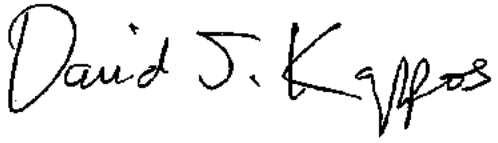
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page Item (56) Line 14 – Delete "Pipkom" and insert -- Pipkorn -- therefor.

On the Title Page Item (56) Line 18 – Delete "Zettersttröm" and insert -- Zetterström -- therefor.

Signed and Sealed this

Second Day of November, 2010



David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 11/01/2010

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
11/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10502685		GOVIND ET AL.	06275-410US1

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
ALTON N.. PRYOR	
ART UNIT	**PAPER**
1616	20101026

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Attached is the IDS filed 11/12/09.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

PTO-90C (Rev.04-03)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.P./

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-0410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant Nayna Govind et al.	
		Filing Date July 27, 2004	Group Art Unit 1616

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1.	6,123,924	09/26/2000	Mistry et al.			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Sub-class	Translation Yes	Translation No
	2.	2 338 753	02/10/2000	Canada				
	3.	WO 99/64014	12/16/1999	WIPO				
	4.	WO 01/89492	11/29/2001	WIPO				
	5.							

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	6.	"Povidone" The United States Pharmacopeia, USP25/NF20, pp.1419-1420, United States Pharmacopeial Convention, Inc., Rockville, MD. (2002)
	7.	Pauwels et al. "Effect of inhaled formoterol and budesonide on exacerbations of asthma," Vol. 337 Number 20, pp. 1405-1411 (and one correction page), November 13, 1997
	8.	Wyser et al., "Neue Aspekte in der Behandlung des Asthma bronchiale und chronisch obstruktiver Lundenkrankeiten," Schweiz Med. Wochenschr, Vol. 127, pages 885-890 (1997), English Summary included
	9.	
	10.	
	11.	
	12.	
	13.	
	14.	
	15.	
	16.	
	17.	
	18.	
	19.	

Examiner Signature	Date Considered
/Alton Pryor/	02/09/2010

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Only the abstract of reference 8 was considered. Other parts of reference 8 are in German.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Patent No.	: 7,759,328	Examiner	: Alton Nathaniel Pryor
Issue Date	: July 20, 2010	Conf. No.	: 7568
Serial No.	: 10/502,685		
Filed	: July 27, 2004		
Title	: COMPOSITION FOR INHALATION		

Attn.: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF REQUEST FOR CERTIFICATE OF CORRECTION

Applicants hereby request that a certificate of correction be issued for the above patent in accordance with the attached request.

All errors sought to be corrected were made in printing by the Patent and Trademark Office, and no fee is believed to be due.

Please apply any charges or credits to deposit account 06-1050, referencing attorney docket 06275-0410US1.

Respectfully submitted,

Date: Sept. 13, 2010

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 26164
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22488698.doc

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

September 13, 2010
Date of Deposit or Transmission

Signature

Karen A. Hawkins
Typed or Printed Name of Person Signing Certificate

Staple Here Only

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,759,328
APPLICATION NO : 10/502,685
DATED : JULY 20, 2010
INVENTOR(S) : NAYNA GOVIND AND MARIA MARLOW

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

First Page, Col. 2, Line 14 – Delete "Pipkom" and insert - - Pipkorn -- therefor.

First Page, Col. 2, Line 18 – Delete "Zettersström" and insert - - Zettersiröm -- therefor.

MAILING ADDRESS OF SENDER:

Janis K. Fraser, Ph.D., J.D.
Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, Minnesota 55440-1022

Electronic Acknowledgement Receipt

EFS ID:	8412593
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Kristi Holmlund
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	14-SEP-2010
Filing Date:	27-JUL-2004
Time Stamp:	12:35:22
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	06275reqcoc.pdf	271648 d54bfe2e075bb75d5ad0c0b20f39f42dbf9f7481	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	271648

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/20/2010	7759328	06275-410US1	7568

26164 7590 06/30/2010

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Nayna Govind, Loughborough, UNITED KINGDOM;
Maria Marlow, Loughborough, UNITED KINGDOM;

PART B – FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax **(571) 273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

26164 7590 02/25/2010

FISH & RICHARDSON P.C.
P.O. Box 1022
Minneapolis, MN 55440-1022

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION

I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

Kristi A. Helmlund	(Depositor's name)
	(Signature)
May 24, 2010	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-0418US1	7508

TITLE OF INVENTION: **COMPOSITION FOR INHALATION**

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEES DUE	DATE DUE
nonprovisional	NO	$1510	$300	$1810	05/25/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
PRYOR, ALTON NATHANIEL	1616	514-167000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

[ ] Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

[ ] "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. **Fish & Richardson P.C.**
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE (CITY and STATE OR COUNTRY)

AstraZeneca AB **SODERTALJE, SWEDEN**

Please check the appropriate assignee category or categories (will not be printed on the patent): [ ] individual [X] corporation or other private group entity [ ] government

4a. The following fee(s) are enclosed:
[X] Issue Fee
[X] Publication Fee (No small entity discount permitted)
[ ] Advance Order - # of Copies _____

4b. Payment of Fee(s):
[ ] A check in the amount of the fee(s) is enclosed.
[ ] Payment by credit card. Form PTO-2038 is attached.
[X] The Director is hereby authorized to charge the required fee(s), or credit any overpayment, to Deposit Account Number 06-1050. (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

[ ] a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. [ ] b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2)

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered agent or; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

(Authorized Signature) /Janis K. Fraser/ (Date) May 24, 2010

Typed or Printed Name: Janis K. Fraser, Ph.D., J.D. Registration No. 34819

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Nayna Govind *et al.*
Serial No. : 10/502,685
Filed : July 27, 2004
Art Unit : 1616
Examiner : Alton Nathaniel Pryor
Conf. No. : 7568
Notice of Allowance Date: February 25, 2010
Title : COMPOSITION FOR INHALATION

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

Applicants recognize that in accordance with M.P.E.P. § 1302.14, the Examiner's reasons for allowance need not set forth all of the details as to why the claims are allowed. In the present application, applicants do not concede that the Examiner's stated reasons for allowance are the only reasons for which the claims are allowable. With respect to the Examiner's comment in the Notice of Allowability that "The claimed invention is specific to chemical components and the amounts thereof," applicants point out that the claims use the open language "comprising," so are not limited to the specified components, and also do not specify the amount of the HFA present in the formulation. Further, applicants do not concede that the amount of any of the various components specified in any of the claims is necessary for patentability.

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.
May 24, 2010
Date of Deposit or Transmission
Signature
Kristi A. Hulmland
Typed or Printed Name of Person Signing Certificate

The fees totaling $1810 for the issue fee ($1510) and the publication fee ($300) are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any additional charges or credits to our deposit account 06-1050, referencing attorney docket 06275-0410US1.

Respectfully submitted,

Date: May 24, 2010

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22423923.doc

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Janis K. Fraser/Kristi Holmlund
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1810**

Electronic Acknowledgement Receipt

EFS ID:	7672223
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Brenda Jurgens
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	24-MAY-2010
Filing Date:	27-JUL-2004
Time Stamp:	15:15:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1810
RAM confirmation Number	1583
Deposit Account	061050
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		06275rnoa.pdf	811814 794641b117e673da9c318ca1c1f220864aa4a012	yes	4

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Post Allowance Communication - Incoming	1	1
Issue Fee Payment (PTO-85B)	2	2
Post Allowance Communication - Incoming	3	4

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	31751 00b660252bfe1d46fd7a9352cc23f07bb0773871	no	2

Warnings:

Information:

Total Files Size (in bytes):	843565

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
		Notice of Allowance Date: February 25, 2010	

Title : COMPOSITION FOR INHALATION

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed February 25, 2010, enclosed are a completed issue fee transmittal form PTOL-85b and a Comments on Statement of Reasons for Allowance.

The fees totaling $1810 for the issue fee ($1510) and the publication fee ($300) are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any additional charges or credits to our deposit account 06-1050, referencing attorney docket 06275-0410US1.

Respectfully submitted,

Date: May 24, 2010

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 26164
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945
22423932.doc

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

May 24, 2010
Date of Deposit or Transmission

Signature

Kristi A. Holmlund
Typed or Printed Name of Person Signing Certificate

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

7590 04/26/2010

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 04/26/2010

PRIORITY ACKNOWLEDGMENT

☑ 1. Receipt is acknowledged of priority papers submitted under 35 U.S.C. 119. The papers have been placed of record in the file.

☐ 2. Applicant's claim for priority, based on papers filed in parent Application Number _____ submitted under 35 U.S.C. 119, is acknowledged.

☐ 3. The priority papers, submitted _____, after payment of the issue fee are

☐ acknowledged
While the priority claim or certified copy filed will be placed in the file record, neither will be reviewed and the patent when published will not include the priority claim.
See 37 CFR 1.55(a)(2).

☐ not acknowledged since the processing fee in 37 CFR 1.17(i) has not been received.

☐ 4. For utility and plant applications filed on or after November 29, 2000, the priority claim is not entered because the claim was not presented within the time limit required by 37 CFR 1.55(a)(1). A petition to accept a delayed claim for priority under 35 U.S.C. 119(a) - (d) or (f), or 365(a) may be filed. See 37 CFR 1.55(c) and MPEP 201.14(a).

Patricia A. Pawesh, for

571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 03/25/2010

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
03/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Response to Rule 312 Communication	Application No.	Applicant(s)
	10/502,685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N. PRYOR	1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ The amendment filed on *15 March 2010* under 37 CFR 1.312 has been considered, and has been:

   a) ☒ entered.

   b) ☐ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

IDS forms dated 11/3/06 and 03/15/10 are attached.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.P./

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant Nayna Govind *et al.*	
		Filing Date July 27, 2004	Group Art Unit 1616

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	BA						
	BB						

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	BC	WO99/15182	April 1, 1999					
	BD							

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	BE	Calverley *et al.*, "Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease" *Eur. Respir. J.* 22:912-919 (2003)
	BF	Cazzola *et al.*, "Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease" *Pulm Pharmacol.* 7:103-7 (1994)
	BG	Lumry, "A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis," *J. Allergy Clin. Immunol.* 104:S150-8 (1999) (abstract only)
	BH	Milgrom and Taussig, "Keeping Children with Exercise-Induced Asthma Active" *Pediatrics* 104:38-42 (1999)
	BI	Pipkorn *et al.*, "Budesonide- a New Nasal Steroid" *Rhinology* 18:171-175 (1980)
	BJ	Renkema *et al.*, "Effects of long-term treatment with corticosteroids in COPD" *Chest* 109:1156-62 (1996)
	BK	Zetterström *et al.*, "Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone" *Eur. Respir. J.* 18:262-268 (2001)
	BL	

Examiner Signature	Date Considered
/Alton Pryor/	10/15/2009

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form (PTO-1449)

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 06275-0410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant Nayna Govind et al.	
		Filing Date July 27, 2004	Group Art Unit 1616

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
/A.P./	1	TurbiScan MA 2000 brochure (6 pages). [Replacement Copy]

Examiner Signature	Date Considered
/Alton Pryor/	03/19/2010

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form (PTO-1449)

PRINTER RUSH

(PTO ASSISTANCE)

Application: 10502685	**Examiner:** Pryor	**GAU:** 1616
From: Lois Stone	**Location:** IDC	**Date:** 03/05/2010

Tracking #: 10502685 Week Date: 09/07/2009

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	11/03/2006	[ ] Foreign Priority
[ ] CLM		[ ] Document Legibility
[ ] HFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Other
[ ] DRW		
[ ] OATH		Attn:
[ ] 312		
[ ] SPEC		

[RUSH] Message:

Please initial/line through citations on IDS dated 11/3/2006.

Thank you,
las

[XRUSH] Response:

IDS Acknowledged.

Initials: ANP

Examiner: PUBS contacts - for DESIGNS: Don Fairchild, 703-756-1566; for ALL OTHER files: Bernadette Queen, 703-756-1565.
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.

REV: May 09

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
		Notice of Allowance Date: February 25, 2010	

Title : COMPOSITION FOR INHALATION

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMUNICATION PURSUANT TO 37 C.F.R. §1.312

This communication is being filed prior to the payment of the issue fee and along with a PTO-1449 form.

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: March 15, 2010

REMARKS

Claims 25, 30-35, 45-52 have been allowed, as indicated in the Notice of Allowance dated February 25, 2010. Enclosed with the Notice of Allowance was an initialed copy of the form PTO-1449 submitted by Applicants on January 25, 2010. All of the references listed on the form PTO-1449 were initialed as having been considered by the Examiner, except reference 9 – Turbiscan MA 2000 brochure – which, as indicated on the form, did not transmit clearly. Applicants thank the Examiner for the courteous telephone conversation with a colleague of the undersigned on March 1, 2010, during which the Examiner kindly suggested that a legible replacement copy of reference 9 be submitted with a communication under 37 C.F.R. § 1.312 so that it can be considered.

Applicants enclose a replacement copy of the reference and a new PTO-1449 form listing just that reference. Applicants believe that the replacement copy submitted herewith is legible and request that the Examiner consider it and return an initialed copy of the enclosed PTO-1449 form to Applicants. If the replacement copy does not transmit clearly, the Examiner is asked to telephone the undersigned to discuss how best to resolve the issue prior to the deadline for filing the issue fee.

No fee is believed to be due. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-0410US1.

Respectfully submitted,

Date: March 15, 2010

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No.: 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22371415.doc

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 06275-0410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))	Applicant Nayna Govind et al.	
	Filing Date July 27, 2004	Group Art Unit 1616

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	1	TurbiScan MA 2000 brochure (6 pages). [Replacement Copy]

Examiner Signature	Date Considered
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Disclosure Form (PTO-1449)

Electronic Acknowledgement Receipt

EFS ID:	7205879
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Kristi Holmlund
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	15-MAR-2010
Filing Date:	27-JUL-2004
Time Stamp:	10:19:01
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		06275Amendment.pdf	370388 dfda1a05f6c5e1bc71d28983ac822e3d87cf2470	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	2
	Information Disclosure Statement (IDS) Filed (SB/08)	3	3

Warnings:					
Information:					
2	NPL Documents	Turbiscan.pdf	1364679 e965d42e49b5e4e67053c76a0051 13a2344 72743	no	6
Warnings:					
Information:					
		Total Files Size (in bytes):	1735067		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26164 7590 02/25/2010

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 02/25/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

TITLE OF INVENTION: COMPOSITION FOR INHALATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	05/25/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
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26164 7590 02/25/2010

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

TITLE OF INVENTION: COMPOSITION FOR INHALATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	05/25/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
PRYOR, ALTON NATHANIEL	1616	514-167000

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☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 02/25/2010

FISH & RICHARDSON P.C.
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EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 02/25/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	ALTON N. PRYOR	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *1/25/10*.

2. ☒ The allowed claim(s) is/are *25,30-35,45-52(claims renumbered 1-15)*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 1/25/10
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

The following is an examiner's statement of reasons for allowance: The results provided in the specification on pages 7-9 for the stability of the instant composition overcomes any obviousness type rejection that could have been deduced from US 20030018019, US 6309623, WO 93/05765 and/or WO 93/11773. The claimed invention is specific to chemical components and the amounts thereof.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALTON N. PRYOR whose telephone number is (571)272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

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Bib Data Sheet

CONFIRMATION NO. 7568

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/502,685	07/27/2004 RULE	424	1616	06275-410US1

APPLICANTS

Nayna Govind, Loughborough, UNITED KINGDOM;
Maria Marlow, Loughborough, UNITED KINGDOM;

** **CONTINUING DATA** **********

This application is a 371 of PCT/SE03/00156 01/29/2003

** **FOREIGN APPLICATIONS** **********

SWEDEN 0200312-7 02/01/2002

Foreign Priority claimed	STATE OR	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged Examiner's Signature Initials	UNITED KINGDOM	16	12	1

ADDRESS

26164

TITLE

Composition for inhalation

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
1080		

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
each inventor	7/31/08	anp
Consulted with A. Marschel: decided 103 rejection should be reinstated and 112 written description should be entered	1/16/08	anp
Allowability Conference with Dr. Ardin Marscel and Sreeni Marschel - Decision was to allow the application.	8/20/09	anp

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
514	165, 463	8/25/09	anp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

ORIGINAL		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED									
514	167	A	0	1	N	45 / 00 (2006.0)										
CROSS REFERENCE(S)		A	6	1	K	31 / 335 (2006.0)										
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
514	463															

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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	2		18	6	34	9	50								
	3		19	7	35	10	51								
	4		20		36	11	52								
	5		21		37										
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	11		27		43										
	12		28		44										
	13		29	12	45										
	14	2	30	13	46										
	15	3	31	14	47										
	16	4	32	15	48										

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/ALTON N PRYOR/ Primary Examiner.Art Unit 1616	2/9/10	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	none	none

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.P./

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 06275-0410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Nayna Govind et al.	
(37 CFR §1.98(b))		Filing Date July 27, 2004	Group Art Unit 1616

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	1	WO 98/15280	04/16/1998	WIPO				
	2	WO 00/53188	09/14/2000	WIPO				
	3	WO 01/78737	10/25/2001	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	4	Brindley, "The chlorofluorocarbon to hydrofluoroalkane transition: The effect on pressurized metered dose inhaler suspension stability," J. Allergy Clin. Immunol., Vol. 104, pages s221-s226 (1999).
	5	Byron, "Respiratory Drug Delivery," CRC Press, Inc., pages 185-201 (1990).
	6	Communication of a Notice of Opposition against Patent No. EP1474117 from the European Patent Office, dated December 4, 2009 (27 pages).
	7	Jinks, "A rapid technique for characterization of the suspension dynamics of metered dose inhaler formulations," Proceedings of Drug Delivery to the Lungs VI., London: The Aerosol Society, 1995; Abstract supplied by The British Library (2 pages).
	8	Turbuhaler MA 2000, Sci-Tec Inc., [online] Retrieved from http://www.sci-tec-inc.com/Turbuhaler%20Classic%20MA%202000.html Retrieved on October 20, 2009 (3 pages).
	9	~~Turbuhaler MA 2000 brochure (2 pages).~~

Reference number 9 did not transmit clearly. For this reason reference 9 was not considered.

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 06275-0410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Nayna Govind et al.	
(37 CFR §1.98(b))		Filing Date July 27, 2004	Group Art Unit 1616

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	1	WO 98/15280	04/16/1998	WIPO				
	2	WO 00/53188	09/14/2000	WIPO				
	3	WO 01/78737	10/25/2001	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	4	Brindley, "The chlorofluorocarbon to hydrofluoroalkane transition: The effect on pressurized metered dose inhaler suspension stability," J. Allergy Clin. Immunol., Vol. 104, pages s221-s226 (1999).
	5	Byron, "Respiratory Drug Delivery," CRC Press, Inc., pages 185-201 (1990).
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	7	Jinks, "A rapid technique for characterization of the suspension dynamics of metered dose inhaler formulations," Proceedings of Drug Delivery to the Lungs VI., London: The Aerosol Society, 1995; Abstract supplied by The British Library (2 pages).
	8	TurbiScan MA 2000, Sci-Tec Inc., [online] Retrieved from http://www.sci-tec-inc.com/Turbiscan%20Classic%20MA%202000.html Retrieved on October 20, 2009 (3 pages).
	9	TurbiScan MA 2000 brochure (2 pages).

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Substitute Disclosure Form (PTO-1449)

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:
A61K 31/57 // (A61K 31/57, 31:165)	A1	WO 98/15280
		(43) International Publication Date: 16 April 1998 (16.04.98)

(21) International Application Number: PCT/SE97/01606

(22) International Filing Date: 24 September 1997 (24.09.97)

(30) Priority Data:
9603669-4 8 October 1996 (08.10.96) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TROFAST, Jan [SE/SE]; Vapenkroken 34, S-226 47 Lund (SE). ULLMAN, Anders [SE/SE]; Långedragsvägen 143A, S-426 74 Västra Frölunda (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NEW COMBINATION

(57) Abstract

The invention provides a composition or kit having as a first active ingredient formoterol, or a salt or solvate derivative thereof, and having as a second active ingredient budesonide, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, and the use of the composition and kit in the treatment of respiratory disorders.

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NEW COMBINATION

Field of the Invention

The present invention provides a new combination of pharmaceutically active substances which is of use in the treatment of respiratory disorders, particularly asthma.

Background to the Invention

Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms include uncontrolled airway inflammation which may lead to mucosal damage and structural changes possibly leading to irreversible narrowing of the airways and fibrosis of the lungs.

The symptoms may be controlled by β_2-adrenoreceptor agonists such as salbutamol, salmeterol, terbutaline and formoterol. Formoterol is advantageous because the duration of its effect is long; it has a fast onset time and because it gives few nocturnal wakenings.

Prophylactic therapy is typically provided by steroids such as beclomethasone diproprionate, fluticasone propionate and budesonide. Of these budesonide is advantageous because it may be given in a high inhaled dose (up to 2 mg daily) with very low systemic effects. Long term clinical studies in adults and children have shown that inhaled budesonide has an excellent safety profile.

Description of the Invention

According to the invention there is provided a composition comprising, in an admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, preferably about 1:32.5.

According to the invention there is further provided a kit comprising:

(i) a vessel containing the first active ingredient;

(ii) a vessel containing the second active ingredient; and

(iii) instructions for the sequential or separate administration of the first and second active ingredients to a patient in need thereof;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, preferably about 1:32.5.

A patient suffering from a respiratory disorder such as asthma can be treated by administering via inhalation a composition according to the invention. Alternatively such a patient can be treated by administering via inhalation, sequentially or separately:

(i) a dose of the first active ingredient; and

(ii) a dose of the second active ingredient;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, preferably about 1:32.5.

It has been found that the combination of active ingredients according to the invention is advantageous because it gives a significantly improved anti-inflammatory effect compared to known treatments. International patent publication no. WO 93/11773 discloses a combination of budesonide and formoterol having a wide weight ratio range. The closest example of a combination disclosed in this document to the system of the invention has a weight ratio of formoterol fumarate dihydrate to budesonide of 0.06:1, i.e. a molar ratio of 1:16.3. The combination of active ingredients according to the invention gives surprisingly better results when used to treat patients suffering from asthma compared to this known combination.

The first and second active ingredients of the kit can be administered sequentially or separately to treat respiratory disorders. By sequential is meant that the first and second active ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 12 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

Preferably the first active ingredient is administered to provide a daily dose of from 10 to 250nmol (preferably from 15 to 120nmol) and the second active ingredient is administered to provide a daily dose of from 0.1 to 10μmol (preferably 0.2 to 5μmol) or from 39 to 4300μg of the second active ingredient (preferably from 86 to 2150μg), subject to the molar ratio of the first active ingredient to the second active ingredient being within the range of from 1:30 to 1:36.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The first active ingredient is preferably formoterol fumarate, especially the dihydrate.

When the first active ingredient is formoterol fumarate dihydrate, the preferred daily dose of the first active ingredient is from 4 to 100μg, more preferably from 6 to 50μg (subject to the molar ratio of the first active ingredient to the second active ingredient being within the range of from 1:30 to 1:36).

Most preferably the composition or kit of the invention comprises 6μg of formoterol fumarate dihydrate and 200μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered up to four times a day.

Alternatively the composition or kit of the invention comprises 12μg of formoterol fumarate dihydrate and 400μg of budesonide, or 9μg of formoterol fumarate dihydrate and 320μg of budesonide, either of which is administered once or twice a day.

Preferably the active ingredient(s) are used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 50μg to 25mg per dose, more preferably in an amount of from 50μg to 10mg, most preferably in an amount of from 100 to 2000μg. Examples of suitable diluents or carriers include lactose, dextran, mannitol and glucose. Preferably lactose is used, especially as the monohydrate.

It should be understood that where reference is made to the amounts of each active ingredient that these are metered amounts. When the active ingredients are administered, the amount of each ingredient inhaled by the patient can differ from the metered amount, e.g. due to retention of the active ingredient in the inhalation device. Furthermore when the active ingredients are formulated separately, the administered amount of each is not necessarily reduced proportionately. Thus the administered ratio of the active ingredients could differ from the metered ratio. Preferably the administered ratio is within the metered ratio specified above.

One or more of the active ingredients used in the invention is preferably in the form of a dry powder, more preferably a finely divided, e.g. a micronised, dry powder, e.g. having a mass median diameter of less than 10μm, for example from 1 to 5μm, most preferably an agglomerated micronised dry powder. As an alternative to agglomeration the finely divided active ingredients may be in the form of an ordered mixture with the one or more pharmaceutically acceptable additives, diluents or carriers. An ordered mixture is the combination of finely divided active ingredient with coarse particles of pharmaceutically acceptable additive, diluent or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art.

According to the invention there is further provided the use of a composition or kit according to the invention in the manufacture of a medicament for use in the treatment of a respiratory disorder, e.g. asthma. The invention also provides the use of budesonide or of formoterol in the manufacture of a kit or of a composition according to the invention for use in the treatment of a respiratory disorder, e.g. asthma.

Administration may be by inhalation orally or intranasally. The ingredients are preferably adapted to be administered from a dry powder inhaler, a pressurised metered dose inhaler, or a nebuliser.

When the ingredients of the composition or kit are adapted to be administered from a pressurised inhaler, they are preferably in micronised form. They are dissolved or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the ingredients of the composition or kit of the invention are adapted to be administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The composition or kit may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day.

The invention is illustrated by the following Examples which are not intended to limit the scope of the application. In the Examples micronisation is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler is a trademark of Astra AB.

Example 1

6 Parts by weight of formoterol fumarate dihydrate was mixed with 794 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 2

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 835 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 3

12 Parts by weight of formoterol fumarate dihydrate was mixed with 588 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 400 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 4

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then

conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 5

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

160 Parts by weight of micronised budesonide was mixed with 840 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 6

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

400 Parts by weight of micronised budesonide was mixed with 600 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then

conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Claims

1. A composition comprising, in admixture:

(a) a first active ingredient selected which is formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

wherein the molar ratio of (a) to (b) in the composition is from 1:30 to 1:36.

2. A composition according to claim 1, wherein the molar ratio is about 1:32.5.

3. A composition according to claim 1 or 2, wherein the first active ingredient is formoterol fumarate dihydrate.

4. A composition according to claim 1, 2 or 3, additionally comprising a pharmaceutically acceptable additive, diluent or carrier.

5. A composition according to any one of the preceding claims for use in the treatment of a respiratory disorder.

6. A kit comprising

(a) a vessel containing a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a vessel containing a second active ingredient which is budesonide;

(c) instructions for the sequential or separate administration of the first and second active ingredients to a patient in need thereof;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36.

7. A kit according to claim 6, wherein the molar ratio is about 1:32.5.

8. A kit according to claim 6 or 7, wherein the first active ingredient is formoterol fumarate dihydrate.

9. A kit according to claim 6, 7 or 8, additionally comprising a pharmaceutically acceptable additive, diluent or carrier suitable for inhalation.

10. A kit according to any one of claims 6 to 9, wherein each ingredient is in the form of a finely divided dry powder and each vessel is a dry powder inhaler.

11. A method of treating a respiratory disorder, which method comprises administering via inhalation to a patient suffering from the disorder a therapeutically effective amount of a composition as defined in any one of claims 1 to 4.

12. A method of treating a respiratory disorder, which method comprises sequentially or separately administering via inhalation to a patient suffering from the disorder

(a) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a dose of a second active ingredient which is budesonide;

wherein the molar ratio of (a) to (b) is from 1:30 to 1:36.

13. Use of a composition according to any one of claims 1 to 4 in the manufacture of a medicament for use in the treatment of a respiratory disorder.

14. Use of a kit according to any one of claims 6 to 10 in the manufacture of a medicament for use in the treatment of a respiratory disorder.

15. Use of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt in the manufacture of a composition according to any one of claims 1 to 4 or of a kit according to any one of claims 6 to 10 for use in the treatment of a respiratory disorder.

16. Use of budesonide in the manufacture of a composition according to any one of claims 1 to 4 or of a kit according to any one of claims 6 to 10 for use in the treatment of a respiratory disorder.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01606

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57 // (A61K 31/57, 31:165)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, JAPIO, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93), page 8 --	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
17 December 1997	03 -02- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01606

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 11, 12
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 13 and 14 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/97

International application No.
PCT/SE 97/01606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311773 A1	24/06/93	AU 673660 B	21/11/96
		AU 3085892 A	19/07/93
		CA 2123909 A	24/06/93
		CZ 9401434 A	15/12/94
		EP 0613371 A	07/09/94
		HR 921445 A	31/12/94
		HU 75156 A	28/04/97
		HU 9401843 D	00/00/00
		JP 7502036 T	02/03/95
		NO 942116 A	07/06/94
		NZ 246050 A	21/12/95
		SK 73394 A	08/03/95
		US 5674860 A	07/10/97

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(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TROFAST, Jan [SE/SE]; AstraZeneca AB, R & D Lund, S-221 87 Lund (SE). BAUER, Carl-Axel [SE/SE]; AstraZeneca AB, R & D Lund, S-221 87 Lund (SE).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

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(54) Title: NEW COMBINATION OF R,R-FORMOTEROL AND BUDESONIDE IN A PHARMACEUTICAL COMPOSITION USEFUL FOR TREATING RESPIRATORY DISORDERS, SUCH AS ASTHMA, RHINITIS AND COPD

(57) Abstract

The invention relates to novel combinations of medicaments useful in the treatment of mild, moderate and severe asthma and other respiratory disorders such as rhinitis and chronic obstructive pulmonary disease (COPD).

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NEW COMBINATION OF R,R-FORMOTEROL AND BUDESONIDE IN A PHARMACEUTICAL COMPOSITION USEFUL FOR TREATING RESPIRATORY DISORDERS, SUCH AS ASTHMA, RHINITIS AND COPD

Field of the invention

This invention relates to improvement in the treatment of mild, moderate and severe asthma and other respiratory disorders such as rhinitis and chronic obstructive pulmonary disease (COPD). More particularly, it relates to the use of the steroidal anti-inflammatory drug budesonide in combination with the strongly active R,R-enantiomer (preferably as the fumarate dihydrate salt) of the long-acting bronchodilator formoterol (R,R;S,S) for the treatment of respiratory disorders such as mild, moderate and severe asthma, rhinitis and COPD, and to pharmaceutical compositions containing the two active ingredients.

Background of the invention

The recognition more than 10 years ago of the fundamentally inflammatory nature of asthma led to the suggestions that control of the underlying airway inflammation could provide the key to the control of asthma at all levels of severity. Nevertheless many patients with asthma of most levels of severity still receive no regular anti-inflammatory treatment and are treated only with intermittent or regular bronchodilator therapy. Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate (BDP), flunisolide, triamcinolone acetonide, dexamethasone, mometasone furoate, fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Long-acting β2-agonists such as formoterol and salmeterol, have different properties from short-acting ones such as terbutaline and salbutamol. These long-acting bronchodilators have been regarded as add-on treatment to steroid therapy. However, the long-acting agonists are considered an alternative to a further increase in the dosage of inhaled steroids. The side-effects of the steroids could therefore be minimized. Therapy should be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for

treating the underlying inflammation. An interesting approach for this treatment strategy would be to combine a β2-agonist with fast onset of action for symptom control together with an anti-inflammatory agent like a glucocorticosteroid.

The most common cause for poor control of asthma is poor compliance in the long-time management of chronic asthma, particularly with prophylatic treatment such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β2-agonist inhalers, since these provide rapid onset of symptoms, but often do not take the prophylactic therapy, such as inhaled steroids, regularly because there is no immediate symptomatic benefit.

Drug stereoisomerism is increasingly being recognized as an issue having clinical, research and regulatory implications. Differences in the pharmaco-dynamic and pharmacokinetic properties of stereoisomers are well documented e.g. the pharmacological properties of drug enantiomers can be dramatically different; one isomer may be predominantly responsible for the desired therapeutic action and the other for the side effects. In the case of formoterol (a mixture of R,R and S,S), the R,R-enantiomer is about 1000 times more potent than the S,S-isomer (see Trofast et al (1991)).

Earlier mentioned combinations of long-acting β-agonists and steroids include the use of salmeterol/beclomethasone dipropionate (US 5,208,226, Glaxo), salmeterol/fluticasone propionate (US 5,270,305, Glaxo) and formoterol/budesonide (US 5,674,860, Astra). The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects.

Summary of the invention

It has now surprisingly been found that a combination of R,R formoterol and budesonide can be used for the treatment of respiratory disorders such as asthma, rhinitis and COPD. According to the invention there is provided a pharmaceutical combination which comprises R,R formoterol in combination with budesonide.

Detailed description of the invention

The present invention provides a novel combination therapy using the long-acting bronchodilator R,R-formoterol (preferably as the fumarate dihydrate salt) and the glucocorticosteroid budesonide.

In a first aspect the present invention provides a pharmaceutical combination which comprises:

(a) R,R-formoterol, or a pharmaceutical acceptable salt or solvate thereof,

(b) budesonide; and optionally

(c) one or more pharmaceutically acceptable additives, diluents or carriers;

Preferably the molar ratio of (a) to (b) is from 1:4 to 1:100.

The word "combination" is used to describe the invention because the components can be administered simultaneously or sequentially for use in therapy. Thus the active ingredients (a) and (b) are not necessarily, but may be, used as an admixture, they still have the desired effect if they are administered sequentially or separately. Preferably they are not administered more than about two hours apart, for example no more than 30 minutes apart.

The first main ingredient of the combination of the invention is the single enantiomer R,R-formoterol i.e. R,R-(N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methyl-ethyl]-amino]-ethyl]phenyl]-formamide, an adrenoceptor agonist which selectively

stimulates β2-receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by endogenous mediators, and increased mucociliary clearance. The compound can be prepared by methods described in "Large-Scale Synthesis of Enantio- and Diastereomerically Pure (R,R)-formoterol" by R. Hett et al. in Organic Process Research & Development, 2 (1998), 96-99 or in "Steric Aspects of Agonism and Antagonism at β-adrenoceptors: Synthesis of and Pharmacological Experiments With the Enantiomers of Formoterol and Their Diastereomers" by J. Trofast et al in Chirality 3 (1991), 443-450.

The other main ingredient is budesonide i.e. 16,17-butylidenebis(oxy)-11,21-dihydroxy-pregna-1,4-diene-3,20-dione. The compound can be prepared by the methods described in US 3,929,768. The compound exists as epimers, and either epimer can be used in the combinations of the invention, including the 22R epimer.

A combination, preferably a fixed combination i.e. given in admixture, of the compounds of the invention will establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies the life for the patients considerably and makes life more comfortable and secure.

According to another aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of R,R-formoterol (and/or physiologically acceptable salt and/or solvate thereof) and budesonide as a preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders such as asthma, rhinitis and COPD. Reference to formoterol and salts and solvates thereof includes all combinations of solvates and salts of formoterol such as solvates of salts.

The invention additionally relates to the use of R,R-formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of pharmaceutical compositions as preparations for simultaneous, sequential or separate

administration of R,R-formoterol and budesonide by inhalation in the treament of respiratory disorders such as asthma, rhinitis and COPD.

According to a further feature of the invention there is provided a method of treating respiratory disorders which comprises the simultaneous, sequential or separate administration by inhalation of effective amounts of R,R-formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

Suitable physiological salts of R,R-formoterol include acid addition salts derived from inorganic and organic acids, such salts as the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluene-sulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballate, hydroxynaphthalenecarboxylate or oleate. R,R-Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of that salt.

The intended dose regimen is once or twice a day, where the suitable daily dose of R,R-formoterol is in the range of from about 5 to about 250 nmol (preferably from about 10 to about 120 nmol) and for budesonide a daily dose of about 0.1 μmol to about 3 μmol with a preferred dose of about 0.1 μmol to about 2 μmol. The doses of R,R-formoterol to budesonide should be selected to be within the molar range of from 1:4 to 1:100. The two drugs may be administered separately in the same ratio. The dose of choice will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

The combination is inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler e.g. multidose reservoir systems from Astra (Turbuhaler®) or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs. A diluent or carrier, generally being non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will

give the medicament a certain taste can be added to the powdered medicament in an amount of from 50 μg to 25 mg per dose, more preferably in an amount of from 50 μg to 10 mg, most preferably in an amount of from 100 to 2000 μg.

One or more of the ingredients is preferably in the form of a dry powder, more preferably a micronized dry powder, morst preferably an agglomerated micronized dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse particles of the pharmaceutically acceptaible additive, diluent or carrier. A fraction of fine particles of carrier may also be present. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is less than 20 μm, preferably less than 10 μm.

When the ingredients of the system are adapted to be administered from a pressurized inhaler, they are preferably in micronized form. They are dissolved, or, preferably suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the ingredients of the system of the invention are adapted to be administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The invention is illustrated by the following examples which are not intended to limit the scope of the application. In the examples micronization is carried out such that the particle size range for each component is suitable for administration by inhalation. The dry powder

formulation containinig an additive, diluent or carrier could be either in agglomerated form or as ordered mixtures .

Example 1.	Per dose
R,R-Formoterol fumarate dihydrate	6 μg
Budesonide	100 μg

Example 2.	
R,R-Formoterol fumarate dihydrate	6 μg
Budesonide	200 μg

Example 3.	
R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	100 μg

Example 4.	
R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	50 μg
Lactose monohydrate	up to 0.5, 1,5,10,20 mg

Example 5.	
R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	100 μg
Lactose monohydrate	up to 0.5, 1, 5, 10, 20 mg

Example 6.

R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	200 μg
Lactose monohydrate	up to 0.5, 1, 5, 10, 20 mg

Example 7.

R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	100 μg
Oleic acid (based on propellant)	0.005 %
Ethanol (based on propellant)	1.5 %
Propellant P134a	up to 25, 50 or 100 μl

Example 8.

R,R-Formoterol fumarate dihydrate	6 μg
Budesonide	200 μg
Oleic acid (based on propellant)	0.01 %
Ethanol (based on propellant)	1.5 %
Propellant P227/P134a (15/85)	up to 25, 50 or 100 μl

Example 9.

2.6 parts of R,R-formoterol fumarate dihydrate and 896.8 parts of lactose monohydrate were mixed in a tumbling mixer to an evenly distributed mixture, whereafter the mixture was micronized in a spiral jet mill using a pressure and feeding suitable to obtain a particle size of less than 3 um. The micronized particles were then treated using a method described in WO 95/05805 to remove amorphous regions in their crystal structure. 98 parts of micronized budesonide were added and the mixture was remicronized at a lower pressure in a spiral jet mill to a homogeneous mixture. The powder was then agglomerated by feeding into a screw feeder (K-tron), sieved, spheronized in a rotating pan, then sieved

again, spheronized once more before final sieving (0.8 mm mesh size) to give a powder suitable for an inhaler.

Example 10.

Example 9 was repeated with identical conditions but using 2.6 parts of micronized R,R-formoterol fumarate dihydrate, 798.8 parts of micronized lactose monohydrate and 196 parts of micronized budesonide.

Claims.

1. A pharmaceutical combination which comprises:
(a) R,R-formoterol, or a pharmaceutical acceptable salt or solvate thereof,
(b) budesonide; and optionally
one or more pharmaceutically acceptable additives, diluents or carriers.

2. A pharmaceutical combination according to claim 1 wherein the molar ratio of (a) to (b) is from 1:4 to 1:100.

3. A pharmaceutical combination according to claim 1 or 2 in which the R,R-formoterol is in the form of the fumarate dihydrate salt.

4. A pharmaceutical combination according to any one of claims 1 to 3 in which the combination is fixed and given in admixture.

5. A pharmaceutical combination according to any one of claims 1 to 4 in a form suitable for administration from a pressurised inhaler.

6. A pharmaceutical combination according to claim 5 comprising
R,R-formoterol, or a pharmaceutical acceptable salt or solvate thereof,
budesonide; and optionally
a propellant and one or more other surfactants and/or one or more excipients.

7. A pharmaceutical combination according to claim 6 in which the propellant is HFA 227.

8. A pharmaceutical combination according to any one of claims 1 to 7 for use for the treatment or prophylaxis of a respiratory disorder.

9. A pharmaceutical combination according to any one of claims 1 to 7 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00418

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/58, A61K 31/165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9815280 A1 (ASTRA AKTIEBOLAG ET AL), 16 April 1998 (16.04.98) --	1-19
A	CHIRALITY, Volume 3, 1991, Trofast, Jan et al, "Steric Aspects of Agonism and Antagonism at Beta-Adrenoceptors:" page 443 - page 450 --	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Information on patent family members

02/12/99

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815280 A1	16/04/98	AU 4578297 A	05/05/98
		BR 9706822 A	23/03/99
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		NO 982414 A	27/05/98
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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **GAVIN, Brian, Charles** [IE/IE]; GlaxoSmithKline, P.O. Box 700, Grange Road, Rathfarnfam, 16 Dublin (IE).

(74) Agent: **LEAROYD, Stephanie, Anne**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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WO 01/78737 A1

(54) Title: MEDICAL COMBINATIONS COMPRISING FORMOTEROL AND BUDESONIDE

(57) Abstract: The present invention is concerned with pharmaceutical formulations comprising a combination of (R,R)-formoterol and budesonide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

MEDICAL COMBINATIONS COMPRISING FORMOTEROL AND BUDESONIDE

The present invention is concerned with combinations of (R,R)-formoterol and budesonide, particularly compositions containing a combination of (R,R)-formoterol and budesonide and the use of such compositions in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Formoterol, i.e. 2'-hydroxy-5'-[(RS)-1-hydroxy-2{[(RS)-p-methoxy-α-methylphenethyl]amino}ethyl]formanilide, particularly its fumarate salt is a well-known adrenoreceptor agonist which is now used clinically in the treatment of bronchial asthma and related disorders. Formoterol includes two asymmetric centres and in a particular form exists as the (R,R)- isomer. The (R,R) isomer of formoterol has been described previously, for example, in WO98/21175 and US5795564.

DE 2,323,215 and US 3,929,768 describe budesonide i.e. (11β,16α)-16,17-[butylidenebis(oxy)]-11,21-dihydroxypregna-1,4-diene-3,20-dione, salts thereof and pharmaceutical formulations thereof. Budesonide is an antiinflammatory corticosteroid, which is now used clinically in the treatment of bronchial asthma and related disorders.

WO 93/11773 describes combinations of budesonide and formoterol but is silent as to the utility of (R,R)-formoterol.

Although (R,R)-formoterol fumarate and budesonide are effective therapies, there exists a clinical need for asthma therapies having potent and selective action and having an advantageous profile of action.

Therefore, according to the present invention there is provided a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination.

According to a further aspect of the present invention, there is provided a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. According to a preferred aspect of the present invention, there is provided a pharmaceutical formulation comprising (R,R)-formoterol fumarate and budesonide, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. In the most preferred aspect, the above pharmaceutical formulations are suitable for administration by inhalation.

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

By the term "physiologically functional derivative" is meant a chemical derivative of (R,R)-formoterol or budesonide having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutically acceptable acid addition salts include but are not limited to those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

Pharmaceutically acceptable esters of (R,R)-formoterol or budesonide may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

As mentioned above, both (R,R)-formoterol and budesonide and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have been described for use in the treatment of respiratory diseases. Therefore, formulations of (R,R)-formoterol and budesonide and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. In a preferred aspect, there is provided such a method which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising (R,R)-formoterol fumarate and budesonide, and a pharmaceutically acceptable carrier or excipient. In

particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In the alternative, there is provided a combination of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In particular, there is provided a pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, (R,R)-formoterol fumarate) and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In a preferred aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

The amount of (R,R)-formoterol and budesonide, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. As a monotherapy, (R,R)-formoterol fumarate is generally administered to adult humans by aerosol inhalation at a dose of 12mcg or 24mcg twice daily. As a monotherapy, budesonide is generally administered to adult humans by aerosol inhalation at a dose of from 200mcg to 1.6mg daily, taken as 2 divided doses.

While it is possible for the active ingredients of the combination to be administered as the raw chemical, it is preferable to present them as a

pharmaceutical formulation. When the individual compounds of the combination are administered separately, they are generally each presented as a pharmaceutical formulation as described previously in the art.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment. It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each component compound, and containing a package insert instructing the patient to the correct use of the invention is a desirable additional feature of the invention.

Hereinafter, the term "active ingredients" means (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably (R,R)-formoterol fumarate, and budesonide, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise the active ingredients in amounts such that each actuation provides therapeutically effective dose, for example, a dose of (R,R)-formoterol of 10mcg to 150mcg, preferably 24mcg and a dose of budesonide of 100mcg to 1.6mg, preferably 200mcg to 1mg, more preferably, 200mcg to 400mcg.

The pharmaceutical formulations according to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists,

iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other β_2-adrenoreceptor agonists (such as salbutamol, salmeterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations for inhalation include powder compositions which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Suitable aerosol formulations include those described in EP 0372777 and WO93/11743. For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns, for example, 1 to 5 microns.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges or for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insuflator may be formulated containing a powder mix of the active ingredients and a suitable powder base such as lactose or starch. In this aspect, the active ingredients are suitably micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the dry powder formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Preferred unit dosage formulations are those containing a pharmaceutically effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient. Thus, in the case of formulations designed for delivery by metered dose pressurised aerosols, one actuation of the aerosol may deliver half of the therapeutically effective amount such that two actuations are necessary to deliver the therapeutically effective dose.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Furthermore, the claimed formulations include bioequivalents as defined by the US Food and Drugs Agency.

For a better understanding of the invention, the following Examples are given by way of illustration.

EXAMPLES

A: Metered Dose Inhalers

Example 1

	Per actuation
(R,R)-formoterol fumarate	24 microgram
Budesonide	200 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

The micronised active ingredients are weighed into an aluminium can, 1,1,1,2-tetrafluoroethane is then added from a vacuum flask and a metering valve is crimped into place.

Similar methods may be used for the formulation of Example 2:

Example 2

	Per actuation
(R,R)-formoterol fumarate	12 microgram
Budesonide	100 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

B: Dry Powder Inhalers

Example 3

	Per cartridge or blister
(R,R)-formoterol fumarate	24 microgram
Budesonide	200 microgram
Lactose Ph. Eur.	to 12.5mg or to 25.0mg

The active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs to be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of Glaxo Group Limited).

Similar methods may be used for the formulations of Example 4:

Example 4

	Per cartridge or blister
(R,R)-formoterol fumarate	12 microgram
Budesonide	100 microgram
Lactose Ph. Eur.	to 12.5mg or to 25.0mg

Claims

1. A pharmaceutical formulation comprising (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof , and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

2. A pharmaceutical formulation comprising (R,R)-formoterol fumarate and budesonide, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

3. A pharmaceutical formulation according to claim 1 or claim 2 which comprises another corticosteroid, another β_2-adrenoreceptor agonist or an anticholinergic agent.

4. A pharmaceutical formulation according to claim 3, wherein the other β_2-adrenoreceptor agonist is salbutamol, salmeterol, fenoterol, terbutaline, or a salt thereof.

5. A pharmaceutical formulation according to claim 3 wherein the anticholinergic agent is ipratropium or tiotropium.

6. A pharmaceutical formulation according to any of claims 1 to 5 wherein the amount of (R,R)-formoterol per unit dose is from 87 micrograms to about 150 micrograms.

7. A pharmaceutical formulation according to any of claims 1 to 6 wherein the amount of budenoside per unit dose is from above 1.3mg to about 1.6mg.

8. A pharmaceutical formulation according to any one of claims 1 to 7 which is suitable for administration by inhalation.

9. A pharmaceutical formulation according to any one of claims 1 to 7 which is suitable for intranasal administration.

10. A pharmaceutical formulation consisting of (R,R)-formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and budesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof , and optionally one or more other therapeutic ingredients, and 1, 1, 1, 2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or mixtures thereof as propellant.

11. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 10.

12. A method according to claim 11 wherein the clinical condition is a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

13. A Rotahaler, Diskus or Diskhaler inhaler containing a formulation according to any of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64014 A (ASTRA AB ;EKSTROEM TOMMY (SE)) 16 December 1999 (1999-12-16) claims 1-24 ---	1-13
X	WO 93 11773 A (ASTRA AB) 24 June 1993 (1993-06-24) cited in the application claims 1-7 ---	1-13
X	WO 99 15182 A (TROFAST JAN ;ASTRA AB (SE); BAUER CARL AXEL (SE)) 1 April 1999 (1999-04-01) claims 1-10 ---	1-13
X	US 6 004 537 A (CAVANAUGH KELLY A ET AL) 21 December 1999 (1999-12-21) claims 1-24 ---	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2001	04/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Herrera, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB 01/01628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 21175 A (SEPRACOR INC) 22 May 1998 (1998-05-22) claims 19-21	1-13
Y	US 5 795 564 A (MORLEY JOHN ET AL) 18 August 1998 (1998-08-18) abstract	1-13
Y	O'CONNOR B J: "COMBINATION THERAPY" PULMONARY PHARMACOLOGY AND THERAPEUTICS, ACADEMIC PRESS, NEW YORK, NY, US, vol. 11, no. 5/6, 1998, pages 397-399, XP000911059 ISSN: 1094-5539 the whole document	1-13
Y	BOWLER S: "LONG ACTING BETA AGONISTS" AUSTRALIAN FAMILY PHYSICIAN, XX, XX, vol. 27, no. 12, December 1998 (1998-12), pages 1115,1117-1118, XP000973076 the whole document	1-13
X	WO 98 15280 A (TROFAST JAN ;ULLMAN ANDERS (SE); ASTRA AB (SE)) 16 April 1998 (1998-04-16) claims 1-16	1-13
A	DE 23 23 215 A (BOFORS AB) 29 November 1973 (1973-11-29) cited in the application	
A	US 3 929 768 A (BRATTSAND RALPH LENNART ET AL) 30 December 1975 (1975-12-30) cited in the application	

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Electronic Acknowledgement Receipt

EFS ID:	6872052
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Kristi Holmlund
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	25-JAN-2010
Filing Date:	27-JUL-2004
Time Stamp:	14:03:15
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		06275ids.pdf	327841 804f6d64cb275b63a0fc4c6e2855 1ec525b9 550c	yes	2

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	1	
	Information Disclosure Statement (IDS) Filed (SB/08)		2	2	
Warnings:					
Information:					
2	Foreign Reference	22345713.pdf	572360 acab11cb839644a3d8f1db3269b8f4dce7356707	no	16
Warnings:					
Information:					
3	Foreign Reference	22345714.pdf	509507 03462c4838ef749880d65b88f3ba2afb30e323ec	no	16
Warnings:					
Information:					
4	Foreign Reference	22345715.pdf	735276 186079528310ff8d11f1d64ac11b0ca3abcf81676	no	16
Warnings:					
Information:					
5	NPL Documents	brindley.pdf	1216077 3388eade0589efea26644d216f08e1a04f623bc9	no	6
Warnings:					
Information:					
6	NPL Documents	byron.pdf	5891067 9b10cf89f46ddc8a8130056316727c97a054a1a1	no	19
Warnings:					
Information:					
7	Foreign Reference	epocomm.pdf	4299506 a4b68e3d54ce4ab7f81bf5b4369c8141f8f9fdbaa	no	27
Warnings:					
Information:					
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Warnings:					
Information:					

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Warnings:					
Information:					
10	NPL Documents	turbiscan2.pdf	958883 4a12f0ce08584a2aea76921a9e7c03e9fd9c26ba	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	15621116	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Please consider the documents listed on the enclosed PTO-1449 form. Copies of foreign patent documents and non-patent literature are enclosed

This statement is being filed after the filing of a Request for Continued Examination on November 12, 2009, and before the receipt of a subsequent Office Action or Notice of Allowance. It is believed no fees are due. Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-0410US1.

Respectfully submitted,

Date: January 25, 2010

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22345727.doc

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: January 25, 2010

Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/502,685
Filing Date	July 27, 2004
First Named Inventor	Nayna Govind et al.
Group Art Unit	1616
Conf No.	7568
Examiner Name	Alton Nathaniel Pryor
Attorney Docket Number	06275-0410US1

This is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. §1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s)

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendment filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☒ Enclosed

      i. ☒ Amendment/Reply

      ii. ☐ Affidavit(s)/Declaration(s)

      iii. ☒ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. §1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. §1.17(i) required)

   b. ☐ Other _____

3. Fee The RCE fee under 37 C.F.R. §1.17(e) is required by 37 C.F.R. §1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 06-1050

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☒ Other Any deficiencies

   b. ☐ Check in the amount of $_____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED

Name (Print/Type)	Janis K. Fraser, Ph.D., J.D.	*Registration No. (Attorney/Agent)*	34,819
Signature		*Date*	Nov. 5, 2009

CERTIFICATE OF ELECTRONIC MAILING OR TRANSMISSION

I hereby certify that this correspondence is being addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 via electronic mailing or transmission to the U.S. Patent and Trademark Office on the date shown below.

Name (Print/Type)	KRISTI A. HOLMLUND		
Signature		*Date*	Nov. 12, 2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Nayna Govind et al.
Serial No. : 10/502,685
Filed : July 27, 2004
Art Unit : 1616
Examiner : Alton Nathaniel Pryor
Confirmation No.: 7568
Notice of Allowance Date: September 9, 2009
Title : COMPOSITION FOR INHALATION

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Please amend the application as indicated on the following pages. This amendment is being filed concurrently with a request for continued examination (RCE).

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: Nov. 12, 2009

Amendments to the Specification:

(I) Please replace the paragraph beginning at page 1, line 32, with the following amended paragraph:

Preferably the PVP is present in an amount of 0.001% w/w. Preferably the PVP is PVP K25 (PVP having a nominal K-value of 25 ~~an approximate molecular weight of 30,000~~).

(II) Please add the following new paragraph after the paragraph ending at page 2, line 33:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic drawing of an Optical Suspension Characterisation (OSCAR) set-up.

FIGs. 2-3 are graphs showing the averages of OSCAR data (lower sensor) for formulations in HFA 227 containing 4.5 µg formoterol; 0.3% w/w PEG 1000; 0.0001% - 0.05% w/w PVP K25; and 160 µg budesonide (FIG. 2) or 80 µg budesonide (FIG. 3).

FIGs. 4-6 are graphs showing the averages of Turbiscan data for formulations in HFA 227 containing 4.5 µg formoterol; 0.3% w/w PEG 1000; 0.0001% - 0.05% w/w PVP K25; and 160 µg budesonide (FIG. 4), 80 µg budesonide (FIG. 5), or 40 µg budesonide (FIG. 6).

FIG. 7 is a graph showing the effect of PEG 1000 concentration on stem return force for formulations containing 4.5 µg formoterol; 160 µg budesonide; and 0.1%, 0.3%, or 0.5% w/w PEG 1000.

FIG. 8 is a graph showing the averages of Turbiscan data for formulations in HFA 227 containing 80 µg budesonide; 4.5 µg formoterol; 0.0001% PVP K25; and 0.005% - 0.5% w/w PEG 1000.

FIGs. 9-11 are a series of digital photographs, taken after standing times of 0 seconds (FIG. 9), 30 seconds (FIG. 10), and 60 seconds (FIG. 11), of suspensions in HFA 227 containing budesonide (160 µg/actuation); formoterol (4.5 µg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGs. 12-14 are a series of digital photographs, taken after standing times of 0 seconds (FIG. 12), 30 seconds (FIG. 13), and 60 seconds (FIG. 14), of suspensions in HFA 227

containing budesonide (80 µg/actuation); formoterol (4.5 µg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGs. 15-16 are digital photographs, taken after standing times of 0 minutes (FIG. 15) and 10 minutes (FIG. 16), of suspensions in HFA 227 containing budesonide (80 µg/actuation); formoterol (4.5 µg/actuation); 0.001% PVP K25; and PEG 1000 at 0.005, 0.05, 0.35, and 0.5% w/w.

(III) Please replace the paragraph beginning at page 7, line 14, with the following amended paragraph:

Figures 9, 10 and 11 show Budesonide 160 µg/shot, Formoterol 4.5 µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at ~~0, 15, 30, and 60 seconds~~ 0, 30, and 60 seconds standing time.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1 – 24 (Canceled)

25. (Currently Amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA227), PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25 ~~an approximate molecular weight of 30,000~~), and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

26 – 29 (Canceled)

30. (Original) A pharmaceutical composition according to claim 25, in which the formoterol fumarate dihydrate is the R, R-enantiomer.

31. (Original) A pharmaceutical composition according to claim 25, in which the budesonide is the 22R-epimer.

32. (Original) A method of treating symptoms of a respiratory disorder, comprising administering to a patient the pharmaceutical composition according to claim 25, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

33. (Original) The method of claim 32, wherein the respiratory disorder is asthma.

34. (Original) The method of claim 32, wherein the respiratory disorder is rhinitis.

35. (Original) The method of claim 32, wherein the respiratory disorder is COPD.

36 – 44 (Canceled)

45. (Original) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 1 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

46. (Original) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

47. (Original) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 4 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

48. (Original) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

49. (Original) The method of claim 32, wherein the concentration of budesonide is 1 mg/ml.

50. (Original) The method of claim 32, wherein the concentration of budesonide is 2 mg/ml.

51. (Original) The method of claim 32, wherein the concentration of budesonide is 4 mg/ml.

52. (Original) The method of claim 32, wherein the concentration of budesonide is 8 mg/ml.

REMARKS

Interview Summary:

Applicants thank the Examiner for telephoning Applicants' undersigned representative on October 19, 2009, to indicate consideration of the references cited in the Form PTO-1449 filed on November 3, 2006 and to suggest amendment of the specification to include a brief description of drawings. Applicants further thank the Examiner for the courtesy of telephone interview with the Applicants' undersigned representative on November 4, 2009, in which Applicants' representative explained that K value represents viscosity, not molecular weight, and so the recitation of molecular weight in the claim was not an accurate description of what "K25" means. The Examiner agreed that the recitation of PVP's molecular weight in the description of the term "PVP K25" in claim 25 could be deleted.

Claim Status:

Claims 25, 30-35, and 45-52 remain pending in the application. Claims 25, 30-35, and 45-52 were previously allowed. Claim 25 has been amended. Claims 1-24, 26-29, and 36-44 were canceled previously.

Claim 25 has been amended to provide a more accurate description of PVP K25. According to page 1419 of the United States Pharmacopeia (reference 6 in the information disclosure statement submitted herewith), PVP is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a "nominal K-value" ranging from 10 to 120. The relevant language is underlined in reference 6 (see middle of left column of page 1419). This is the standard terminology for PVP, well known by those of ordinary skill in the art. No new matter has been added.

The specification has been amended to include a brief description of the drawings, as requested by the Examiner. The description of PVP at page 1 has been amended to reflect the change in claim 25. A typographical error at page 7 has also been corrected.

As the initialed version of Form PTO-1449 filed with an IDS on November 3, 2006, still has not appeared on PAIR, Applicants respectfully ask the Examiner to have it uploaded or otherwise provided to the Applicants.

Applicants ask that all claims be allowed in view of the amendment to the claims. This amendment is being filed with a request for continued examination (RCE) along with the fee required under 37 C.F.R. §1.17(e). Please apply any other charges or credits to Deposit Account No. 06-1050 referencing Attorney Docket No. 06275-0410US1.

Respectfully submitted,

Date: November 12, 2009

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Nayna Govind et al.
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MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants request consideration of the references listed on the attached PTO-1449 form. Under 37 C.F.R. § 1.98 (a)(2)(ii), only copies of foreign patent documents and/or non-patent literature are enclosed.

This statement is being filed with a Request for Continued Examination (RCE). It is believed that no further fee for this Information Disclosure Statement is required. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-0410US1.

Respectfully submitted,

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Reg. No. 50,680

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No.: 26164
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-0410US1	Application No. 10/502,685
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))	Applicant Nayna Govind et al.	
	Filing Date July 27, 2004	Group Art Unit 1616

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1.	6,123,924	09/26/2000	Mistry et al.			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Sub-class	Translation Yes	Translation No
	2.	2 338 753	02/10/2000	Canada				
	3.	WO 99/64014	12/16/1999	WIPO				
	4.	WO 01/89492	11/29/2001	WIPO				
	5.							

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	6.	"Povidone" The United States Pharmacopeia, USP25/NF20, pp.1419-1420, United States Pharmacopeial Convention, Inc., Rockville, MD. (2002)
	7.	Pauwels et al. "Effect of inhaled formoterol and budesonide on exacerbations of asthma," Vol. 337 Number 20, pp. 1405-1411 (and one correction page), November 13, 1997
	8.	Wyser et al., "Neue Aspekte in der Behandlung des Asthma bronchiale und chronisch obstruktiver Lundenkrankeiten," Schweiz Med. Wochenschr, Vol. 127, pages 885-890 (1997), English Summary included
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Substitute Disclosure Form (PTO-1449)

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(72) Inventeurs/Inventors:
KELLER, MANFRED, DE;
HERZOG, KURT, CH;
MULLER-WALZ, RUDI, DE;
KRAUS, HOLGER, CH

(73) Propriétaire/Owner:
JAGO RESEARCH AG, CH

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : FORMULATIONS POUR AEROSOLS A USAGE MEDICAL
(54) Title: MEDICINAL AEROSOL FORMULATIONS

(57) Abrégé/Abstract:
A pressure-liquefied propellant mixture for aerosols, comprising dinitrogen monoxide and a hydrofluoroalkane having 1 to 3 carbon atoms, in particular 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane, makes possible an improvement in the wetting properties of pharmaceutically active compounds, whereby the formulation problems existing with hydrofluoroalkanes can be overcome with respect to suspension and solution aerosols and thus improved medicinal aerosol formulations can be obtained. With the aid of dinitrogen monoxide, it is also possible to influence the pressure and thus the particle size distribution specifically and, by displacement of oxygen from the hydrofluoroalkanes, to improve the storage stability of oxidation-sensitive active compounds. If desired, the propellant mixture can additionally contain carbon dioxide.

Abstract

A pressure-liquefied propellant mixture for aerosols, comprising dinitrogen monoxide and a hydrofluoroalkane having 1 to 3 carbon atoms, in particular 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane, makes possible an improvement in the wetting properties of pharmaceutically active compounds, whereby the formulation problems existing with hydrofluoroalkanes can be overcome with respect to suspension and solution aerosols and thus improved medicinal aerosol formulations can be obtained. With the aid of dinitrogen monoxide, it is also possible to influence the pressure and thus the particle size distribution specifically and, by displacement of oxygen from the hydrofluoroalkanes, to improve the storage stability of oxidation-sensitive active compounds. If desired, the propellant mixture can additionally contain carbon dioxide.

Medicinal aerosol formulations

The present invention relates to a pressure-liquefied propellant mixture based on hydrofluoroalkanes, the use of this propellant mixture in aerosol formulations, and a process for the preparation of the aerosol formulations.

Many gases, such as carbon dioxide and nitrogen, can indeed be liquefied under pressure, but are not suitable as propellants for metered-dose aerosols, because the internal pressure in the container decreases very greatly as it becomes more empty. For this reason, only those propellants are used for medicinal metered-dose aerosols, which propellants can be liquefied at room temperature and in any case only lead to a slight decrease in the internal pressure in the container when the contents are successively removed by spraying. These include the short-chain alkanes, such as propane, butane and isobutane, and the chlorofluorocarbons (CFCs), such as trichlorofluoromethane (F11), dichlorodifluoromethane (F12) and 1,2-dichloro-1,1,2,2-tetrafluoroethane (F114).

WO-A-93/17665 in fact discloses a method for the administration of physiologically active compounds, in which a supercritical liquid solution is formed from a supercritical liquid solvent and the active compound and this is then converted into the subcritical range. The supercritical solvent used was carbon dioxide, it being stated that, in addition to carbon dioxide, dinitrogen oxide, chlorofluorocarbons such as dichlorodifluoromethane and trichlorofluoromethane, xenon, sulfur hexafluoride, ethanol, acetone, propane, water and mixtures thereof are suitable.

In Research Disclosure (1978), 170, 58, XP-002090730, it was further mentioned that some fluorocarbon and chlorofluorocarbon propellants can be used in aerosol products such as hairsprays, deodorants

and antiperspirants as co-propellants together with carbon dioxide or dinitrogen monoxide. The 2,2-dichloro-1,1,1-trifluoroethane (F123), 1,2-dichloro-1,1-difluoroethane (F132b), 2-chloro-1,1,1-trifluoroethane (F133a), 1,1-dichloro-1-fluoroethane (F141b) and 1-chloro-1,1-difluoroethane (F142b) mentioned as examples are chlorinated and, moreover, not very customary propellants. A hairspray in which trifluoromonochloroethane (F133a) together with carbon dioxide and/or dinitrogen monoxide is used as a propellant mixture is also disclosed in US-A-4 397 836.

On account of the ozone problem caused by the elimination of free-radical chlorine atoms from CFCs, in the Montreal Agreement many countries came to an understanding that they would no longer use CFCs as propellants in future. Suitable CFC substitutes for the medicinal field are fluorinated alkanes (in the context of the present invention also designated as HFA), especially 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), as these are inert and have a very low toxicity. On account of their physical properties, such as pressure, density, etc., they are particularly suitable for replacing CFCs such as F11, F12 and F114 as propellants in metered-dose aerosols.

US-A-4 139 607, on the other hand, proposed a propellant system formed from liquefied bis(difluoromethyl) ether and gaseous carbon dioxide, which in contrast to combinations of carbon dioxide with other known propellants such as trichlorofluoromethane or methylene chloride should afford satisfactory aerosol samples, but, however, has not been accomplished. The document in fact mentions that other propellants such as dinitrogen monoxide, hydrocarbons and fluorohydrocarbons or liquid carriers, such as ethanol, perchloroethylene, trichloroethylene, acetone, amyl acetate, water and the like, can be added

to the propellant system; the disclosed formulations, however, mostly contain about 50% of ethanol. In Derwent Abstract AN 89-184245, it is only stated that in aerosol pressure packs for the administration of medicaments instead of CFCs, hydrocarbons, such as butane and pentane, other compressed gases, such as carbon dioxide, dimethyl ether, nitrogen and dinitrogen oxide, or fluorohydrocarbons could also be used.

Medicinal aerosol preparations containing hydrofluoroalkanes such as HFA 134a are already embraced by the teaching of US-A-2 868 691 and US-A-3 014 844 and disclosed in DE-A-2 736 500 and EP-A-0 372 777. Examples of formulations containing HFA 227 are found, for example, in WO-A-91/11495, EP-A-0 504 112 and EP-B-0 550 031. It is known from various publications that the customary excipients used in CFC-containing metered-dose aerosols, such as lecithin, sorbitan trioleate and oleic acid, only dissolve inadequately in hydrofluoroalkanes such as HFA 134a and HFA 227, because a chain extension and the substitution of the chlorine atoms by fluorine atoms leads to a worsening of the solubility properties of the permitted excipients mentioned. Even in the case of CFCs, which are considerably better solvents than HFAs, ethanol or other cosolvents were often added to improve the solubility in order to be able to administer pharmaceutical substances such as isoprenaline and epinephrine (cf. US-A-2 868 691) as an aerosol. It was therefore obvious to improve not only the solubility of CFCs, but also that of HFAs, by addition of ethanol. Examples of this are found in the technical literature and in various patent applications. Alternatively to this, there are a number of developments of pressure-liquefied aerosol preparations containing HFA 134a and/or HFA 227 which use propellant-soluble excipients, such as fluorinated surface-active substances (WO-A-91/04011), mono- or diacetylated glycerides (EP-A-0 504 112) or polyethoxylated compounds

(WO-A-92/00061), which can be dissolved in the necessary amount in the two propellants even without addition of ethanol.

For CFC-free medicinal aerosol preparations having a high vapor pressure, the propellant preferably used today is usually HFA 134a (vapor pressure about 6 bar at 20°C) and for those with a lower vapor pressure it is HFA 227 (vapor pressure about 4.2 bar at 20°C). Both propellants differ with respect to their density (about 1.4 mg/ml for HFA 227 and about 1.2 mg/ml for HFA 134a at 20°C), which is particularly of importance for suspensions. If the active compound has a higher density than the propellant, sedimentation occurs; if its density is lower, flotation occurs. To solve the problem, it is therefore suggested under certain circumstances to use propellant mixtures and/or, to lower the density, to add cosolvents such as ethanol, diethyl ether or other low-boiling solvents or propellants such as n-butane. A significant disadvantage of the hydrofluoroalkanes is their relatively low dissolving power in comparison with CFCs, in particular in comparison with F11. The solvent properties decrease with increasing chain length in the sequence F11 > HFA 134a > HFA 227. For this reason, the suspending aids customarily used in CFCs, such as sorbitan trioleate, lecithin and oleic acid, can no longer be dissolved in the customary concentrations (weight ratios of typically approximately 1:2 to 1:20, based on the active compound) by addition of polar solvents without increasing the hydrophilicity.

It is generally known that in the case of suspension formulations only active compound particles which are smaller than 6 µm are respirable. For the desired deposition thereof in the lungs, these must therefore be comminuted or micronized before processing by means of special procedures, such as using pinned-disk, ball or air-jet mills. A grinding process as a rule leads to an increase in surface area, which is

accompanied by an increase in the electrostatic charge of the micronized active compound, on account of which the flow behaviour and the active compound dispersion is usually impaired. As a result of the interfacial and charge activities, there is often an agglomeration of active compound particles or alternatively adsorption of active compound at interfaces, which becomes conspicuous, for example, in the accumulation on equipment or container surfaces.

In aerosol preparations in which the active compound is present suspended in liquefied propellant, adsorption or ring formation in the container can occur at the place where the liquid phase changes into the gas phase. Without wetting the micronized active compound particles or conducting away charges and modifying their surface properties, problems can occur during dispersion or suspension, in the hydrofluoroalkanes mentioned. The lack of wetting or dispersion of the active compound particles also results in these in many cases having a high adsorption tendency and adhering to surfaces, such as the container inner wall or the valve, which then leads to an underdosage and to a poor dosage accuracy from puff of spray to puff of spray. In the case of suspensions, it is therefore necessary as a rule to add a surface-active substance or a glidant in order to lower the adsorption at interfaces, to stabilize the suspensions and to ensure the dosage accuracy. A change or reduction in the proportion of the inhalable, respirable particles, the so-called fine particle fraction (FPF) or fine particle dose (FPD), occurring in the course of storage, which leads to a decrease in the activity of the HFA preparation, is particularly problematical.

To overcome the problems presented above, as a rule surface-active substances are therefore added, as were already used earlier in the CFC-containing formulations. Alternatively to this, in certain cases a

modification of the surface properties by means of various measures (e.g. coating) may help to minimize these undesired effects. Because, however, surface-active agents such as oleic acid, sorbitan trioleate and lecithin only dissolve inadequately in hydrofluoroalkanes such as HFA 134a and HFA 227, in many cases ethanol is or must be added as a cosolvent so that the pharmaceutical technology problems can be controlled better.

If, however, ethanol is added in a higher concentration, the density of the propellant mixture is reduced, which can lead to an undesired sedimentation of active compound, especially in the case of suspensions. Moreover, a "wet spray" can undesirably be obtained, because the propellant evaporates much more rapidly than ethanol. In addition, however, as a result of the increase in solubility during storage, the active compounds can also start to dissolve, which then leads to crystal growth and thus, in turn, to a reduction in the amount of inhalable, respirable particles, the so-called fine particle dose (FPD).

To measure the aerodynamic particle size distribution or the proportion of the dose which can be deposited in the lungs, the so-called fine particle dose (FPD), of inhalable, respirable particles in an aerosol, impactors, such as the 5-stage multistage liquid impinger (MSLI) or the 8-stage Andersen cascade impactor (ACI), which are described in Chapter <601> of the United States Pharmacopeia (USP) or in the Inhalants Monograph of the European Pharmacopeia (Ph. Eur.) are suitable. Using these apparatuses, the aerodynamic deposition behaviour of the aerosol cloud can be investigated in the laboratory (in vitro). By means of a "log-probability plot" (logarithmic representation of the probability distribution), the mean aerodynamic particle diameter (Mass Median Aerodynamic Diameter (MMAD)) of aerosol preparations can then be calculated. From this, it can be deduced

whether the active compound is more likely to be deposited in the upper or lower area of the lungs.

If the active compound is present in the HFA propellant/ethanol mixture not in suspended form, but in dissolved form, problems with respect to the standard deviation of the dosage accuracy per stroke are usually less pronounced. If, however, a larger amount of ethanol is used for this, on rinsing empty the container a "head space" effect occurs as follows: the proportion of ethanol, which has a lower vapor pressure and a lower density, increases and that of propellant having higher density and higher vapor pressure decreases. On spraying or as the container becomes more empty, the concentration ratio of propellant to ethanol changes, which on account of the density difference leads to a reduction in the mass of a puff of spray and thus also in the content of a puff of spray or active compound. It is additionally disadvantageous that at higher ethanol concentrations of, for example, 10%-30%, the content of inhalable particles (<6 µm) usually decreases, because the spray affords droplets having a greater aerodynamic diameter on account of the different evaporation properties of ethanol in comparison to the propellant. As a result of this, there is a reduction in the fine particle dose (FPD) which is crucial for the activity.

In a solution aerosol with the same ethanol content, a higher fine particle fraction (FPF), i.e. a greater percentage of inhalable droplets, is customarily obtained with HFA 134a in comparison to HFA 227, which is to be attributed to the higher pressure of HFA 134a. In principle, it is true that the higher the internal pressure in the aerosol container, the finer the particle spectrum of the aerosol cloud. Solution aerosols having a low ethanol content therefore as a rule have a smaller MMAD (0.8-1.5 µm) than suspension aerosols (2-4 µm), when using fine atomizing nozzles. This is connected with the fact that

droplets are generated as an aerosol cloud in the case of solution aerosols and particles in the case of suspension aerosols.

For the topical application of active compounds in the area of the bronchi and bronchioles, particle sizes of about 2-4 µm are advantageous, as are customarily achieved with suspension formulations. Smaller particles which pass into the alveolar area are partly exhaled (< 0.5 µm) or pass into the systemic circulation by absorption. It follows from this that aerosol preparations for systemic application should favourably have particle sizes of about 0.5 µm - 2 µm, where, for example, a monodisperse aerosol having a very high proportion of particles in the range of about 1 µm would be particularly advantageous. Depending on the desired site of deposition, a smaller or larger MMAD and, if appropriate, a monodisperse distribution spectrum are therefore preferred. The following holds with respect to the aerodynamics: the greater the mass of the particles the greater their tendency to fly on in a straight line. It results from this that if there is a change in the direction of flow, impaction of particles occurs. It is known from deposition studies that even in the case of an optimum inhalation maneuver only about 20% of the particles emitted from a metered-dose aerosol pass into the lungs and almost 80% impact in the oropharynx.

In the case of ethanol-containing solution aerosols, unfortunately there are frequently problems concerning the active compound stability. Active compounds, such as fenoterol and salbutamol are affected by this, which is why such active compounds have preferably been formulated as suspensions until now. To reduce their solubility in the propellant mixture, the polar salts such as fenoterol hydrobromide are also frequently employed.

The invention is therefore based on making available a propellant system with which:

- active compounds can be better wetted;
- suspension aerosols having improved suspension and shelf-life properties can be prepared;
- solution aerosols having improved storage stability and lower addition of ethanol can be prepared;
- the dosage accuracy can be improved;
- the particle size distribution spectrum and the MMAD can be better adjusted; and/or
- the fine particle dose (FPD) can be increased and the oropharyngeal deposition can be reduced.

This is achieved according to the invention by a pressure-liquefied propellant mixture for aerosols, comprising dinitrogen monoxide and a hydrofluoroalkane of the general formula

$$C_xH_yF_z \qquad (I)$$

in which x is the number 1, 2 or 3, y and z are each an integer ≥ 1 and $y + z = 2x + 2$.

Surprisingly, it was in fact found that the targets mentioned are achieved and propellant mixtures having more advantageous properties can be obtained if a small amount of dinitrogen monoxide (laughing gas) is added to propellants based on hydrofluoroalkanes. If desired, a small amount of carbon dioxide, which brings about similar improvements, can additionally be added to the propellant. Gas mixtures of this type - in contrast to dinitrogen oxide or carbon dioxide as the sole propellant - show only a slight decrease in the internal pressure in the container as it becomes more empty, which makes possible their use as propellants for metered-dose aerosols. As is illustrated in Table 1 with the aid of some examples, propellant mixtures of this type can be employed in a wide temperature range for metered-dose aerosols. This effect is also observed if the propellant mixture or the aerosol formulation additionally contains a cosolvent such as ethanol.

Table 1

Temperature dependence of N_2O-containing hydrofluoroalkanes with or without ethanol (EtOH) as cosolvent

Parts by weight				Pressure (bar) at				
HFA 227	HFA 134a	N_2O	EtOH	4°C	20°C	30°C	40°C	50°C
600	0	2	0	2.00	3.75	5.25	7.25	9.50
600	0	6	0	2.25	4.50	6.00	8.25	10.50
555	0	2	45	1.50	3.25	4.75	6.75	8.25
555	0	6	45	2.00	4.00	5.50	7.25	9.25
420	0	2	180	1.00	2.50	3.75	5.00	6.50
420	0	6	180	1.75	3.25	4.50	6.00	7.50
420	0	12	180	2.75	4.50	6.00	7.50	9.25
0	600	2	0	2.50	5.50	7.50	10.00	12.50
0	600	6	0	3.00	6.00	8.00	10.50	13.75
240	360	2	0	2.50	5.00	7.00	9.25	12.00
240	360	6	0	3.00	5.50	7.50	10.00	13.00
0	420	2	180	2.50	4.50	6.00	8.00	10.25
0	420	6	180	3.00	5.25	6.75	8.75	11.00

Surprisingly, it has further been found that by the addition of dinitrogen oxide and, if desired, carbon dioxide to hydrofluoroalkanes such as HFA 134a and/or HFA 227 the suspension of pharmaceutical active compounds is facilitated and the tendency to adhesion and adsorption of active compounds on interfaces is decreased. Using propellant mixtures of this type, suspensions which are distinguished by controlled flocculation can therefore be prepared more easily, and as a result of the better suspension properties, in many cases the addition of - in some cases undesired - surface-active suspension aids and/or cosolvents can be dispensed with or at least their proportion can be decreased. By addition of glidants such as glycerol or polyethylene glycol, suspension or solution aerosols having improved properties can often be obtained.

In addition, it has been found that the undesired deposition of active compound in the oropharynx can be reduced and at the same time the FPD can be increased.

With the aid of dinitrogen oxide and, if desired, carbon dioxide, it is also possible to displace oxygen from the hydrofluoroalkanes, as a result of which the storage stability of oxidation-sensitive active compounds is improved. Moreover, by addition of dinitrogen oxide and, if desired, carbon dioxide, the internal pressure in the aerosol container can be adjusted such that in comparison to a conventional CFC or HFA metered-dose aerosol the FPF and MMAD can be virtually aligned as appears most sensible for the respective application. It is thus possible to produce MDIs (Metered-dose Inhalers) for both topical application and systemic administration. In particular for systemic administration, completely new possibilities of use are opened up, because virtually monodisperse aerosols having high respirable fractions can be produced in combination with suitable atomizing nozzles.

The propellant mixture according to the invention thus also offers advantages in the case of suspension and solution aerosol formulations, in which a surface-active agent and/or a cosolvent is necessary or desired. On the one hand, the use of propellants which contain dinitrogen oxide and, if desired, carbon dioxide frequently permits a reduction in the amount of cosolvent needed and a better solubility of conventional surface-active agents. On the other hand, the disadvantageous influence of cosolvents such as ethanol on the droplet size can be avoided completely or to the greatest possible extent, since as a result of a corresponding increase in the concentration of dinitrogen oxide and, if desired, carbon dioxide even at comparatively high cosolvent concentrations, the internal pressure and the deposition behaviour can be

adjusted such that both the fine particle dose and the MMAD can be adjusted in a therapy-compliant manner.

The preparation of the propellant mixtures according to the invention can be carried out in a manner known per se by introducing dinitrogen monoxide and, if desired, carbon dioxide, under pressure into a hydrofluoroalkane of the formula I.

The propellant mixture according to the invention is suitable in principle for any desired aerosol applications such as cosmetic and household sprays. On account of the advantages described - such as the small fall in the internal pressure on emptying, lower temperature dependence and easier adjustability of the internal pressure, improved wetting properties for pharmaceutical active compounds and usability of conventional surface-active agents such as oleic acid, lecithin and sorbitan trioleate - the propellant mixture according to the invention, however, is especially also suitable for medicinal aerosol formulations and in particular for inhalation aerosols.

The invention therefore likewise relates to a medicinal aerosol formulation, comprising an efficacious amount of a pharmaceutically active compound, and a pressure-liquefied propellant mixture, containing dinitrogen monoxide and a hydrofluoroalkane of the general formula

$$C_xH_yF_z \qquad (I)$$

in which x is the number 1, 2 or 3, y and z are each an integer ≥ 1 and $y + z = 2x + 2$.

Examples of suitable hydrofluoroalkanes which can be used in the propellant mixtures and aerosol formulations according to the invention are: difluoromethane (HFA 32), pentafluoroethane (HFA 125), 1,1,2,2,-tetrafluoroethane (HFA 134), 1,1,1,2-tetrafluoroethane (HFA 134a), 1,1,2-trifluoroethane (HFA

143), 1,1,1-trifluoroethane (HFA 143a), 1,1-difluoroethane (HFA 152a), 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), hexafluoropropane (HFA 236), pentafluoropropane (HFA 245) and the like. In general, hydrofluoroalkanes having 2 or 3 hydrocarbons are preferred. Particularly preferred propellant mixtures and aerosol formulations are those which contain 1,1,1,2-tetrafluoroethane (HFA 134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) or a mixture of the two, for example a 1:1 mixture.

The propellant mixtures and aerosol formulations according to the invention preferably contain at least approximately 0.0001% by weight, in particular at least approximately 0.01% by weight, of dinitrogen monoxide. If desired, the propellant mixtures and aerosol formulations can additionally contain a small amount of carbon dioxide. The content of dinitrogen monoxide and carbon dioxide is dependent, inter alia, on the pressure desired, the nature of the hydrofluoroalkanes used and the nature and amount of possible further propellants and cosolvents and the like. In general, however, the content of dinitrogen monoxide or the content of dinitrogen monoxide and carbon dioxide together is approximately 0.0001 to 10% by weight, preferably approximately 0.01 to 6% by weight and particularly preferably approximately 0.1 to 3% by weight. In the case of medicinal aerosols and in particular in inhalation aerosols, in general a content of dinitrogen monoxide or of dinitrogen monoxide and carbon dioxide together of approximately 0.01 to 2% by weight, typically approximately 0.1 to 1.0% by weight, is preferred; as a rule higher concentrations are only indicated if the formulation contains a comparatively high content of cosolvents such as ethanol or water.

The expression "pharmaceutically active compound" in the context of the present invention comprises therapeutically active compounds and vaccines and other substances for health prophylaxis. Suitable

pharmaceutically active compounds for the aerosol formulations according to the invention are basically all active compounds which can be administered as an aerosol, such as beta-mimetics, corticosteroids, anticholinergics, cyclooxygenase, mast cell, lipoxygenase and proteolytic enzyme inhibitors, arachidonic acid, leukotriene, thromboxane, sodium/potassium channel, neurokinin, tachykinin, bradykinin, muscarine, histamine, phosphodiesterase, platelet-activating factor and selectin antagonists, potassium channel blockers, antiinfectives, antibiotics, pentamidine, cytostatics, fungistatics, free-radical scavengers, vitamins, hormones, immunostimulants, immunosuppressants, mucolytics, heparin, antidiabetics, analgesics, soporifics and the like, for example:

- beta-mimetics such as salbutamol, formoterol, salmeterol, fenoterol, clenbuterol, terbutaline, bambuterol, broxaterol, epinephrine, isoprenaline, orciprenaline, hexoprenaline, tolbuterol, reproterol, bamethan, tetroquinol, levalbuterol etc.,
- corticoids such as beclomethasone, dexamethasone, ciclomethasone, triamcinolone, budesonide, butixocort, ciclesonide, fluticasone, flunisolide, icomethasone, mometasone etc.,
- anticholinergics and spasmolytics such as atropine, glycopyrronium bromide, scopolamine, N-butylscopolamine, trospium chloride, ipratropium bromide, oxitropium bromide, tiotropium bromide, droferine, oxybutinin, moxaverine etc.,
- mast cell and histamine inhibitors such as cromoglycic acid, nedocromil, pemirolast etc., and 5-lipoxygenase inhibitors such as zileuton, linazolast etc.,
- leukotriene antagonists such as iralukast, zafirlukast, montelukast, roflumilast, imitrodast, ontozolast and pranlukast, sodium channel antagonists such as amiloride, potassium channel antagonists such

as bimakalim, arachidonic acid antagonists such as 2-benzoxazolamine, histamine receptor antagonists such as epinastine, cetrizine, mizolastine and mequitamium,

- anti-migraine agents such as ergot alkaloids, methysergide, ergotamine, serotonin, sumatriptan, zolmitriptan, cyclandelate etc.,
- analgesics such as fentanyl, morphine, buprenorphine, opium, heroin, nalbuphine, pentazocine, oxycodone, tramadol, pethidine, tilidine, methadone, nefopam, dextropropoxyphene, piritramide etc.,
- mucolytics such as RNase, acetylcysteine, ambroxol, apafant, bromhexine, human lung surfactant etc.,
- antiemetics such as bromopride, domperidone, metoclopramide, triethylperazine, trifluoropromazine, meclozine, chlorophenoxamine, dimenhydrinate etc.,
- antibiotics such as penicillins (e.g. azocillin), cephalosporins (e.g. cefotiam or ceftriaxone), carbapenems, monobutams, aminoglycosides (e.g. streptomycin, neomycin, gentamycin, amikacin or tobramycin), quinolones (e.g. ciprofloxacin), macrolides (e.g. erythromycin), nitroimidazoles (e.g. tinidazole), lincosamides (e.g. clindamycin), glycopeptides (e.g. vancomycin), polypeptides (e.g. bacitracin) etc.,
- vitamins and free-radical scavengers such as vitamin A, B, C, D or E, catalase, superoxide dismutase, reduced glutathione etc.,
- antidiabetics such as glibenclamide, glipizide, gliclacide, glimepiride, troglitazone etc.,
- soporifics such as benzodiazepines, piperidinediones, antihistamines etc.,
- neuroleptics, antidepressants and anticonvulsants such as benzodiazepines, phenothiazines, butyrophenones, sulpiride, hydantoins, barbiturates, succinimides, carbamazepine etc.,
- hormones such as androgens (e.g. testosterone), antioestrogens, oestrogens (e.g. estradiol),

gestagens (e.g. progesterone), corticosteroids, calcitonin, parathyrin, somatotropin, oxytocin, prolactin, glucagon, erythropoietin, atriopeptin, melanotropin, thyrotopin, gonadotropin, vasopressin, insulin etc.,

- potency agents such as phentolamine, sildenafil, alprostadil etc.,
- cytostatics such as nitrogen mustard derivatives (e.g. ifosphamide), N-nitrosourea derivatives (e.g lomustine), antagonists of purine and pyrimidine bases (e.g fluorouracil), platinum complexes (e.g. carboplatin), anthracyclines (e.g. doxorubicin), podophylline derivatives (podophyllotoxin).

The active compounds mentioned can optionally be used in the form of their isomers, enantiomers or racemates and, in the case of acids or bases, as such or in the form of their pharmaceutically acceptable salts or derivatives. The optimum amount of active compound in the formulations according to the invention depends on the particular active compound. As a rule, however, aerosol formulations are preferred which contain at least approximately 0.0001 and at most approximately 5% by weight, in particular approximately 0.01 to 3% by weight, of active compound.

Examples of active compounds which can be preferably used are the antiasthmatics such as beta-minetics, corticosteroids and anticholinergics and antiallergics such as mast cell inhibitors. Aerosol formulations which contain salbutamol, formoterol, salmeterol, fluticasone, budesonide, ciclesonide, glycopyrronium, tiotropium, cromoglycic acid, nedocromil, mometasone, sildenafil, beclomethasone, levalbuterol or a pharmaceutically acceptable salt or derivative of these active compounds are particularly preferred.

Depending on the nature of the active compounds and further additives, the aerosol formulations according to the invention can be present in the form

of suspensions, emulsions or solutions. The aerosol formulations can be prepared in a manner known per se by introducing dinitrogen monoxide under pressure into a liquefied hydrofluoroalkane of the formula I and adding the pharmaceutically active compound. The dinitrogen monoxide and the active compound can basically be added in any desired sequence. In the case of suspension formulations, however, as a rule it is preferred firstly to introduce the dinitrogen monoxide into the propellant and then to add the micronized active compound. The micronization of the active compound can take place in a known manner and is preferably carried out such that a particle size of approximately 0.5 to 6 µm is obtained. If carbon dioxide is additionally added to the aerosol formulation, this can be introduced under pressure to the liquefied hydrofluoroalkane either separately or together with the dinitrogen monoxide.

The propellant mixtures and aerosol formulations according to the invention can contain one or more hydrofluoroalkanes and, if desired, further propellants. Preferably, however, they contain no chlorofluorocarbons. Particularly preferred propellant mixtures and aerosol formulations are in general those which - apart from compounds such as water, lower alkanes, lower alcohols and lower ethers which can be used, if desired, as cosolvents - contain as propellants only dinitrogen monoxide and one or more hydrofluoroalkanes of the formula I and, if desired carbon dioxide. The hydrofluoroalkane or the hydrofluoroalkanes and the carbon dioxide concentration are preferably selected such that an internal pressure of approximately 3 to 10 bar, particularly preferably approximately 3.5 to 6 bar, can be established at 20°C in the aerosol container.

The aerosol formulations according to the invention are suitable for suspension, emulsion and solution formulations, and they can contain customary

additives such as cosolvents, glidants or lubricants (e.g. glycerol) and surface-active agents. The addition of the active compound and possible further additives can be carried out in a manner known per se. As a result of the improvement of the fine particle fraction achievable according to the invention and the simultaneous reduction in the undesired oropharyngeal deposition, it is frequently possible to decrease the active compound concentration significantly in comparison to a CFC-containing metered-dose aerosol.

The use of a cosolvent is frequently indicated, in particular in solution formulations, but can occasionally also be advantageous in suspension formulations.

Suitable cosolvents are in particular water, lower alcohols, lower alkanes and lower ethers, preferably water, alcohols having 1 to 3 carbon atoms, alkanes having 3 to 6 carbon atoms and dialkyl ethers having 2 to 4 carbon atoms, such as water, ethanol, propanol, isopropanol, ethylene glycol, propylene glycol, glycerol, propane, butane, isobutane, pentane, dimethyl ether, diethyl ether and the like. Diethyl ether and in particular ethanol are particularly preferred. The proportion of cosolvent in the propellant mixtures and aerosol formulations according to the invention, if present, can in general be approximately 0.01 to 40% by weight, in particular approximately 0.1 to 15% by weight, based on the total mixture or the total formulation.

The proportion of one or more hydrofluoroalkanes of the formula I in the propellant mixtures and aerosol formulations according to the invention is in general at least approximately 40% by weight, preferably at least approximately 64% by weight and particularly preferably at least approximately 87% by weight, of the total mixture or of the total formulation. In the case of the medicinal aerosol formulations, however, the proportion of

hydrofluoroalkanes with respect to the content of active compound, surface-active agent and possible further additives can also be lower and can be, for example, at least approximately 30% by weight.

The use of a surface-active agent is frequently indicated, in particular in the case of suspension formulations, but can also be advantageous in solution formulations, e.g. for valve lubrication. In principle all customary surface-active agents are suitable, such as oleic acid, lecithin, sorbitan trioleate, cetylpyridinium chloride, benzalkonium chloride, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (10) stearyl ether, polyoxyethylene (2) oleyl ether, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, polyoxypropylene/polyoxyethylene block copolymers, polyoxypropylene/polyoxyethylene/ethylenediamine block copolymers, ethoxylated castor oil and the like. In general, oleic acid, sorbitan trioleate and lecithin are preferred. The proportion of surface-active agent, if present, can preferably be approximately 0.0001 to 1% by weight, in particular approximately 0.001 to 0.1% by weight, based on the total formulation. Preferably, however, the aerosol formulations according to the invention can also be essentially free of surface-active agents, i.e. can contain less than 0.0001% by weight of surface-active agents.

Furthermore, the aerosol formulations according to the invention can contain, if desired, buffer substances or stabilizers such as citric acid, ascorbic acid, sodium EDTA, vitamin E, N-acetylcysteine and the like. In general, such substances, if present, are used in amounts of not more than approximately 1% by weight, for example approximately 0.0001 to 1% by weight, based on the total formulation.

The aerosol formulations according to the invention can be prepared in a manner known per se using stirrers and homogenizers. For filling, known

processes, such as the cold- or pressure-filling technique or modifications of these techniques, can be employed. Suitable containers are, for example, pressure-resistant containers made of glass, plastic or aluminum, which can be equipped with metered-dose valves of, for example 10 to 140 µl and can be provided with commercially available - also inspiration-triggered - mouth tube adapters.

In the preparation of aerosol formulations, the propellant mixtures according to the invention thus offer a number of advantages, such as better wetting of active compound, improved suspension and shelf-life properties of suspension formulations, improvement in the dosage accuracy, increase in the fine particle dose and, if desired, a decrease in the amounts of cosolvent or the wide avoidance of the disadvantages of high amounts of cosolvent.

The invention therefore likewise relates to the use of the propellant mixtures according to the invention as propellants for aerosols, the use for medicinal aerosols and in particular for nasal or inhalant aerosols (which can preferably have an aerodynamic particle or droplet diameter of approximately 0.5 to 40 µm, in particular approximately 0.5 to 6 µm) being preferred, and the use in a pressure-resistant container having a metered-dose valve and a suitable adapter for the atomization or inhalation of pharmaceutical active compounds.

Using the propellant system according to the invention, it is possible to prepare, for example, a budesonide metered-dose aerosol which, in comparison to a CFC-containing commercial product (Pulmicort®, Astra, Sweden) has a far better dosage accuracy and an FPF which is almost twice as high. Supplementary to this, the deposition in the mouth tube is approximately halved and that in the "sample induction port" (artificial oropharynx) is reduced from about 50% to 20%. The formulation according to the invention thus

makes it possible to formulate the metered-dose aerosol more advantageously with respect to a number of aspects, as the respirable dose can be virtually doubled and the undesired oropharyngeal in-vitro deposition in the sample induction port can be reduced, as can be shown by the example of beclomethasone dipropionate, budesonide and disodium cromoglycate. It is therefore to be expected that in the case of budesonide the same therapeutic effect as, for example, with the commercial product Pulmicort® is presumably achieved using half the dosage.

The invention is illustrated further by the following examples. The homogenization of active compound suspensions was in each case carried out using a rotor-stator homogenizer (Kinematika).

Example 1

100 g of micronized disodium cromoglycate are weighed into a pressure addition vessel. After sealing and evacuating the addition vessel, 8.5 kg of HFA 227, which have previously been treated with 3% by weight of ethanol and aerated with dinitrogen oxide and adjusted to a pressure of 5 bar (20°C) in another pressure addition vessel, are added with stirring. After homogenizing, the suspension obtained is dispensed by means of the pressure-filling technique into aluminum containers sealed with metered-dose valves.

Example 2

2 g of micronized ipratropium bromide are weighed into a pressure addition vessel. After sealing and evacuation thereof, 6.0 kg of a mixture of HFA 227 and HFA 134a (weight ratio 80:20), which have previously been aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar at 20°C in another pressure addition vessel, are added. After homogenizing this mixture, the suspension obtained is dispensed by

means of the pressure-filling technique into containers which are equipped with a metered-dose valve.

Example 3

5 g of micronized glycopyrronium bromide are weighed into a pressure addition vessel. After sealing and evacuation thereof, 10 kg of HFA 227, which have previously been treated with 1% by weight of ethanol and aerated with dinitrogen oxide and adjusted to a pressure of 5.25 bar (20°C) in another pressure addition vessel, are added. After homogenizing this mixture, the suspension obtained is dispensed by means of the pressure-filling technique into pressure-resistant glass containers sealed with metered-dose valves.

Example 4

0.6 g of micronized formoterol fumarate and 20 g of micronized glycopyrronium bromide are weighed into a pressure addition vessel. After sealing and evacuating the addition vessel, 6.5 kg of a propellant mixture of HFA 227 and HFA 134a (weight ratio 70:30), which have previously been treated with 2% by weight of ethanol and aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar (20°C), are added with stirring. After homogenizing, the suspension obtained is dispensed by means of the pressure-filling technique into aluminum containers sealed with metered-dose valves.

Example 5

120 g of beclomethasone dipropionate are weighed into an addition vessel and dissolved in 6 kg of ethanol in which 10 g of oleic acid have previously been dissolved. 1 g of this solution in each case is dispensed into aluminum containers and these are subsequently sealed with metered-dose valves. In a pressure addition vessel, HFA 227 is aerated with

dinitrogen oxide and adjusted to a pressure of 5.5 bar at 20°C. 11 g of this mixture per container are in each case fed in under pressure and the latter is then treated in an ultrasonic bath.

Example 6

10 g of micronized levalbuterol sulphate are weighed into a pressure addition vessel. After sealing and evacuation thereof, 13 kg of HFA 227, which have previously been treated with 650 g of ethanol and aerated with dinitrogen oxide and adjusted to a pressure of 5.25 bar (20°C), are added. After homogenizing this mixture, the suspension obtained is dispensed into pressure-resistant containers which are equipped with metered-dose valves.

Example 7

120 g of fluticasone are weighed into an addition vessel and dissolved in 6 kg of ethanol in which 6 g of oleic acid have previously been dissolved. 1.2 g of this solution in each case are dispensed into pressure-resistant containers and these are subsequently sealed with metered-dose valves. In a pressure addition vessel, HFA 134a is aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar at 20°C. 12 g of this mixture in each case are fed in under pressure per container and these are then treated in an ultrasonic bath.

Example 8

3.0 g of micronized budesonide are weighed into a pressure addition vessel. After sealing and evacuation thereof, a mixture of 0.85 kg of HFA 134a and 0.85 kg of HFA 227, which have previously been aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar (20°C) in another pressure addition vessel, is added. After homogenizing this mixture, the suspension obtained is dispensed by means of the

pressure-filling technique into aluminum containers sealed with metered-dose valves.

Example 9

3.0 g of micronized fluticasone propionate and 0.15 g of micronized formoterol fumarate are weighed into a pressure addition vessel. After sealing and evacuation thereof, a mixture of 0.5 kg of HFA 134a and 1.5 kg of HFA 227, which have previously been treated with 2% by weight of ethanol and aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar (20°C), is added. After homogenizing this mixture, the suspension obtained is dispensed into pressure-resistant containers which are sealed with metered-dose valves.

Example 10

5 g of micronized salmeterol xinafoate and 2 g of micronized glycopyrronium bromide are weighed into a pressure addition vessel. After sealing and evacuating the addition vessel, 70 kg of HFA 227, which have previously been treated with 2% by weight of ethanol and aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar (20°C), are added with stirring. After homogenizing, the suspension obtained is dispensed by means of the pressure-filling technique into aluminum containers sealed with metered-dose valves.

Example 11

10 g of sildenafil and 0.1 g of δ-tocopherol are weighed into an addition vessel and dissolved in 100 g of ethanol in which 0.1 g of lecithin has previously been dissolved. 1 g of this solution in each case is dispensed into pressure-resistant containers and these are subsequently sealed with metered-dose valves. In a pressure addition vessel, HFA 134a is aerated with dinitrogen oxide and adjusted to a

pressure of 6.5 bar at 20°C. 7 g of this mixture in each case are fed in under pressure per container, which are then treated in an ultrasonic bath.

Example 12

120 g of beclomethasone dipropionate are weighed into an addition vessel and dissolved in 6 kg of ethanol in which 120 g of glycerol have previously been dissolved. 1 g of this solution in each case is dispensed into aluminum containers and these are subsequently sealed with metered-dose valves. In a pressure-addition vessel, HFA 227 is aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar at 20°C. 11 g of this mixture in each case are fed in under pressure per container and these are then treated in an ultrasonic bath.

Example 13

10 g of sildenafil and 0.1 g of δ-tocopherol are weighed into an addition vessel and dissolved in 100 g of ethanol in which 1 g of glycerol has previously been dissolved. 1 g of this solution in each case is dispensed into pressure-resistant containers and these are subsequently sealed with metered-dose valves. In a pressure addition vessel, HFA 227 is aerated with dinitrogen oxide and adjusted to a pressure of 6 bar at 20°C. 6 g of this mixture in each case are fed in under pressure per container, which are then treated in an ultrasonic bath.

Example 14

1.6 g of micronized budesonide are weighed into a pressure addition vessel. After sealing and evacuation thereof, a mixture of 20 g of propylene glycol, 30 g of ethanol and 950 g of HFA 227, which have previously been aerated with dinitrogen oxide and adjusted to a pressure of 5.5 bar (20°C) in another pressure addition vessel, is added. After homogenizing

this mixture, the suspension obtained is dispensed by means of the pressure-filling technique into aluminum containers sealed with metered-dose valves.

Example 15

1.6 g of micronized budesonide are weighed into a pressure addition vessel. After sealing and evacuation thereof, a mixture of 50 g of glycerol, 150 g of ethanol and 800 g of HFA 134a, which has previously been aerated with dinitrogen oxide and adjusted to a pressure of 6.5 bar (20°C) in another pressure addition vessel, is added. After homogenizing this mixture, the solution obtained is dispensed by means of the pressure-filling technique into aluminum containers sealed with metered-dose valves.

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CLAIMS:

1. A pressure-liquefied propellant mixture for aerosols, comprising dinitrogen monoxide and a hydrofluoroalkane of the general formula:

$$C_xH_yF_z \qquad (I)$$

wherein x is 1, 2 or 3, y and z are each an integer $\geq$ 1, and $y + z = 2x + 2$.

2. The propellant mixture as claimed in claim 1, which comprises at least 40% by weight of a hydrofluoroalkane of the general formula I.

3. The propellant mixture as claimed in claim 2, which comprises at least 64% by weight of a hydrofluoroalkane of the general formula I.

4. The propellant mixture as claimed in any one of claims 1 to 3, wherein the hydrofluoroalkane of the general formula I is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or a mixture thereof.

5. The propellant mixture as claimed in any one of claims 1 to 4, which has a pressure of 3 to 10 bar at 20°C.

6. The propellant mixture as claimed in any one of claims 1 to 5, which further comprises carbon dioxide.

7. The propellant mixture as claimed in any one of claims 1 to 6, comprising at least 0.0001% by weight of dinitrogen monoxide.

8. The propellant mixture as claimed in any one of claims 1 to 6, comprising 0.0001 to 10% by weight of dinitrogen monoxide or dinitrogen monoxide and carbon dioxide combined.

9. The propellant mixture as claimed in any one of claims 1 to 8, further comprising 0.01 to 40% by weight of a cosolvent.

10. The propellant mixture as claimed in claim 9, wherein the cosolvent is water, ethanol, propanol, ethylene glycol, propylene glycol, glycerol, propane, butane, isobutane, pentane, dimethyl ether, diethyl ether or a mixture thereof.

11. A medicinal aerosol formulation, comprising an efficacious amount of a pharmaceutically active compound and a pressure-liquefied propellant mixture as claimed in any one of claims 1 to 10.

12. The aerosol formulation as claimed in claim 11, further comprising a surface-active agent.

13. The aerosol formulation as claimed in claim 12, comprising 0.0001 to 1% by weight of a surface-active agent.

14. The aerosol formulation as claimed in claim 11, which is essentially free of a surface-active agent.

15. The aerosol formulation as claimed in any one of claims 11 to 14, wherein the pharmaceutically active compound is salbutamol, formoterol, salmeterol, fluticasone, budesonide, ciclesonide, glycopyrronium, tiotropium, cromoglycic acid, nedocromil, mometasone, sildenafil, beclomethasone, levalbuterol or a pharmaceutically acceptable salt or derivative thereof.

16. A process for the preparation of a medicinal aerosol formulation as defined in any one of claims 11 to 15, comprising introducing dinitrogen monoxide under pressure into a liquefied hydrofluoroalkane of the general

formula (I) as defined in claim 1, and adding the pharmaceutically active compound.

17. Use of a pressure-liquefied propellant mixture as claimed in claims 1 to 10, as a propellant for an aerosol.

18. The use as claimed in claim 17, as a propellant for a medicinal aerosol.

19. The use as claimed in claim 18, wherein the medicinal aerosol is a nasal or inhalant aerosol.

20. Use of a pressure-liquefied propellant mixture as claimed in any one of claims 1 to 10 in a pressure-resistant container having a metered-dose valve and a suitable adapter for the atomization or inhalation of a pharmaceutically active compound.

FETHERSTONHAUGH & CO.
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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: EKSTRÖM, Tommy [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).

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(57) Abstract

The present invention relates to use of a composition for symptomatic relief, when needed, comprising, in admixture (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and (b) a second active ingredient which is budesonide; for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma. The invention further relates to a method for prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition comprising the first and second active ingredients as defined previously.

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USE OF A COMPOSITION COMPRISING FORMOTEROL AND BUDESONIDE FOR THE PREVENTION OR TREATMENT OF AN ACUTE CONDITION OF ASTHMA

FIELD OF THE INVENTION

The present invention relates to use of a composition for symptomatic relief, when needed, comprising, in admixture

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma. The invention further relates to a method for prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition comprising the first and second active ingredients as defined previously.

BACKGROUND OF THE INVENTION

Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms may be controlled by β_2-adrenoceptor agonists such as terbutaline, salbutamol, formoterol and salmeterol. Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate, fluticasone propionate, mometasone furoate and budesonide.

In spite of modern maintenance treatment too many asthmatic patients are undertreated for a number of reasons with a negative impact on their quality of life. Too complicated therapy with different medications and devices may lead to misunderstanding and commu-

nication problems between patient and doctor. Poor compliance is a common phenomenon. Improved patient education may partly counteract this, but does not completely solve the problem. A new and more simple approach to asthma treatment could thus be of tremendous help for many patients suffering from respiratory disease, particularly asthma. The combination of budesonide and formoterol in the same device as suggested in PCT applications WO 93/11773 and WO 98/15280 (both to Astra AB of Sweden) offers a favorable pathway to improve today's asthma management with an excellent safety profile. However, although having an adequate regular, e.g. bid, treatment with such a combination, many patients will now and then run into acute situations with a higher frequency and severity of exacerbations, when additional medication is needed. Such an additional medication is often a β_2-adrenoceptor agonist with fast onset, normally terbutaline or salbutamol. A second medicament is thus needed, and this can negatively affect the overall compliance of the patient. There is thus need for a neat way of handling maintenance treatment together with the treatment of acute situations which .

SUMMARY OF THE INVENTION

It is an object of the present invention to provide use of a suitable composition for the manufacture of a medicament for the treatment of acute episodes of asthma as a complement to maintenance treatment.

More specifically, according to the invention there is provided use of a composition for symptomatic relief when needed comprising, in admixture

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma.

Use of the present composition, when needed, relates to use of said composition during one or more of the following conditions:

i) an acute condition of asthma, i.e. acute asthma attacks,

ii) intermittent asthma and/or

iii) short periods (episodes) of acute attacks of bronchospasms in chronic asthma.

Acute asthma attacks may occur on an irregular basis when exposed to an agent e.g. during the pollen season, a virus infection, cold air, perfumes or any other agent(s) triggering an asthma attack in the patient.

It lies within the scope of the present invention, to use the compositions comprising active compounds (a) and (b) for treating acute conditions of asthma, intermittent asthma and episodes in chronic asthma, in addition to treating chronic asthma on a regular basis, with the same active compounds (a) and (b) or one or more different active compounds, preferably selected from short-acting β-agonists, long-acting β-agonists and glucocorticosteroids.

We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions.

According to a further aspect of the invention a method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma, when needed, which comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide.

According to the present invention it has surprisingly been found that the medicament can be administered when needed to a patient with an acute attack of asthma.

The recommended dose regimen described in the prior art as disclosed above is twice a day. This dose recommendation was a result of a concern not to have too high an administration of the active compounds. However, in the present invention it has been found that it is possible for the patient to administer this mixture as often as needed.

The combination of formoterol and budesonide can be used as a rescue medication. Worsening of symptoms can be counteracted by incremental use of the combination for symptom relief, e.g. during exacerbations with the additional steroid component coming in as early as possible to suppress the enhanced airway inflammation. The long duration of formoterol will reduce the risk of too frequent dosing. When taking the combination budesonide/formoterol when needed the severity of exacerbations can be reduced. The as needed use (Pro Re Nata, PRN) will also minimize the difficulty of predicting which patients will be controlled on a low dose of inhaled steroid rather than increasing the steroid dose before adding a long-acting β_2-agonist. Under-treatment with inhaled glucocorticosteroids following a too low maintenance dose will be more or less "self-corrected" by the rescue usage according to the present invention. The PRN use of the combination will always give some beneficial anti-inflammatory effects even if it is used by the patient only for rescue purposes. A treatment for patients suffering from respiratory disease, particularly asthma (including allergic conditions, e.g. episodic or intermittent asthma), will therefore be to use the combination formoterol/budesonide for maintenance therapy as well as on an as needed basis (for rescue purposes), e.g. for prevention of exercise and/or allergen induced asthma.

DETAILED DESCRIPTION OF THE INVENTION

Formoterol is a compound which can exist in several stereochemical forms. The present invention includes the individual stereoisomers as well as mixtures thereof. It is intended that the present invention includes geometrical isomers, rotational isomers, racemates, diastereomers and enantiomers, in particular the R,R enantiomer of formoterol.

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids such as the hydrochloride, hydrobromide, sulfate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxy-naphthalene-carboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of this salt.

The present invention also encompasses compositions comprising the 22R epimer of budesonide as the second active ingredient.

A suitable unit dose of formoterol (as fumarate dihydrate) is in the range of from 1 µg to 48 µg, preferably from 2 µg to 24 µg, and more preferably between 3 µg and 12 µg. The daily dose of formoterol (as fumarate dihydrate), including maintenance therapy, should be in the range of from 1 µg to 100 µg, preferably from 2 µg to 60 µg, and more preferably from 3 µg to of 48 µg.

A suitable unit dose of budesonide is in the range of from 20 µg to 1600 µg, suitably from 30 µg to 800 µg, preferably from 50 µg to 400 µg, and more preferably between 100 µg and 200 µg. The daily dose of budesonide, including maintenance therapy, should be in the range of 20 µg to 4800 µg, preferably from 30 µg to 3200 µg, and more preferably from 40 µg to 1600 µg. The particular dose regimen will depend on the patient (age, sex, weight etc.) and the severity of the disease (mild, moderate, severe asthma etc.).

The molar ratio of the first active ingredient (as formoterol) to the second active ingredient of the invention. suitably lies in the range of from 1:1 to 1:100, preferably from 1:1 to 1:70, and more preferably from 1:1 to 1:50.

Preferably the mixture comprises one or more pharmaceutically acceptable additives, diluents or carriers, more preferably in an amount of from 50 µg to 4000 µg in each dose, most preferably in an amount of from 100 µg to 2000 µg and most preferably from 100 µg to 1000 µg. Examples of suitable additives. diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, and more preferably as the monohydrate.

One or more of the ingredients of the mixture may be in the form of dry powder. more preferably a small particle dry powder, most preferably an agglomerated small particle dry powder. Alternatively one or more of the active ingredients (a) or (b) are in the form of an ordered mixture with diluent, additive or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is preferably less than 10 µm.

Administration may be by inhalation orally or intranasally. The ingredients of the system are preferably adapted to be administered from a dry powder inhaler, a pressurized metered dose inhaler, or a nebulizer.

When the ingredients of the system are adapted to be administered from a pressurized inhaler, they are preferably in a small particle form. They are dissolved, or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluorocarbons. Especially preferred propellants are P134a (tetrafluoroethane), P152a (difluoroethane) and P227 (heptafluropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an antioxidant and/or a stabilizing agent.

When the ingredients of the system of the invention are adapted to be administered via a nebulizer they may be in the form of a nebulized aqueous suspension or solution, with or without suitable pH or tonicity adjustment, either as a unit dose or multidose formulation.

EXAMPLES

The ingredients can be formulated as illustrated by the following examples which are not intended to limit the scope of the invention.

In the examples micronization is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler® is a trademark of Astra AB.

EXAMPLE 1

4.5 Parts by weight of formoterol fumarate dihydrate were mixed with 915 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 2

9 Parts by weight of formoterol fumarate dihydrate were mixed with 831 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low

pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 3

6 Parts by weight of formoterol fumarate dihydrate were mixed with 894 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 4

12 Parts by weight of formoterol fumarate dihydrate were mixed with 788 parts by weight of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronized budesonide were added to the conditioned product by mixing and homogenizing with a low pressure jet mill. The mixture was then spheronized using the process of EP-A-721 331 and filled into the storage compartment of Turbuhaler.®

EXAMPLE 5

A patient on maintenance treatment with the fixed combination formoterol fumarate dihydrate/budesonide in a dose of 4.5/80 µg or 4.5/160 µg bid additionally uses the same combination either for rescue purposes once or twice daily to treat sporadic breakthrough symptoms, or as needed to treat exacerbations during one or two weeks, with a maximum daily dose of 36/640 µg (8 puffs of 4.5/80 µg) and 36/1280 µg (8 puffs of 4.5/160 µg), respectively.

EXAMPLE 6

A patient with intermittent asthma uses the fixed combination formoterol fumarate dihydrate/budesonide as sole medication to be taken as needed until the asthma resolves. The highest recommended daily dose will be either 36/640 µg (8 puffs of 4.5/80 µg) or 36/1280 µg (8 puffs of 4.5/160 µg) for a period not exceeding 8-120 weeks. If symptoms still persist after that period of time - regular maintenance therapy should be considered.

CLAIMS

1. Use of a composition for symptomatic relief, when needed, comprising, in admixture

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma.

2. Use according to claim 1, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100, preferably from 1:1 to 1:70.

3. Use according to claim 1 or 2, wherein the first active ingredient is formoterol fumarate dihydrate.

4. Use according to any previous claim, wherein the first active ingredient is the R,R enantiomer of formoterol.

5. Use according to any previous claim, wherein a unit dose of formoterol lies in the range of from 1 μg to 48 μg, preferably between 3 μg to 12 μg, calculated as formoterol fumarate dihydrate.

6. Use according to any previous claim, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μg to 100 μg, preferably from 2 μg to 60 μg, calculated as formoterol fumarate dihydrate.

7. Use according to any previous claim, wherein the second active ingredient is the 22R epimer of budesonide.

8. Use according to any previous claim, wherein a unit dose of budesonide lies in the range of from 20 µg to 1600 µg, preferably between 50 µg to 400 µg.

9. Use according to any previous claim, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 µg to 4800 µg, preferably from 30 µg to 3200 µg.

10. Use according to any previous claim, wherein the particle size of the active ingredients (a) and (b) is less than 10 µm.

11. Use according to any previous claim, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

12. Use according to claim 11, wherein the pharmaceutically acceptable additive, diluent or carrier is lactose monohydrate.

13. A method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma, when needed, which comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and

(b) a second active ingredient which is budesonide.

14. The method according to claim 13, wherein the molar ratio of (a) to (b) calculated as formoterol to budesonide is from 1:1 to 1:100, preferably from 1:1 to 1:70.

15. The method according to claim 13 or 14, wherein the first active ingredient is formoterol fumarate dihydrate.

16. The method according to any of claims 13 to 15, previous claim, wherein the first active ingredient is the R,R enantiomer of formoterol.

17. The method according to any of claims 13 to 16, wherein a unit dose of formoterol lies in the range of from 1 μg to 48 μg, preferably between 3 μg to 12 μg, calculated as formoterol fumarate dihydrate.

18. The method according to any of claims 13 to 17, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μg to 100 μg, preferably from 2 μg to 60 μg, calculated as formoterol fumarate dihydrate.

19. The method according to any of claims 13 to 18, wherein the second active ingredient is the 22R epimer of budesonide.

20. The method according to any of claims 13 to 19, wherein a unit dose of budesonide lies in the range of from 20 μg to 1600 μg, preferably between 50 μg to 400 μg.

21. The method according to any of claims 13 to 20, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 μg to 4800 μg, preferably from 30 μg to 3200 μg.

22. The method according to any of claims 13 to 21, wherein the particle size of the active ingredients (a) and (b) is less than 10 μm.

23. The method according to any of claims 13 to 22, wherein the composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers.

24. The method according to claim 23, wherein the pharmaceutically acceptable additive, diluent or carrier is lactose monohydrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01031

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57 // (A61K 31/57, 31:165)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93), See page 1409 - page 1410 ---	1-24
X	The New England Journal of Medicine, Volume 337, No 20, November 1997, Romain A. Pauwels et al, "Effect of Inhaled Formoterol and Budesonide on Exacerbations of Asthma" page 1405 - page 1411 --- --------	1-24

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 Sept 1999	11 -10- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/01031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-24
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Claims 13-24 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/99

International application No.
PCT/SE 99/01031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311773 A1	24/06/93	AU 673660 B	21/11/96
		AU 3085892 A	19/07/93
		CA 2123909 A	24/06/93
		CZ 9401434 A	15/12/94
		EP 0613371 A	07/09/94
		HR 921445 A	31/12/94
		HU 75156 A	28/04/97
		HU 9401843 D	00/00/00
		JP 7502036 T	02/03/95
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		NZ 246050 A	21/12/95
		SG 48301 A	17/04/98
		SK 73394 A	08/03/95
		US 5674860 A	07/10/97

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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TROFAST, Eva** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **MALMQVIST-GRANLUND, Karin** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **NILSSON, Per-Gunnar** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **THALBERG, Kyrre** [NO/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/89492 A1

(54) Title: NOVEL COMPOSITION

(57) Abstract: The invention relates to novel pharmaceutical compositions useful in the treatment of respiratory disorders such as asthma, rhinitis and chronic obstructive pulmonary disease (COPD).

Novel composition

Field of the invention

The present invention relates to a stable powder formulation comprising formoterol or enantiomers of formoterol, a glucocorticosteroid and a carrier or diluent for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases such as asthma, COPD and rhinitis.

Background of the invention

Stability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product. When mixing different ingredients in a pharmaceutical formulation there exists the possibility of interactions taking place between the components. In addition, each component may have different degradation characteristics.

Formoterol is a highly potent and selective β2-agonist with a long duration of action when inhaled. Compared to other β-adrenergic compounds it has a unique chemical structure with a formamido group substituted on the benzene ring. It has two asymmetric carbon atoms in the molecule making four stereoisomers possible. Most studies, clinical and preclinical, appear to have been performed with the fumarate (as dihydrate) of the enantiomeric mixture designed R;R + S;S. The R;R enantiomer is the most potent of the four enantiomers.

The stability profile of the drug formoterol (mainly as fumarate dihydrate) has been evaluated by investigating the influence of variables such as storage time, temperature, relative humidity, light and pH on the content of formoterol and determining the amount of chromatographic impurities. Formoterol (as fumarate dihydrate) has been demonstrated to be stable under long-term storage even at high temperatures and high relative humidities.

However, the chemical structure of formoterol makes the molecule prone to chemical degradation when in contact with e.g. a reactive species like an aldehyde or under stress conditions e.g. a milling process.

Potent drugs for administration by inhalation are generally formulated in association with carriers/diluents such as lactose to facilitate accurate dosing from an inhaler. These formulations have generally consisted of coarse particles of a carrier together with fine particles of the drug(s), optionally together with small particles of carrier/diluent, which combination is generally known as an ordered mixture. An alternative to such a formulation is to agglomerate the small particles of the drug(s) and the carrier/diluent to agglomerates.

Formoterol (as fumarate dihydrate) as well as a carbohydrate such as lactose (preferably as the monohydrate) are very stable compounds individually, but degradation products are formed when the two compounds are mixed. A mixture of formoterol fumarate dihydrate and lactose monohydrate can be regarded as a three component system composed of formoterol fumarate, lactose and water. By sorption of water a saturated aqueous lactose solution is formed at the surface of the powder mixture. A certain amount of formoterol fumarate dissolves in this aqueous solution and is thereby susceptible to degradation. Therefore, the relative humidity, as well as the storage temperature, will influence the stability of the powder mixture.

When adding a third ingredient in the mixture the formation of degradation products would be expected to be higher due to the complexity and the possibility for many degradation processes. It would therefore be desirable to develop a formulation with good stability in spite of the complex mixture of compounds having reactive chemical functions such as an amine (formoterol), formamide (formoterol), carbohydrate (e.g. lactose) and a keto function (glucocorticosteroid). The presence of hydrates (formoterol fumarate dihydrate, lactose monohydrate) will make it even more complex.

Description of the invention

In accordance with the present invention, there is provided a pharmaceutical composition in the solid state comprising, in admixture, a first active ingredient which is micronised formoterol or an enantiomer thereof, a second active ingredient which is a micronised glucocorticosteroid and a carrier or diluent, the composition having a high storage stability.

By the term "high storage stability" is meant that the decomposition of formoterol in the formulation will be less than 10 % when stored in open dishes at 40°C and 75 % relative humidity for 6 months when the content of formoterol is less than about 1.0% (w/w), preferably less than 0.8 % (w/w) and most preferably less than about 0.6 % (w/w) in the formulation or, when stored in a dry powder device, a decomposition of less than about 2.5 % under the same conditions.

The formulations having the desired stability are prepared using a novel process which involves:

1. preparing a mixture of micronised first active ingredient and micronised carrier/diluent
2. optionally adding further micronised carrier/diluent to the mixture
3. addition and mixing of pre-micronised hydrophobic second active ingredient, the second active ingredient being optionally pre-mixed with micronised carrier/diluent, and
4. either subjecting the mixture to agglomeration and spheronisation, or adding coarse carrier/diluent.

The first active ingredient and carrier/diluent can be prepared according to step 1 by micronising the two components together or each can be micronised individually and then combined to give a micronised mixture. Preferably the two components are mixed together and then micronised.

Preferably at step 3 the pre-micronised hydrophobic second active ingredient is added alone, ie in the absence of further micronised carrier/diluent.

Preferably step 4 involves subjecting the mixture to agglomeration and spheronisation.

By "micronised" is meant milling to give the a desired particle size or obtaining a desired particle size by any other means for producing small particles such as direct precipitation.

Optionally the mixture/ingredients can be conditioned at any suitable stage of the process, such as between steps 1 and 2, and/or the further pre-micronised carrier/diluent can be conditioned prior to addition at step 2, and/or the further pre-micronised carrier/diluent can be conditioned prior to addition at step 3, and/or the mixture can be conditioned between the agglomeration and spheronisation in step 4.

Conditioning can be carried out according to the procedures described in WO 95/05805 or by selecting the process parameters such as relative humidity in such a way that the final product when submitted to water vapour gives off heat of less than 1.2 joules per gram for the particles having a mean particle size of less than 10 μm as described and measured in US 5.874,063.

The invention therefore provides a pharmaceutical formulation in the solid state comprising, in admixture, a first active ingredient which is micronised formoterol or an enantiomer thereof, a second active ingredient which is a micronised glucocorticosteroid and a carrier/diluent and having a high storage stability characterised in that the formulation is prepared by micronisation of the first active ingredient and carrier/diluent, optionally followed by mixing pre-micronised coarser carrier/diluent, mixing with micronised hydrophobic second active ingredient., and finally either subjecting the mixture to agglomeration and spheronisation or adding coarse carrier/diluent.

The formoterol can be in the form of a mixture of enantiomers. Preferably the formoterol is in the form of a single enantiomer, preferably the R;R enantiomer. The formoterol can be in the form of the free base, salt or solvate, or a solvate of a salt, preferably the formoterol is in the form of its fumarate dihydrate salt. Other suitable physiologically salts include chloride, bromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, benzenesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricaballate, hydroxynapaphthalenecarboxylate or oleate.

Preferably the second active ingredient is a micronised glucocorticosteroid such as budesonide, fluticasone propionate, mometasone furoate, ciclesonide and epimers, esters, salts and solvates of these compounds. More preferably the second active ingredient is budesonide or an epimer thereof, most preferably the 22R-epimer of budesonide.

Preferably the carrier is a carbohydrate having a high storage stability, preferably a reducing carbohydrate such as lactose, glucose, galactose, mannose, xylose, maltose, cellobiose, mellibiose, maltotriose (e.g. as monohydrate). More preferably the carrier is lactose.

As used herein the term micronised carrier/diluent refers to carrier/diluent having a mean particle size of less than about 25 μm, preferably less than about 10 μm, more preferable less than about 5 μm. The micronised carrier can be produced using processes known in the art such as micronisation or direct precipitation. The term coarse carrier/diluent refers to carrier/diluent having a mean particle size of greater than about 25 μm.

As used herein the term micronised first active ingredient or micronised second active ingredient means active ingredient having a mean particle size of less than about 10 μm, preferably less than about 5 μm.

The pharmaceutical compositions according to the invention can be used for the treatment or prophylaxis of a respiratory disorder, in particular the treatment or prophylaxis of asthma, rhinitis or COPD.

In a further aspect the invention provides a method of treating a respiratory disorder, in particular asthma, rhinitis or COPD, in a mammal which comprises administering to a patient a pharmaceutical composition as herein defined.

The compositions of the invention can be inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler e.g. multidose reservoir systems from AstraZeneca (Turbuhaler®) or Schering-Plough or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs. Doses will be dependent on the severity of the disease and the type of patient.

The process of the invention is shown schematically in Figure 3.

Experimental section

The invention is illustrated by the following examples which are not intended to limit the scope of the application. In the examples micronisation is carried out such that the particle size range for each of the active components is suitable for administration by inhalation. The determination of the formoterol degradation products was performed by reversed phase liquid chromatography, on a two column system using LiChrospher 60 RP-select B. 5 μm particles with octylsilane as stationary phase. UV-detector at 214 nm. Evaluation was done as area-% since the degradation products were not fully known.

Example 1

The following example is a reference example in which the formulation is prepared in a conventional manner.

Formoterol fumarate dihydrate (26 g) and lactose monohydrate (4.974 kg) are mixed for one or two hours in a tumbling mixer. This mixture was micronised in a spiral jet mill in order to attain a particle size suitable for inhalation. Micronisation of substances into the low micron range (1-5 μm) may induce disturbances in the crystallinity of the substance. Amorphous areas are introduced, especially at the surfaces of the micronised substance. This morphological change of the substances will increase the sensitivity to humidity and thereby being an potential implement to stability problems. The crystal structure of the substance mixture was restored in a controlled way according to US 5.874.063 or US 5.709.884.

To improve the flowability of the cohesive powder it was spheronised to agglomerates at room temperature at a controlled relative humidity of less than 50 %.

Stability data of a formoterol fumarate dihydrate (5 mg/g)/lactose monohydrate (995 mg/g) micronised mixture and stored in open dishes at 40°C and 75 % relative humidity for 6 months. Results see figure 1 (A).

Example 2.

The following example is a reference example in which the formulation is prepared in a conventional manner.

The micronised and spheronised formoterol fumarate dihydrate/lactose monohydrate formulation according to example 1 was filled in the powder device Turbuhaler® (AstraZeneca) and stored for 6 months at 40°C and 75 % relative humidity. Results see figure 2 (A).

Example 3.

Formoterol fumarate dihydrate (0.2 kg) and lactose monohydrate (34 kg) are mixed for one or two hours in a tumbling mixer. This mixture was micronised in a spiral jet mill in order to attain a particle size suitable for inhalation. The crystal structure was restored in a controlled way according to US 5.874.063 or US 5.709.884. This conditioned product is mixed with micronised budesonide (3 kg) for thirty to sixty minutes in a tumbling mixer. As a second mixing step the powder was fed to a modified spiral jet mill, operating at a very low milling pressure and a high flow of nitrogen. This will break up agglomerates without causing a further size reduction of the particles (and thereby creating amorphous areas and as a consequence loss of stability) while improving the homogeneous distribution of budesonide in the powder.
To improve the flowability of the cohesive powder it was spheronised to agglomerates at room temperature at a controlled relative humidity of less than 50 %.

Stability data of a formoterol fumarate dihydrate (5 mg/g)/budesonide (90 mg/g)/lactose monohydrate (905 mg/g) micronised mixture and stored in open dishes at 40°C and 75 % relative humidity for 6 months. Results see figure 1(B).

Example 4.

The micronised and spheronised formoterol fumarate dihydrate (5 mg/g)/budesonide (90 mg/g)/lactose monohydrate (905 mg/g) according to example 3 was filled in the dry powder device Turbuhaler® (AstraZeneca) and stored for 6 months at 40°C and 75 % relative humidity. Results see figure 2 (B).

Claims.

1. A pharmaceutical composition comprising, in admixture, a first active ingredient which is micronised formoterol optionally in the form of a salt or solvate or a solvate of a salt, a second active ingredient which is a micronised glucocorticosteroid and a pharmaceutically acceptable carrier/diluent, the composition having a high storage stability.

2. A pharmaceutical composition according to claim 1 in which formoterol is in the form of its fumarate dihydrate salt

3. A pharmaceutical composition according to claim 1 or 2 in which the formoterol is in the form of the single R,R-enantiomer.

4. A pharmaceutical composition according to any one of claims 1 to 3 in which the second active ingredient is budesonide.

5. A pharmaceutical composition according to any one of claims 1 to 3 in which the second active ingredient is the 22R-epimer of budesonide.

6. A pharmaceutical composition according to any one of claims 1 to 5 in which the carrier/diluent is lactose.

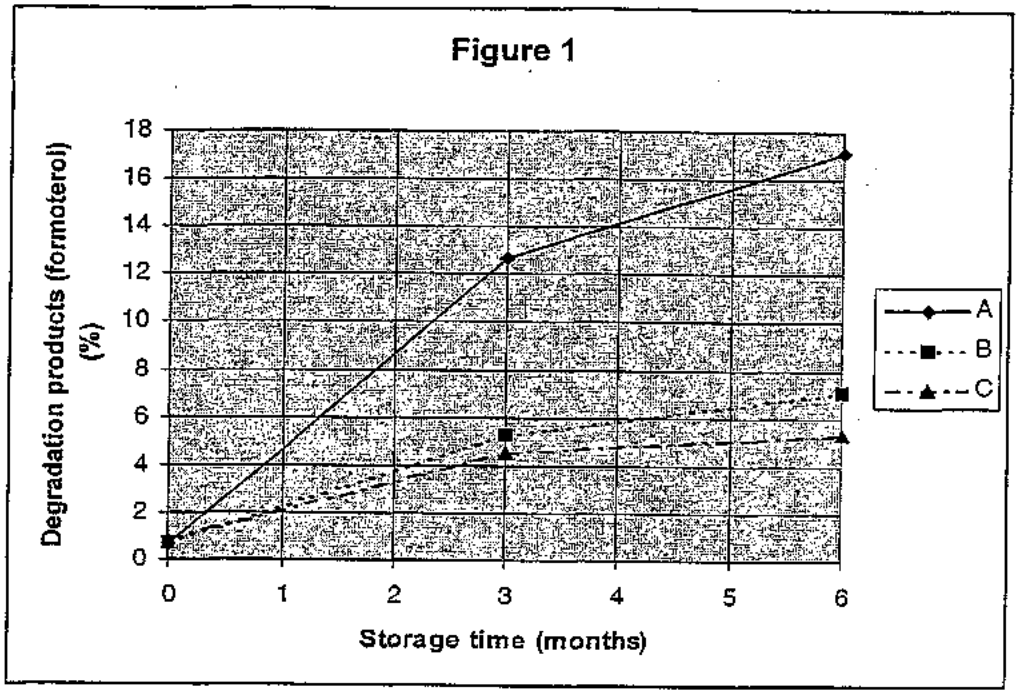
7. A pharmaceutical composition according to any one of claims 1 to 6 in which the particle size of the active ingredients is less than about 10 μm.

8. A pharmaceutical composition according to any one of claims 1 to 7 for use for the treatment or prophylaxis of a respiratory disorder.

9. A pharmaceutical composition according to any one of claims 1 to 7 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

10. A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to any one of claims 1 to 7.

Stability data for formoterol / lactose vs formoterol / budesonide / lactose (open dishes)



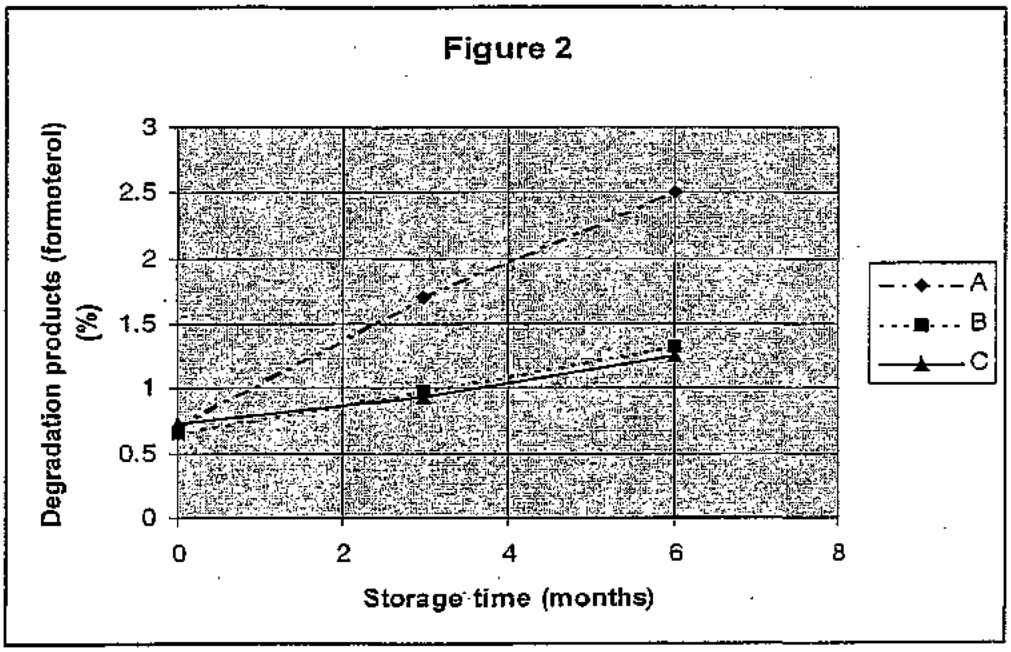
A= formoterol fumarate dihydrate (0.5%) / lactose monohydrate (99,5%) according to example 1

B= formoterol fumarate dihydrate (0.5%) / budesonide (9%) / lactose monohydrate (90.5%)

C= formoterol fumarate dihydrate (0.5%) / budesonide (18%) / lactose monohydrate (81.5%)

Stability data for formoterol / lactose vs formoterol / budesonide / lactose (Turbuhaler)

Figure 2

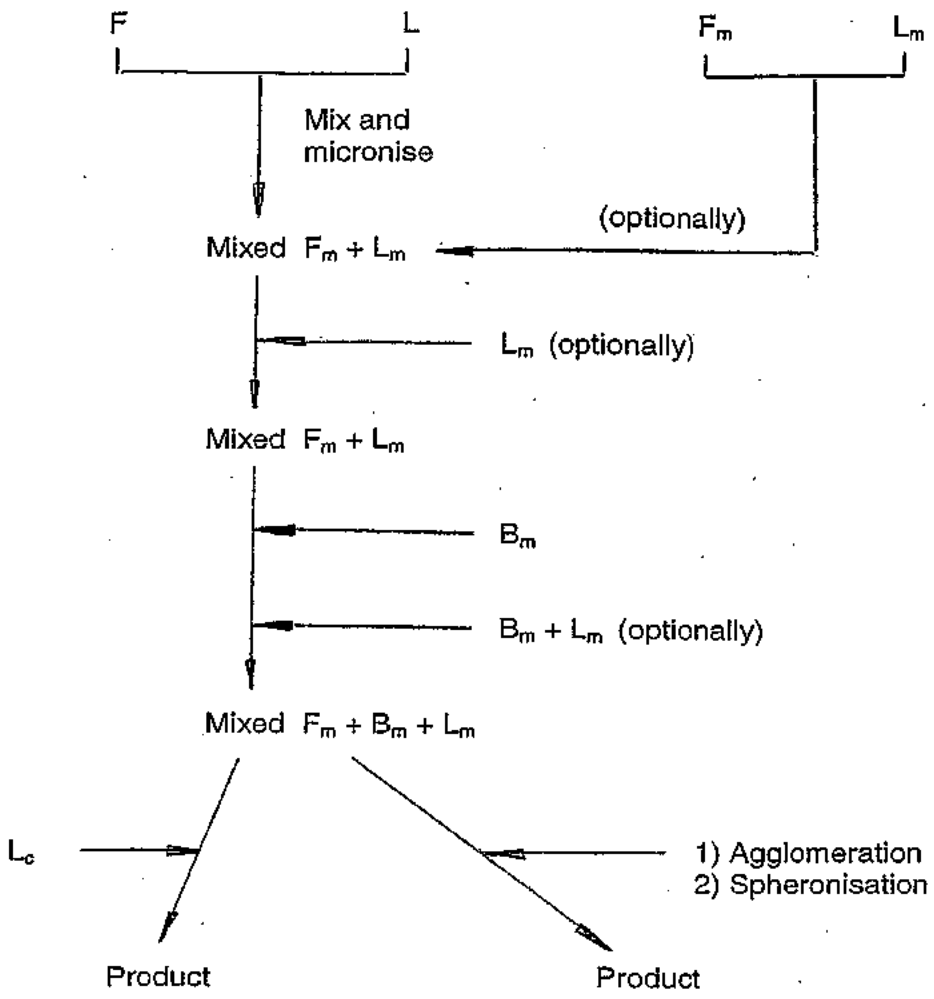


A= formoterol fumarate dihydrate (0.5%) / lactose monohydrate (99,5%); 4.5µg formoterol fumarate dihydrate / dose according to example 2.

B= formoterol fumarate dihydrate (0.5%) / budesonide (9%) / lactose monohydrate (90.5%); 4.5µg formoterol fumarate dihydrate / 80 µg budesonide/dose

C= formoterol fumarate dihydrate (0.5%) / budesonide (18%) / lactose monohydrate (81.5%); 4.5µg formoterol fumarate dihydrate / 160 µg budesonide/dose

Figure 3



L = carrier/diluent
F = formoterol
L_c = coarse particles of carrier/diluent
L_m = small particles of carrier/diluent produced by methods like micronisation, direct precipitation etc.
F_m = small particles of formoterol produced by methods like micronisation, direct precipitation etc.
B_m = small particles of glucocorticosteroid produced by methods like micronisation, direct precipitation etc.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01118

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/72, A61K 31/165, A61K 31/58, A61P 11/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6030604 A (JAN TROFAST), 29 February 2000 (29.02.00), the claims and column 3, lines 27-30 --	1-10
A	US 5795564 A (GUNNAR ABERG ET AL), 18 August 1998 (18.08.98) --	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2001	04 -10- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01118

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01118

Claim 10 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6030604 A	29/02/00	AU 731192 B	29/03/01
		AU 5785998 A	07/08/98
		BR 9811249 A	05/09/00
		CZ 9902557 A	13/10/99
		EE 9900295 A	15/02/00
		EP 1007017 A	14/06/00
		EP 1012576 A	28/06/00
		HU 0000714 A	28/08/00
		IL 130838 D	00/00/00
		JP 2000506967 T	06/06/00
		JP 2001508793 T	03/07/01
		NO 993539 A	20/09/99
		PL 334527 A	28/02/00
		SE 9700135 D	00/00/00
		SK 95999 A	18/01/00
		TR 9901690 T	00/00/00
		US 6147750 A	14/11/00
		WO 9831352 A	23/07/98
		ZA 9800078 A	20/07/98
		US 5980949 A	09/11/99
		US 5983956 A	16/11/99
US 5795564 A	18/08/98	US 6068833 A	30/05/00

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Janis K. Fraser/Kristi Holmlund
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**810**

Electronic Acknowledgement Receipt

EFS ID:	6439384
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	COMPOSITION FOR INHALATION
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Denise Siede
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	12-NOV-2009
Filing Date:	27-JUL-2004
Time Stamp:	12:30:23
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$810
RAM confirmation Number	15281
Deposit Account	061050
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Request for Continued Examination (RCE)	06275rce.pdf	75472 b480604554b7586124b9ddd22af6dea911c34a0c	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Amendment Submitted/Entered with Filing of CPA/RCE	06275amend.pdf	273808 439061146f61ed1bd1a126c1f892ee6029f6548e4	no	9
Warnings:					
Information:					
3		06275ids.pdf	96758 5c8af9c6b5ca6441718768641f928cf5d119ad8	yes	2
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	1	
	Information Disclosure Statement (IDS) Filed (SB/08)		2	2	
Warnings:					
Information:					
4	Foreign Reference	21887577.pdf	1398385 37ca318cb952b72d62f0862394576dea21efa24	no	31
Warnings:					
Information:					
5	Foreign Reference	22299358.pdf	630592 7ee3b221ecbba1c2a16c3611a1dc2ba085680a01	no	18
Warnings:					
Information:					
6	Foreign Reference	22299128.pdf	794826 2277c92add2c45fac401f8d9f293cf213f6f6d69	no	19
Warnings:					
Information:					
7	NPL Documents	22299911.pdf	150770 5e937f307103d632b27de945252c54378ddad310	no	8
Warnings:					
Information:					

8	NPL Documents	Povidone.pdf	319491 a0c434752188256524becd68e7d2059cd15e21aa6	no	3
Warnings:					
Information:					
9	NPL Documents	Wyser.pdf	489836 e3985aacaef028f8abb706c2b1b6be3b787a2ec0	no	6
Warnings:					
Information:					
10	Fee Worksheet (PTO-875)	fee-info.pdf	30191 7424c7672627d77b19c3b95ea8e1fcfb08d9e5b7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4260129		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/502,685	Filing Date 07/27/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/12/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 15	Minus	** 41	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***8	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DORIS m. BURNS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

26164 7590 09/09/2009

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 09/09/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

TITLE OF INVENTION: COMPOSITION FOR INHALATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	12/09/2009

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26164 7590 09/09/2009

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P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

TITLE OF INVENTION: COMPOSITION FOR INHALATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	12/09/2009

EXAMINER	ART UNIT	CLASS-SUBCLASS
PRYOR, ALTON NATHANIEL	1616	514-167000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address Form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 09/09/2009

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 09/09/2009

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	ALTON N. PRYOR	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/24/09*.

2. ☒ The allowed claim(s) is/are *25,30-35,45-52(claims renumbered 1-15)*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

The following is an examiner's statement of reasons for allowance: The results provided in the specification on pages 7-9 for the stability of the instant composition overcomes any obviousness type rejection that could have been deduced from US 20030018019, US 6309623, WO 93/05765 and/or WO 93/11773. The claimed invention is specific to chemical components and the amounts thereof.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALTON N. PRYOR whose telephone number is (571)272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 7568

SERIAL NUMBER	FILING or 371(c) DATE / RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/502,685	07/27/2004	424	1616	06275-410US1

APPLICANTS
Nayna Govind, Loughborough, UNITED KINGDOM;
Maria Marlow, Loughborough, UNITED KINGDOM;

**** CONTINUING DATA ***************************
This application is a 371 of PCT/SE03/00156 01/29/2003

**** FOREIGN APPLICATIONS ***************************
SWEDEN 0200312-7 02/01/2002

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/ALTON NATHANIEL PRYOR/ Examiner's Signature	☐ Initials	UNITED KINGDOM	16	12	1

ADDRESS

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022
UNITED STATES

TITLE

Composition for inhalation

FILING FEE RECEIVED	FEES: Authority has been given in Paper
3400	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:

- ☐ All Fees
- ☐ 1.16 Fees (Filing)
- ☐ 1.17 Fees (Processing Ext. of time)
- ☐ 1.18 Fees (Issue)
- ☐ Other _____
- ☐ Credit

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	**Art Unit**
	ALTON N PRYOR	1616

ORIGINAL		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED									
514	167	A	0	1	N	45 / 00 (2006.0)										
CROSS REFERENCE(S)		A	6	1	K	31 / 335 (2006.01.01)										
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
514	463															

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17	5	33	8	49								
	2		18	6	34	9	50								
	3		19	7	35	10	51								
	4		20		36	11	52								
	5		21		37										
	6		22		38										
	7		23		39										
	8		24		40										
	9	1	25		41										
	10		26		42										
	11		27		43										
	12		28		44										
	13		29	12	45										
	14	2	30	13	46										
	15	3	31	14	47										
	16	4	32	15	48										

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 15	
/ALTON N PRYOR/ Primary Examiner.Art Unit 1616 8/26/09 (Primary Examiner) (Date)	O.G. Print Claim(s) none	O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
each inventor	7/31/08	anp
Consulted with A. Marschel: decided 103 rejection should be reinstated and 112 written description should be entered	1/16/08	anp
Allowability Conference with Dr. Ardin Marscel and Sreeni Marschel - Decision was to allow the application.	8/20/09	anp

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
514	165, 463	8/25/09	anp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind et al.	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT

Please amend the above-identified application as follows:

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: August 21, 2009

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1 – 24 (Canceled)

25. (Currently amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA227), PVP K25 (polyvinyl pyrrolidone with an approximate molecular weight of 30,000)~~polyvinylpyrrolidone (PVP)~~, and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

26 -29 (Canceled)

30. (Currently amended) A pharmaceutical composition according to claim 25, in which the formoterol fumarate dihydrate is ~~in the form of~~ the R, R-enantiomer.

31. (Currently amended) A pharmaceutical composition according to claim 25, in which the budesonide is ~~in the form of~~ the 22R-epimer.

32. (Currently amended) A method of treating [[the]] symptoms of a respiratory disorder, comprising administering to a patient [[a]] the pharmaceutical composition according to claim 25, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

33. (Previously presented) The method of claim 32, wherein the respiratory disorder is asthma.

34. (Previously presented) The method of claim 32, wherein the respiratory disorder is rhinitis.

35. (Previously presented) The method of claim 32, wherein the respiratory disorder is COPD.

36 – 44 (Canceled)

45. (Currently amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25 , and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 1 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

46. (Currently amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

47. (Currently amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a

concentration of 4 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

48. (Currently amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

49. (Previously presented) The method of claim 32, wherein the concentration of budesonide is 1 mg/ml.

50. (Previously presented) The method of claim 32, wherein the concentration of budesonide is 2 mg/ml.

51. (Previously presented) The method of claim 32, wherein the concentration of budesonide is 4 mg/ml.

52. (Previously presented) The method of claim 32, wherein the concentration of budesonide is 8 mg/ml.

REMARKS

Applicants thank the Examiner for telephoning Applicants' undersigned representative on August 18 and 20, 2009, respectively, to propose the amendments reflected above. Applicants agreed to file the amendments as this Supplementary Amendment. Upon entry of the amendment, claims 25, 30-35, and 45-52 will be pending, claim 27 having been newly canceled. Applicants reserve the right to pursue claims with broader scope in a continuation application. Independent claims 25 and 45-48 are amended to incorporate the limitation of claim 27 (now canceled). Claims 30-32 are amended in accordance with suggestions from the Examiner; these amendments to claims 30-32 do not affect their scope. Applicants understand that this amendment puts all of the claims in condition for allowance, and such action is requested.

It is believed that no fees are due. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: August 21, 2009

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer Number 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22253108.doc

Electronic Acknowledgement Receipt

EFS ID:	5929995
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	21-AUG-2009
Filing Date:	27-JUL-2004
Time Stamp:	11:36:07
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		response410US1.pdf	83666 96cd393256033dea88c461e11a73db607de114d6	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	5
Warnings:			
Information:			
	Total Files Size (in bytes):	83666	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/502,685	07/27/2004	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 08/21/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 15	Minus	** 41	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 5	Minus	***8	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KENDALL E. JONES/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind et al.	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN REPLY TO ACTION OF JANUARY 27, 2009

Please amend the above-identified application as follows:

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: May 26, 2009

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1 – 24 (Canceled)

25. (Currently amended) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA227), polyvinylpyrrolidone (PVP), and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w. ~~HFA227, PVP, and PEG, wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w, and the budesonide is present at a concentration of 4 mg/ml.~~

26. (Canceled)

27. (Currently amended) A pharmaceutical composition according to claim 25, in which the PVP is PVP K25 (PVP with an approximate molecular weight of 30,000).

28 – 29 (Canceled)

30. (Previously presented) A pharmaceutical composition according to claim 25, in which the formoterol fumarate dihydrate is in the form of the R, R-enantiomer.

31. (Previously presented) A pharmaceutical composition according to claim 25, in which the budesonide is in the form of the 22R-epimer.

32. (Previously presented) A method of treating the symptoms of a respiratory disorder, comprising administering to a patient a pharmaceutical composition according to claim 25, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

33. (Previously presented) The method of claim 32, wherein the respiratory disorder is asthma.

34. (Previously presented) The method of claim 32, wherein the respiratory disorder is rhinitis.

35. (Previously presented) The method of claim 32, wherein the respiratory disorder is COPD.

36 – 44 (Canceled)

45. (New) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 1 mg/ml, the PVP is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

46. (New) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the

PVP is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

47. (New) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 4 mg/ml, the PVP is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

48. (New) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 8 mg/ml, the PVP is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

49. (New) The method of claim 32, wherein the concentration of budesonide is 1 mg/ml.

50. (New) The method of claim 32, wherein the concentration of budesonide is 2 mg/ml.

51. (New) The method of claim 32, wherein the concentration of budesonide is 4 mg/ml.

52. (New) The method of claim 32, wherein the concentration of budesonide is 8 mg/ml.

REMARKS

I. Claim Status:

Upon entry of the above amendments, claims 25, 27, 30-35, and 45-52 will be pending in the application. Claims 25 and 27 have been amended. Claims 45-52 are new. Claims 1-3, 5-9, 12-24, 26, 28-29, and 36-44 have been newly canceled. Claims 4 and 10-11 were canceled previously.

Claim 25 has been amended to a) limit PEG to PEG-1000 (supported at page 4, line 16 of the specification); b) spell out the full chemical names of HFA227, PVP, and PEG (supported in the specification at page 1, line 24; in previously entered claim 1; and in Exhibits A-C of the communication filed on April 30, 2008); and c) limit the concentrations of formoterol fumarate dihydrate, PVP, and PEG-1000, while expressing the concentration of budesonide as a range instead of a single concentration (supported in the specification at page 5, lines 15-20, as well as in previously entered claims 40 and 29). Claim 27 has been amended to include a description of the term "PVP K25." Support for this amendment can be found in previously entered claim 3.

Support for new claims 45-52 can be found throughout the specification, especially at page 5, lines 18-20, and and the tables on pages 6 and 8.

No new matter has been added through these amendments.

II. Claim Rejection under 35 U.S.C. §112, First Paragraph (Written Description):

Claims 1-3, 5-9, and 12-24 remain rejected for allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph. According to the Office: "[n]o description of solvate salt of formoterol [is] provided in the specification" (Office Action, page 2). Applicants do not concede that the claims lack written description for this or any other reason, and in fact point out that formoterol fumarate dihydrate (a solvate of a salt of formoterol) is disclosed in numerous places in the specification (e.g., at page 5, lines 14-18). However, solely in the interest of furthering prosecution, Applicants have canceled claims 1-3, 5-9, and 12-24, rendering the rejection of these claims moot. The remaining claims, all of which recite formoterol fumarate dihydrate in particular, were not rejected for lack of written description.

III. Claim Rejection under 35 U.S.C. §112, First Paragraph (Enablement):

Claims 1-3, 5-9, and 12-24 remain rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. According to the Office: "the specification, while being enabled for compositions comprising components formoterol fumarate d[i]hydrate, does not reasonably provide enablement for compositions comprising solvates and salts of formoterol." (Office Action, page 3). Applicants do not concede that the claims are not enabled for the reason of record or any other reason. However, solely in the interest of furthering prosecution, Applicants have canceled claims 1-3, 5-9, and 12-24, rendering the rejection of these claims moot. The remaining claims recite formoterol fumarate dihydrate; the enablement of this claim element has been acknowledged by the Office (*vide supra*).

IV. Claim Rejection under 35 U.S.C. §103(a):

Claims 1-3, 5-9, and 12-44 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over U.S. Patent App. Pub. No. 2003/0018019 to Meade et al. ("Meade") and U.S. Patent No. 6,309,623 to Weers ("Weers"). Claims 1-3, 5-9, and 12-24, 26, 28-29, and 36-44 have been canceled, making the rejection moot with respect to these claims. As to the remaining claims, Applicants respectfully traverse the rejection in light of the above amendments and for the reasons provided below.

In response to the Office Action of January 29, 2007, Applicants submitted (on August 21, 2007) amendments, arguments, and a declaration under 37 C.F.R. §1.132 from the inventor with supplemental data. Despite this, the Office has maintained the rejection under 35 U.S.C. §103(a).

According to the Office Action (at page 8):

> "With respect to the experimental results provided by the Applicants, the claims are much broader than what are being interpreted as unexpected results. Since dispersion results are concentration dependent as well as shown in the specification, the claims would overcome the 103 rejection to the extent of the unexpected data provided by the Applicants." (emphasis added)

The Office Action at page 8 provides a list of four aspects of the claims considered by the Office to be broader in scope than the unexpected results provided by the Applicants. Applicants' remarks on the four aspects follow:

1) The Office Action alleges that "formoterol fumarate dehydrate" is used in all formulations, whereas the claims recite "formoterol or a salt thereof, or a solvate of a salt thereof." The claims as presently amended all recite "formoterol fumarate dihydrate."

2) The Office Action alleges that "the specification at page 5 states that only 0.001 % PVP is used in all formulations." Applicants respectfully disagree. The description on page 5 to which the Office Action refers is of a formulation used for an "initial evaluation" (see page 5, line 11). As is clear from the experiments described on pages 6-12 and in Figures 2-6, several different PVP concentrations were used in further evaluations. Nevertheless, the issue is moot in light of the current amendments.

3) The Office Action alleges that a) PEG-1000 is used in all formulations, whereas the claims recite PEG broadly; and b) PEG 1000 is used only at 0.1 % w/w or 0.3% w/w in all of the formulations, whereas the claims do not recite the amount of PEG used. While not conceding that these observations are pertinent to the issue of whether the claims are commensurate in scope to the unexpected results, Applicants have, in the interest of obtaining allowance, incorporated both of the above limitations into the claims.

4) The Office Action points out that the formulations disclosed in the specification at page 5 utilized 0.09 mg/ml formoterol fumarate dihydrate. Applicants do not agree that this observation has any relevance to the issue of whether the claims are commensurate in scope to the unexpected results. However, to facilitate rapid allowance of the claims, Applicants have amended the claims to specify the concentration of formoterol fumarate dihydrate.

In view of the foregoing, Applicants submit that the issues raised in the Office Action have been fully met, and respectfully request that the rejection of the claims under 35 U.S.C. §103(a) be reconsidered and withdrawn.

The fee in the amount of $130.00 for Petition for One Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-0410US1.

Respectfully submitted,

Date: May 26, 2009

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No.: 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22173674.doc

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	5391168
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	26-MAY-2009
Filing Date:	27-JUL-2004
Time Stamp:	11:27:07
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	7872
Deposit Account	061050
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		response410us1.pdf	303671 9fcd67d5545164294810427b1dfdf09e5b2832b8	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30016 cadab1166806ee36638e1c7b65d94b6265974f3f	no	2

Warnings:

Information:

Total Files Size (in bytes):	333687

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☒ To be Mailed
10/502,685	07/27/2004	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 05/26/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 16	Minus	** 41	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 5	Minus	***8	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GOIGA N. DUCKETT/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 01/27/2009

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	**PAPER NUMBER**
1616	

NOTIFICATION DATE	DELIVERY MODE
01/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	ALTON N. PRYOR	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 12-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9,12-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection. Previous rejections not addressed below have been withdrawn.

Claims are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. No description of solvate salt of formoterol provided in the specification.

Determination of Claim Scope

Claims 1-3,5-9,12-24 of the instant application claim a pharmaceutical composition comprising formoterol or salt thereof or a solvate of a salt thereof in claim 1 of the instant application.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates of a salt of formoterol Applicants are referring. Applicants' specification does not disclose how to make any particular solvate of a salt of formoterol nor do Applicants depict chemical structures of formoterol as any particular solvate of a salt in their disclosure.

Possession Based on Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the formation of a particular solvate of a salt for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 18), therefore, the generic reference to a solvate of a salt of formoterol in the instant specification does not provide adequate written support for claims drawn to any solvate of a salt of this compound. An ordinary skilled artisan would conclude that Applicants were not in possession of any particular solvate of a salt of any of the compounds of corresponding to formoterol of the claimed composition. Furthermore, because Applicants' generic reference to solvate of a salt of formoterol does not permit the ordinary skilled artisan to clearly envisage what specific formoterol were in Applicants' possession, the only reasonable conclusion said artisan would make was that Applicants were not in possession of solvate of a salt of formoterol and had not reduced to practice the preparation, isolation, and characterization of said solvates.

The remaining claims are rejected as depending from a rejected claim.

Claims 1-3,5-9,12-24 **are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising components formoterol fumarate dehydrate, does not reasonably provide enablement for compositions comprising solvates of salts of formoterol.** The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the subgenera of formoterol solvates.

Nature of the invention/State of the Prior Art

Claims 1-3,5-9,12-44 of the instant application which claim a pharmaceutical composition comprising budesonide, HFA 227, PVP, PEG and formoterol or a salt

thereof or a solvate of a salt thereof is representative of the nature of Applicants' invention. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 18).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and pseudopolymorphs (e.g. hydrates and solvates) of chemical compounds, as set forth above by the teachings of Vippagunta et al.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvate of a salt of formoterol.

In conclusion, the specification, while being enabling for compositions comprising budesonide, HFA 227, PVP, PEG and formoterol fumarate dihydrate, does not reasonably provide enablement for compositions comprising solvate of salt of formoterol.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3,5-9,12-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al (US 20030018019; 1/23/03) and Weers et al (US 6309623; 10/30/01). Meade teaches a pharmaceutical composition comprising anticholinergics, corticosteroids including budesonide, and betamimetics including formoterol. See abstract, paragraphs 3-5,16. Meade teaches that the formoterol can exist in the form of formoterol fumarate and as the enantiomeric salt of R,R stereoisomer. See paragraphs 9-12. Meade teaches that budesonide can be present in the form its enantiomers, mixture of enantiomers, or in the form of racemates. See paragraph 20. Meade teaches that propellant gas such as HFA 227, co-solvent such as polyethylene glycol (PEG), and surfactants such as polyvinylpyrrolidone (PVP) can be added the composition. See paragraphs 14 and 50. Meade teaches that the pharmaceutical composition is used to treat diseases of the respiratory tract such as asthma and chronic obstructive pulmonary disease (COPD). See paragraph 18. Meade does not teach 1) an exemplified a pharmaceutical composition comprising budesonide (also 22R epimer), formoterol, HFA227, PEG, and PVP and administering the composition to a patient having a respiratory disorder; 2) the instant types of PEG such as PEG 1000 and PVP such as PVP K25, 3) the instant amounts of PVP and PEG. Weers teaches that drugs such as budesonide and formoterol are administered to patients for the treatment of

respiratory disorders. See column 19 lines 30-67, claims 72,74,87. It would have been obvious to one having ordinary skill in the art to have modified the invention of Meade to additionally administer the pharmaceutical composition to a patient for the treatment of respiratory disease. One would have been motivated to do this since Weers teaches that drugs such as budesonide and formoterol are administered to said patients for treatment of respiratory disorders. An artisan would have been expected to arrive at the instant composition comprising budesonide, formoterol, HFA227, PEG, and PVP since the composition is suggested by Weers and would have been expected to function effectively in the treatment of respiratory disorders. Also note that it would have been obvious to employ the 22R epimer of budesonide since Meade teaches that budesonide can be present in the form its enantiomers, mixture of enantiomers, or in the form of racemates (which includes the 22R epimer) of budesonide. It would have been obvious to an artisan to employ PEG-1000 and PVP K25 at the time of the prior art invention in place of PEG and PVP. One would have been motivated to do this with an expectation of success because PEG-1000 is structurally similar to PEG and PVP 25K is structurally similar to PVP 25K. Note, in the absence of unexpected results structurally similar compounds belonging to the same family are expected to possess similar chemical and physical properties, and thus yield similar results. With respect to the instant amounts of PEG (0.05 - 0.35 % w/w) and PVP (0.0005 – 0.5% w/w), one would have been expected to determine the optimum amount of PVP and PEG (which may have fallen within the instant range). One would have been motivated to do this because optimum

amounts of excipients (solvents, surfactants, etc.) enhance the effectiveness / delivery of the active ingredients.

With respect to the experimental results provided by the Applicants, the claims are much broader than what are being interpreted as unexpected results. Since dispersion results are concentration dependent as well as shown in the specification, the claims would overcome the 103 rejection to the extent of the unexpected data provided by the Applicants.

Below are aspects of the claims that are far broader in scope than the results provided by the Applicants:

1) The claims recite "formoterol or a salt thereof, or a solvate of a salt thereof" . However, the specification at page 5 recites that "formoterol fumarate dehydrate" is used in all formulations. The claim are not commensurate in scope with the unexpected results.

2) The claims recite that PVP is used in the concentration range of 0.001% to 0.01% w/w when the budesonide is present at 4 mg/ml and 8 mg/ml, 0.0001% to 0.001% w/w when the budesonide is present at 1 mg/ml. The concentration of PVP used is 0.001 % w/w when the budesonide is present at 2 mg/ml. However, the specification at page 5 states that only 0.001% PVP is used in all formulations. The claim is not commensurate in scope with the unexpected results.

3) Many of the claims recite PEG broadly. However, the specification at page 5 states the use of PEG-1000 in all formulations. The PEG 1000 is only used at 0.1% w/w or 0.3% w/w in all of the formulations. On the other hand, many of the claims do not

recite the amount of PEG 1000 actually used. The claims are not commensurate in scope with the unexpected results.

4) Many of the claims recite the use of formoterol fumarate dihydrate without specifying an amount. However, the specification at page 5 states the use of 0.09 % w/w formoterol fumarate dehydrate in all formulations. The claims are not commensurate in scope with the unexpected results.

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alton N. Pryor whose telephone number is 571-272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/31/2008	01/16/2009							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	-	-							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	-	-							
	11	-	-							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							
	15	✓	✓							
	16	✓	✓							
	17	✓	✓							
	18	✓	✓							
	19	✓	✓							
	20	✓	✓							
	21	✓	✓							
	22	✓	✓							
	23	✓	✓							
	24	✓	✓							
	25		✓							
	26		✓							
	27		✓							
	28		✓							
	29		✓							
	30		✓							
	31		✓							
	32		✓							
	33		✓							
	34		✓							
	35		✓							
	36		✓							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/31/2008	01/16/2009							
	37		✓							
	38		✓							
	39		✓							
	40		✓							
	41		✓							
	42		✓							
	43		✓							
	44		✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
each inventor	7/31/08	anp
Consulted with A. Marschel: decided 103 rejection should be reinstated and 112 written description should be entered	1/16/08	anp

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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Bib Data Sheet

CONFIRMATION NO. 7568

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/502,685	07/27/2004 RULE	424	1616	06275-410US1

APPLICANTS

Nayna Govind, Loughborough, UNITED KINGDOM;
Maria Marlow, Loughborough, UNITED KINGDOM;

** **CONTINUING DATA** **********

This application is a 371 of PCT/SE03/00156 01/29/2003

** **FOREIGN APPLICATIONS** **********

SWEDEN 0200312-7 02/01/2002

Foreign Priority claimed	STATE OR	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged Examiner's Signature Initials	UNITED KINGDOM	16	12	1

ADDRESS

26164

TITLE

Composition for inhalation

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
1080	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind et al.	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN REPLY TO ACTION OF AUGUST 1, 2008

Please amend the above-identified application as follows:

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: October 31, 2008

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A pharmaceutical composition comprising formoterol or a salt ~~or solvate~~ thereof, or a solvate of a salt thereof; budesonide; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG), wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w and the budesonide is present at a concentration of 4 mg/ml.

2. (Previously presented) A pharmaceutical composition according to claim 1 wherein the PEG is present at a concentration from about 0.05 to about 0.35% w/w.

3. (Previously presented) A pharmaceutical composition according to claim 1 in which the PVP is PVP K25 (PVP with an approximate molecular weight of 30,000).

4. (Canceled)

5. (Previously presented) A pharmaceutical composition according to claim 1 in which the PEG is PEG 1000 (PEG with an average molecular weight of 1000).

6. (Previously presented) A pharmaceutical composition according to claim 1 in which the PEG is present at a concentration of 0.3% w/w.

7. (Currently amended) A pharmaceutical composition according to claim 1 in which formoterol is in the form of ~~its fumarate dihydrate~~ a salt.

8. (Currently amended) A pharmaceutical composition according to claim 1 in which the formoterol or salt ~~or solvate~~ thereof, or solvate of a salt, is in the form of the R, R-enantiomer.

9. (Previously presented) A pharmaceutical composition according to claim 1 in which the budesonide is in the form of the 22R-epimer.

10-11. (Canceled)

12. (Previously presented) A method of treating the symptoms of a respiratory disorder, comprising administering to a patient a pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

13. (Previously presented) The method of claim 12, wherein the respiratory disorder is asthma.

14. (Previously presented) The method of claim 12, wherein the respiratory disorder is rhinitis.

15. (Previously presented) The method of claim 12, wherein the respiratory disorder is COPD.

16. (Currently amended) A pharmaceutical composition comprising formoterol, or a salt ~~or solvate~~ thereof, or a solvate of a salt thereof; budesonide; HFA227; PVP; and PEG, wherein the PVP is present at a concentration of 0.001% w/w and the budesonide is present at a concentration of 2 mg/ml.

17. (Currently amended) A pharmaceutical composition comprising formoterol, or a salt ~~or solvate~~ thereof, or a solvate of a salt thereof; budesonide; HFA227; PVP; and PEG, wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w and the budesonide is present at a concentration of 8 mg/ml.

18. (Currently amended) A pharmaceutical composition comprising formoterol, or a salt ~~or solvate~~ thereof, or a solvate of a salt thereof; budesonide; HFA227; PVP; and PEG, wherein the PVP is present at a concentration of 0.0001% to 0.001% w/w and the budesonide is present at a concentration of 1 mg/ml.

19. (Previously presented) The pharmaceutical composition of claim 1, wherein the concentration of PVP is 0.001% or 0.01% w/w.

20. (Previously presented) The pharmaceutical composition of claim 1, wherein the concentration of PVP is 0.001% w/w.

21. (Previously presented) The pharmaceutical composition of claim 17, wherein the concentration of PVP is 0.001% or 0.01% w/w.

22. (Previously presented) The pharmaceutical composition of claim 17, wherein the concentration of PVP is 0.001% w/w.

23. (Previously presented) The pharmaceutical composition of claim 18, wherein the concentration of PVP is 0.0001%, 0.0005%, or 0.001% w/w.

24. (Previously presented) The pharmaceutical composition of claim 18, wherein the concentration of PVP is 0.001% w/w.

25. (new) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG, wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w, and the budesonide is present at a concentration of 4 mg/ml.

26. (new) A pharmaceutical composition according to claim 25, wherein the PEG is present at a concentration from about 0.05 to about 0.35% w/w.

27. (new) A pharmaceutical composition according to claim 25, in which the PVP is PVP K25.

28. (new) A pharmaceutical composition according to claim 25, in which the PEG is PEG 1000.

29. (new) A pharmaceutical composition according to claim 25, in which the PEG is present at a concentration of 0.3% w/w.

30. (new) A pharmaceutical composition according to claim 25, in which the formoterol fumarate dihydrate is in the form of the R, R-enantiomer.

31. (new) A pharmaceutical composition according to claim 25, in which the budesonide is in the form of the 22R-epimer.

32. (new) A method of treating the symptoms of a respiratory disorder, comprising administering to a patient a pharmaceutical composition according to claim 25, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

33. (new) The method of claim 32, wherein the respiratory disorder is asthma.

34. (new) The method of claim 32, wherein the respiratory disorder is rhinitis.

35. (new) The method of claim 32, wherein the respiratory disorder is COPD.

36. (new) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG, wherein the PVP is present at a concentration of 0.001% w/w, and the budesonide is present at a concentration of 2 mg/ml.

37. (new) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG, wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w, and the budesonide is present at a concentration of 8 mg/ml.

38. (new) A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP, and PEG, wherein the PVP is present at a concentration of 0.0001% to 0.001% w/w, and the budesonide is present at a concentration of 1 mg/ml.

39. (new) The pharmaceutical composition of claim 25, wherein the concentration of PVP is 0.001% or 0.01% w/w.

40. (new) The pharmaceutical composition of claim 25, wherein the concentration of PVP is 0.001% w/w.

41. (new) The pharmaceutical composition of claim 37, wherein the concentration of PVP is 0.001% or 0.01% w/w.

42. (new) The pharmaceutical composition of claim 37, wherein the concentration of PVP is 0.001% w/w.

43. (new) The pharmaceutical composition of claim 38, wherein the concentration of PVP is 0.0001%, 0.0005%, or 0.001% w/w.

44. (new) The pharmaceutical composition of claim 38, wherein the concentration of PVP is 0.001% w/w.

REMARKS

Upon entry of the above amendment, claims 1 - 3, 5 - 9, and 12 - 44 will be pending, claims 25 - 44 having been newly added. The amendments to claims 1, 7, 8, 16, 17, and 18 are supported in the specification at page 2, lines 7 - 15. New claims 25 - 44 are supported by claims 1 -3, 5 - 9 and 12 - 24, respectfully, and by the specification at, e.g., page 2, lines 7 - 9. No new matter has been added.

Applicants note with appreciation that all previous rejections have been withdrawn. Claims 1 - 3, 5 - 9, and 12 - 24 were newly rejected under 35 U.S.C. § 112, paragraph 1, for lack of written description and lack of enablement, based on the inclusion of solvates of formoterol in the claims.[1] Although Applicants disagree with the rejection, in an effort to move this application to allowance, Applicants have amended claims 1 - 3, 5, 6, 8, 9, and 12 - 24 to have a scope the Examiner indicates satisfies the written description and enablement requirements: where the formoterol ingredient is limited to formoterol or a salt thereof or a solvate of a salt. Claim 7 now recites that formoterol is in the form of a salt, so it also should be allowable. New claims 25 - 44 all specify a single disclosed species, formoterol fumarate dihydrate.

Applicants submit that all of the claims satisfy the written description and enablement requirements. Withdrawal of the rejections and prompt allowance is respectfully requested.

[1] Applicants point out claim 7 does not (and did not prior to amendment) encompass solvates of formoterol per se, so was apparently included in these rejections in error.

The $1920.00 for the required fee for excess claims is being paid on the electronic filing system by deposit account authorization. Apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: Oct. 31, 2008

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No.: 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22059052.doc

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1615	20	52	1040
Independent claims in excess of 3	1614	4	220	880
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1920**

Electronic Acknowledgement Receipt

EFS ID:	4212975
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	31-OCT-2008
Filing Date:	27-JUL-2004
Time Stamp:	13:51:16
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1920
RAM confirmation Number	18604
Deposit Account	061050
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		response410us1.pdf	254040 276b412e899d1f8905ee5466d55554684090da840	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	7	
	Applicant Arguments/Remarks Made in an Amendment		8	9	
Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	31481 62ee0297d63206f9cd4ba79b69f97aa606996d3b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	285521		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/502,685	Filing Date 07/27/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	10/31/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 41	Minus	** 21	= 20	X $ =		OR	X $52=	1040
	Independent (37 CFR 1.16(h))	* 8	Minus	***4	= 4	X $ =		OR	X $220=	880
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	1920

AMENDMENT		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/NICOLE LOVE-HENSLEY/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 08/01/2008

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
08/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	ALTON N. PRYOR	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 12-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9,12-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection. Previous rejections not addressed below have been withdrawn.

Claims are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Determination of Claim Scope

Claims 1-3,5-9,12-24 of the instant application claim a pharmaceutical composition comprising formoterol solvates in claim 1 of the instant application.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates of formoterol Applicants are referring. Applicants' specification does not disclose how to make any particular solvate or hydrate of formoterol nor do Applicants depict chemical structures of formoterol as any particular hydrate or solvate in their disclosure.

Possession Based on Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 18), therefore, the generic reference to a solvate of either formoterol in the instant specification does not provide adequate written support for claims drawn to any solvate or hydrate of this compound. An ordinary skilled artisan would conclude that Applicants were not in possession of any particular solvate or hydrate of any of the compounds of corresponding to formoterol of the claimed composition. Furthermore, because Applicants' generic reference to solvates or hydrates of formoterol does not permit the ordinary skilled artisan to clearly envisage what specific formoterol were in Applicants' possession, the only reasonable conclusion said artisan would make was that Applicants were not in possession of solvates and/or hydrates of formoterol and had not reduced to practice the preparation, isolation, and characterization of said solvates and hydrates.

The remaining claims are rejected as depending from a rejected claim.

Claims 1-3,5-9,12-24 **are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising components formoterol in the form of formoterol and formoterol solvate salts thereof, does not reasonably provide enablement for compositions comprising solvates or hydrates of formoterol.** The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the subgenera of formoterol solvates.

Nature of the invention/State of the Prior Art

Claims 1-3,5-9,12-24 of the instant application which claim a pharmaceutical composition comprising budesonide, HFA 227, PVP, PEG and formoterol or salt or

solvate thereof, or a solvate of a salt is representative of the nature of Applicants' invention. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 18).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and pseudopolymorphs (e.g. hydrates and solvates) of chemical compounds, as set forth above by the teachings of Vippagunta et al.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvate or hydrate of formoterol.

In conclusion, the specification, while being enabling for compositions comprising budesonide, HFA 227, PVP, PEG and formoterol or salt or a solvate of a salt, does not reasonably provide enablement for compositions comprising solvates or hydrates of any formoterol.

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALTON N. PRYOR whose telephone number is (571)272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616

Notice of References Cited	Application/Control No. 10/502,685	Applicant(s)/Patent Under Reexamination GOVIND ET AL.	
	Examiner ALTON N. PRYOR	Art Unit 1616	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Vippagunta et al. "Crystalline Solids," Advanced Drug Delivery Reviews, 2001, 48, pp 18.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/31/2008								
	1	✓								
	2	✓								
	3	✓								
	4	-								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	-								
	11	-								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
	17	✓								
	18	✓								
	19	✓								
	20	✓								
	21	✓								
	22	✓								
	23	✓								
	24	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10502685	GOVIND ET AL.
	Examiner	Art Unit
	ALTON N PRYOR	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
each inventor	7/31/08	anp

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind et al.	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN REPLY TO ACTION OF JANUARY 31, 2008

Please amend the above-identified application as follows:

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: April 30, 2008

Amendments to the Specification:

Replace the paragraph beginning at page 1, line 27 with the following amended paragraph:

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227 (1,1,1,2,3,3,3-heptafluoropropane), PVP and PEG characterized in that the PVP is present from about 0.0005 to about 0.03 %_w/w and the PEG is present from about 0.05 to about 0.35% w/w.

Replace the paragraph beginning at page 1, line 32 with the following amended paragraph:

Preferably the PVP is present in an amount of 0.001% w/w. Preferably the PVP is PVP K25 (PVP having an approximate molecular weight of 30,000).

Replace the paragraph beginning at page 1, line 35 with the following amended paragraph:

Preferably the PEG is present in an amount of 0.3% w/w. Preferably the PEG is PEG 1000 (PEG having an average molecular weight of 1000 Daltons).

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A pharmaceutical composition comprising formoterol or a salt or solvate thereof, or a solvate of a salt; budesonide; 1,1,1,2,3,3,3-heptafluoropropane (HFA 227)~~HFA 227~~; polyvinylpyrrolidone (PVP)~~PVP~~ and polyethylene glycol (PEG)~~PEG~~, wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w and the budesonide is present at a concentration of 4 mg/ml.

2. (Previously presented) A pharmaceutical composition according to claim 1 wherein the PEG is present at a concentration from about 0.05 to about 0.35% w/w.

3. (Currently amended) A pharmaceutical composition according to claim 1 in which the PVP is PVP K25 (PVP with an approximate molecular weight of 30,000).

4. (Canceled)

5. (Currently amended) A pharmaceutical composition according to claim 1 in which the PEG is PEG 1000 (PEG with an average molecular weight of 1000).

6. (Previously presented) A pharmaceutical composition according to claim 1 in which the PEG is present at a concentration of 0.3% w/w.

7. (Previously presented) A pharmaceutical composition according to claim 1 in which formoterol is in the form of its fumarate dihydrate salt.

8. (Previously presented) A pharmaceutical composition according to claim 1 in which the formoterol or salt or solvate thereof, or solvate of a salt, is in the form of the R, R-enantiomer.

9. (Previously presented) A pharmaceutical composition according to claim 1 in which the budesonide is in the form of the 22R-epimer.

10-11. (Canceled)

12. (Previously presented) A method of treating the symptoms of a respiratory disorder, comprising administering to a patient a pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

13. (Previously presented) The method of claim 12, wherein the respiratory disorder is asthma.

14. (Previously presented) The method of claim 12, wherein the respiratory disorder is rhinitis.

15. (Previously presented) The method of claim 12, wherein the respiratory disorder is COPD.

16. (Previously presented) A pharmaceutical composition comprising formoterol, or a salt or solvate thereof, or a solvate of a salt; budesonide; HFA 227; PVP; and PEG, wherein the

PVP is present at a concentration of 0.001% w/w and the budesonide is present at a concentration of 2 mg/ml.

17. (Previously presented) A pharmaceutical composition comprising formoterol, or a salt or solvate thereof, or a solvate of a salt; budesonide; HFA 227; PVP; and PEG, wherein the PVP is present at a concentration of 0.001% w/w to 0.01% w/w and the budesonide is present at a concentration of 8 mg/ml.

18. (Previously presented) A pharmaceutical composition comprising formoterol, or a salt or solvate thereof, or a solvate of a salt; budesonide; HFA 227; PVP; and PEG, wherein the PVP is present at a concentration of 0.0001% to 0.001% w/w and the budesonide is present at a concentration of 1 mg/ml.

19. (Previously presented) The pharmaceutical composition of claim 1, wherein the concentration of PVP is 0.001% or 0.01% w/w.

20. (Previously presented) The pharmaceutical composition of claim 1, wherein the concentration of PVP is 0.001% w/w.

21. (Previously presented) The pharmaceutical composition of claim 17, wherein the concentration of PVP is 0.001% or 0.01% w/w.

22. (Previously presented) The pharmaceutical composition of claim 17, wherein the concentration of PVP is 0.001% w/w.

23. (Previously presented) The pharmaceutical composition of claim 18, wherein the concentration of PVP is 0.0001%, 0.0005%, or 0.001% w/w.

24. (Previously presented) The pharmaceutical composition of claim 18, wherein the concentration of PVP is 0.001% w/w.

REMARKS

The specification has been amended at page 1 to define the terms HFA 227, PVP K25, and PEG 1000. These terms were in common use at the time of this application's filing (see the attached Exhibits A-C), and a person of ordinary skill would have understood their meaning. No new matter has been added.

Claims 1-3, 5-9, and 12-24 remain pending and under examination. Claims 4, 10, and 11 were cancelled previously. By way of this amendment, claim 1 has been amended to spell out the full names of HFA 227, PVP, and PEG. Support for these amendments can be found in the specification at page 1, lines 21-36, and in Exhibits A-C. In addition, descriptions of the terms "PVP K25" and PEG 1000" have been added to claims 3 and 5, respectively. No new matter has been added.

Applicants wish to thank Examiner Pryor for interviewing this case with applicants' representative on April 23, 2008 to discuss the rejections made in the pending Office Action. The present amendments and comments are in accordance with Examiner Pryor's suggestions.

35 U.S.C. § 112, second paragraph

The Office Action mailed January 31, 2008 (the "Office Action") rejected claims 1-3, 5-9, and 21-24 as allegedly indefinite because of the use of "abbreviations (PVP, HFA 227, PEG, etc.)" (Office Action at page 2). As requested by the Examiner, the claims have been amended to reflect the full names of the compounds. The specification at page 1, line 22, teaches that "PVP" stands for polyvinylpyrrolidone and that "PEG" stands for polyethylene glycol. As the Examiner noted during the interview on April 23, 2008, the terms "HFA 227", "PVP K25", and "PEG 1000" are well known in the art and were commonly used at the priority date. A person of ordinary skill would have been well aware that "HFA 227" referred to 1,1,1,2,3,3,3-heptafluoropropane, that "PVP K25" referred to PVP with a K-value of 25, corresponding to an approximate molecular weight of 30,000, and that "PEG 1000" referred to PEG with an average molecular weight of 1000 Daltons. This is demonstrated, for example, by The Handbook of Pharmaceutical Excipients (3rd Edition, A.H. Kibbe (*Ed.*), Washington D.C., American

Pharmaceutical Association, 2000) (the "Handbook") which was published well before the earliest priority date accorded to this application. For example, the Handbook teaches at pages 234-235 (see Exhibit A) that "HFA 227" stands for 1,1,1,2,3,3,3-heptafluoropropane. With regard to "PEG 1000", the Handbook teaches at page 392 (Exhibit B) that "the number which follows PEG indicates the average molecular weight of the polymer" and that PEG 1000 has an average molecular weight of 950 to 1050 Daltons (see Table I of Exhibit B). With regard to PVP, the Handbook at page 433 (Exhibit C) teaches that the approximate molecular weight for PVP with a K-value of 25 (i.e., PVP K25) is 30,000.

In view of the amendments and applicants' demonstration that one of skill in the art would have readily understood these abbreviations at the time of filing, applicants ask that the rejection be reconsidered and withdrawn.

35 U.S.C. § 112, first paragraph

Claims 1-3, 5-9, and 12-16 were rejected as allegedly lacking written description support. According to the Office, "[c]laims reciting 2 mg/mL and 4 mg/mL budesonide set forth new matter issues" (Office Action at page 2).

In the interview conducted April 23, 2008, applicants' representative explained why the specification supports budesonide concentrations of 2 mg/ml and 4 mg/ml. The Examiner concurred and asked that the support for budesonide concentrations of 2 mg/ml and 4 mg/ml be explained in applicants' response.

According to the MPEP § 2163 (II) (A) (3) (b):

> To comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation." Hyatt v. Boone, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998). See also In re Wright, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989)...

Applicants submit that a person of ordinary skill in the art could have easily determined that budesonide concentrations of 2 mg/ml and 4 mg/ml were implicitly described in the originally filed specification.

The specification at page 5, lines 16-20, teaches that multiple formulations were prepared and put into metered dose canisters.

> For all formulations, the formoterol fumurate dihydrate concentration remained constant at 0.09 mg/ml (equivalent to 4.5 mcg formoterol fumurate dihydrate per actuation) and the budesonide concentration varied between approximately 1 mg/ml to 8 mg/ml (equivalent to 40 mcg to 320 mcg per actuation). (emphasis added)

In view of this teaching, a person of ordinary skill would have understood that, in the described experiments, the 1 mg/ml budesonide concentration was equivalent to 40 mcg budesonide per actuation and that the 8 mg/ml budesonide concentration was equivalent to 320 mcg budesonide per actuation. Since the volume per actuation was constant (as indicated by the 4.5 mcg formoterol dose per actuation shown for all formulations in the table at page 6 and described in the above-cited passage), a person of ordinary skill would have recognized that the dose of budesonide per actuation was directly proportional to the budesonide concentration. Based on this, a person of ordinary skill could have easily calculated the budesonide concentrations equivalent to 80 mcg and 160 mcg per actuation (also shown in the table at page 6). If 1 mg/ml is equivalent to 40 mcg (numerical values differ by a factor of 40) and 8 mg/ml is equivalent to 320 mcg (again, numerical values differ by a factor of 40), it follows that 80 mcg per actuation must be equivalent to a budesonide concentration of 2 mg/ml and 160 mcg per actuation must be equivalent to 4 mg/ml. These are the budesonide concentrations at issue in this new matter rejection.

A person of ordinary skill would have realized, based on the description at page 5, lines 16-20, that the 80 mcg per actuation and 160 mcg per actuation shown in various tables in the specification necessarily corresponded to budesonide concentrations of 2 mg/ml and 4 mg/ml, respectively. These concentrations have implicit and inherent support in the originally

filed disclosure. For at least these reasons, applicants respectfully request that the rejection be withdrawn.

No fees are believed to be due at this time. Please apply any charges (including for any extension of time that may be required) or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: April 30, 2008_____

/Janis K. Fraser/_____
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

DocNo 21912640

Exhibit A

Heptafluoropropane (HFC)

1. Nonproprietary Names

None adopted.

2. Synonyms

HFA227; HFC227; 2-hydroperfluoropropane; propellant 227; R-227; *Solkane 227.*

3. Chemical Name and CAS Registry Number

1,1,1,2,3,3,3-Heptafluoropropane [431-89-0]

4. Empirical Formula and Molecular Weight

C_3HF_7 170.0

5. Structural Formula

6. Functional Category

Aerosol propellant.

7. Applications in Pharmaceutical Formulation or Technology

Heptafluoropropane (P-227) is classified as a hydrofluorocarbon (HFC) aerosol propellant since the molecule consists only of carbon, fluorine, and hydrogen atoms. It does not contain any chlorine and therefore, does not affect the ozone layer, nor does it have an effect upon global warming. In this regard, it is considered as an alternative propellant to CFCs for metered-dose inhalers. While some of its physical and chemical properties are known, little has been published in regard to its use as a replacement for CFCs in metered-dose inhalers. Its vapor pressure is somewhat lower than tetrafluoroethane and dichlorodifluoromethane but considerably higher than the vapor pressure used to formulate most metered-dose inhalers. Similar to tetrafluoroethane, it is not a good solvent for medicinal agents or for the commonly used surfactants and dispersing agents used in the formulation of MDIs.

Although there are no metered-dose inhalers formulated with this propellant currently available, a great deal of work is being carried out in regard to its use as a propellant.

8. Description

Heptafluoropropane is a liquefied gas and exists as a liquid at room temperature when contained under its own vapor pressure, or as a gas when exposed to room temperature and atmospheric pressure. The liquid is practically odorless and colorless. The gas in high concentration has a faint ether-like odor. Heptafluoropropane is noncorrosive, nonirritating, and nonflammable.

9. Pharmacopeial Specifications

–

10. Typical Properties

Boiling point: -16.5°C
Density:
1.415 g/cm^3 for liquid at 20°C;
1.323 g/cm^3 for liquid at 40°C.
Flammability: nonflammable
Freezing point: -131°C
Solubility: soluble 1 in 1725 parts of water at 20°C
Surface tension: 6.96 mN/m at 20°C

11. Stability and Storage Conditions

Heptafluoropropane is a nonreactive and stable material. The liquefied gas is stable when used as a propellant and should be stored in a metal cylinder in a cool, dry place.

12. Incompatibilities

The major incompatibility of heptafluoropropane is its lack of miscibility with water and its poor solubility characteristics when used with medicinal agents and the commonly used MDI surfactants.

13. Method of Manufacture

–

14. Safety

Heptafluoropropane is used as a fire extinguisher and is applicable as a non-CFC propellant in various metered-dose inhalers. Heptafluoropropane is regarded as nontoxic and nonirritating when used as directed. No acute or chronic hazard is present when used normally. Inhaling high concentrations of heptafluoropropane vapors can be harmful and is similar to inhaling vapors of other propellants. Deliberate inhalation of vapors of heptafluoropropane can be dangerous and may cause death. The same labeling required of CFC aerosols would be required for those containing heptafluoropropane as a propellant (except for the EPA requirement). (*See* Chlorofluorocarbons, Section 14.)

15. Handling Precautions

Heptafluoropropane is usually encountered as a liquefied gas and appropriate precautions for handling should be taken. Eye protection, gloves, and protective clothing are recommended. Heptafluoropropane should be handled in a well-ventilated environment. The vapors are heavier than air and do not support life and therefore, when cleaning large tanks which have contained this propellant, adequate provisions for oxygen in the tanks must be made in order to protect workers cleaning the tanks. Although nonflammable, when heated to decomposition heptafluoropropane will emit hydrogen fluoride and carbon monoxide.

16. Regulatory Status

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17. Pharmacopeias

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18. Related Substances

Difluoroethane; tetrafluoroethane.

19. Comments

The use of heptafluoropropane as a propellant for MDIs has been the subject of many patents throughout the world. These patents cover the formulation of MDIs, use of specific surfactants, cosolvents, etc. and the formulator is referred to the patent literature prior to formulating an MDI with any HFC as the propellant. The formulation of MDI with tetrafluoroethane and heptafluoropropane propellant is complicated since they may serve as a replacement for dichlorodifluoromethane or dichlorotetrafluoroethane. The use of an HFC as the propellant also requires a change in manufacturing procedure which necessitates a redesign of the filling and packaging machinery for an MDI.

20. Specific References

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21. General References

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22. Authors

CJ Sciarra, JJ Sciarra.

Exhibit B

Polyethylene Glycol

1. Nonproprietary Names

BP: Macrogol 300
Macrogol 400
Macrogol 1000
Macrogol 1540
Macrogol 4000
Macrogol 6000
Macrogol 20 000
Macrogol 35 000

JP: Macrogel 400
Macrogel 1500
Macrogel 4000
Macrogel 6000
Macrogel 20 000

PhEur: Macrogolum 300
Macrogolum 400
Macrogolum 1000
Marcogolum 1500
Macrogolum 3000
Macrogol 4000
Macrogol 6000
Macrogol 20 000
Macrogol 35 000

US: Polyethylene glycol

2. Synonyms

Breox PEG; *Carbowax*; *Hodag PEG*; *Lutrol E*; PEG; polyoxyethylene glycol.

3. Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxy-poly(oxy-1,2-ethanediyl) [25322-68-3]

4. Empirical Formula Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$

Where m represents the average number of oxyethylene groups.

Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number one more than the value of m in the previous formula.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number which follows PEG indicates the average molecular weight of the polymer.

5. Structural Formula

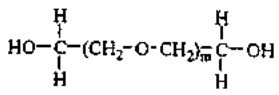

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190-210
PEG 300	6.4	285-315
PEG 400	8.7	380-420
PEG 540 (blend)	—	500-600
PEG 600	13.2	570-613
PEG 900	15.3	855-900
PEG 1000	22.3	950-1050
PEG 1450	32.5	1300-1600
PEG 1540	28-36	1300-1600
PEG 2000	40-50	1800-2200
PEG 3000	60-75	2700-3300
PEG 3350	75.7	3000-3700
PEG 4000	69-84	3000-4800
PEG 4600	104.1	4400-4800
PEG 8000	181.4	7000-9000

6. Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin, *see* Section 14. Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases.[1] Solid grades are generally employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases[2] where they have the following advantages over fats: the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; physical stability on storage is better; suppositories are readily miscible with rectal fluids. Disadvantages of using polyethylene glycols are: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart

plasticity to granules.[3] However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[4-6] a mixture of the powdered constituents with 10-15% w/w PEG 6000 is heated to 70-75°C. The mass becomes paste-like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[7] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.[7] The presence of polyethylene glycols, especially liquid grades, in film coats tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of over-heating.

In addition, polyethylene glycols have been used in the preparation of urethane hydrogels which are used as controlled-release agents.

8. Description

The USP describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight, but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG >1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9. Pharmacopeial Specifications

See Table II.

10. Typical Properties

Density:
1.11-1.14 g/cm^3 at 25°C for liquid PEGs;
1.15-1.21 g/cm^3 at 25°C for solid PEGs.

Flash point:
182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.

Freezing point:
< -65°C PEG 200 sets to a glass;
-15 to -8°C for PEG 300;
4-8°C for PEG 400;
15-25°C for PEG 600.

Melting point:
37-40°C for PEG 1000;
44-48°C for PEG 1500;
40-48°C for PEG 1540;
45-50°C for PEG 2000;
48-54°C for PEG 3000;
50-58°C for PEG 4000;
55-63°C for PEG 6000;
60-63°C for PEG 8000;
60-63°C for PEG 20 000.

Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g., PEG 4000 and above, are not hygroscopic. *See* Figs. 1-3.[a]

Particle size distribution: *see* Figs. 4-7.[a]

Refractive index:
n_D^{25} = 1.459 for PEG 200;
n_D^{25} = 1.463 for PEG 300;
n_D^{25} = 1.465 for PEG 400;
n_D^{25} = 1.467 for PEG 600.

Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol, and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic): *see* Tables III and IV.

[a] *Handbook of Pharmaceutical Excipients*, First Edition.

11. Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, nor do they become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.[9] Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry, place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Table II: Pharmacopeial specifications of polyethylene glycol.

Test	JP PEG 400	JP 1500	JP 4000	JP 6000	JP 20 000	PhEur 300	PhEur 400	PhEur 1000	PhEur 1500	PhEur 4000	USP
Appearance of solution	—	+	+	+	+	+	+	+	+	+	+
Characters	+	+	+	+	+	+	+	+	+	+	—
Freezing point	—	—	—	—	—	—	—	35-40°C	42-48°C	53-58°C	—
Congealing point	—	37-41°C	53-57°C	56-61°C	56-64°C						
Viscosity	—	—	—	—	—	+	+	+	+	+	*See* Table III
Average molecular weight	380-420	—	2600-3800	7300-9300	15 000-25 000	+	+	+	+	+	*See* Table III
Acidity/alkalinity	+	+	+	+	+	+	+	+	+	+	—
pH (5% w/v solution)	4.0-7.0	4.0-7.0	4.0-7.5	4.5-7.5	4.5-7.5	—	—	—	4.0-7.0	4.5-7.5	4.5-7.5
Hydroxyl value	340-394	264-300	—	—	—	340-394	264-300	107-118	70-80	25-32	—
Reducing substances	—	—	—	—	—	+	+	+	+	+	—
Residue on ignition	≤ 0.1%	≤ 0.1%	≤ 0.25%	≤ 0.25%	≤ 0.25%	—	—	—	—	—	≤ 0.1%
Sulfated ash	—	—	—	—	—	≤ 0.2%	≤ 0.2%	≤ 0.2%	≤ 0.2%	≤ 0.2%	—
Limit of ethylene glycol and diethylene glycol	≤ 0.25%	+	—	—	—	≤ 0.4%	≤ 0.4%	—	—	—	≤ 0.25%
Ethylene oxide	—	—	—	—	—	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm	≤ 10 ppm
1,4-dioxane	—	—	—	—	—	—	—	—	—	—	≤ 10 ppm
Heavy metals	≤ 20 ppm	≤ 20 ppm	—	—	—	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm	≤ 5 ppm
Organic volatile impurities	—	—	—	—	—	—	—	—	—	—	+
Water	≤ 1.0%	≤ 1.0%	≤ 1.0%	≤ 1.0%	≤ 1.0%	≤ 2.0%	≤ 2.0%	≤ 2.0%	≤ 1.0%	≤ 1.0%	—

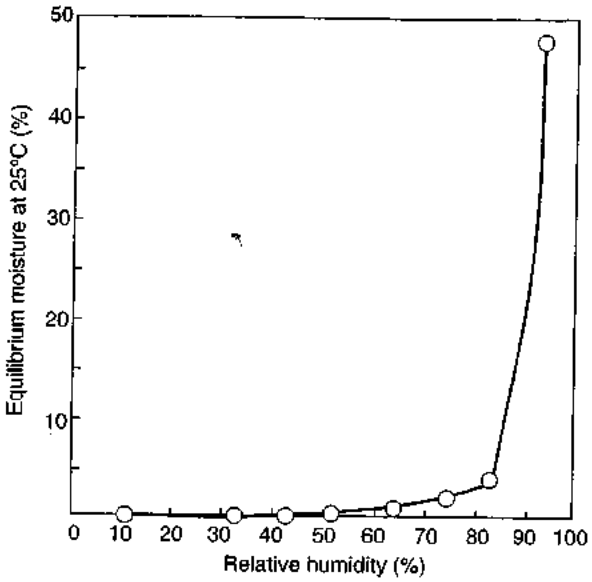

Fig. 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot #B192-8209) at 25°C.

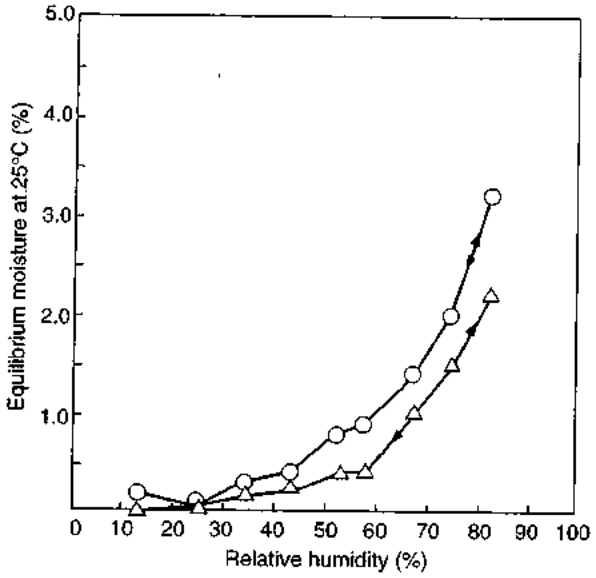

Fig. 2: Equilibrium moisture content of PEG 4000 at 25°C.
○ : PEG 4000 powder (Union Carbide Corp, Lot #B-251)
△ : PEG E-4000 (BASF, Lot #WPYA-575B)

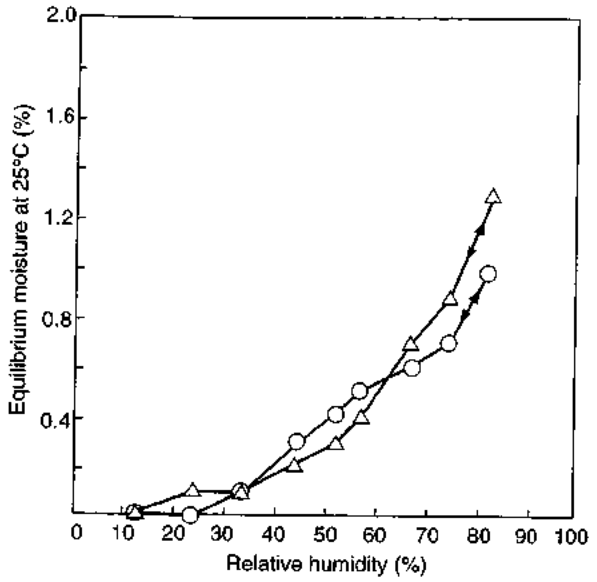

Fig. 3: Equilibrium moisture content of PEG 6000 at 25°C.
○ : PEG 6000 powder (Union Carbide Corp, Lot #B-507)
△ : PEG E-6000 (BASF, Lot #WPNA-124B)

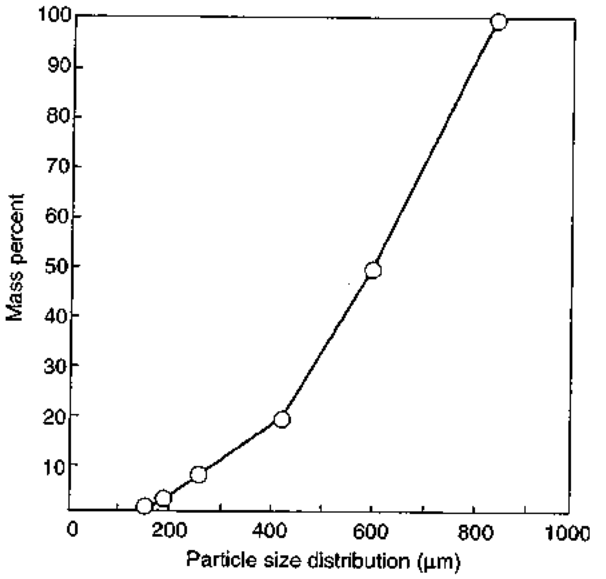

Fig. 4: Particle size distribution of PEG 4000 flakes.

12. Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity due to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some colors.

The antibacterial activity of certain antibiotics, particularly penicillin and bacitracin, is reduced in polyethylene glycol bases. The preservative efficacy of the parabens may also be impaired due to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet-film coatings, leading to interaction with core components.

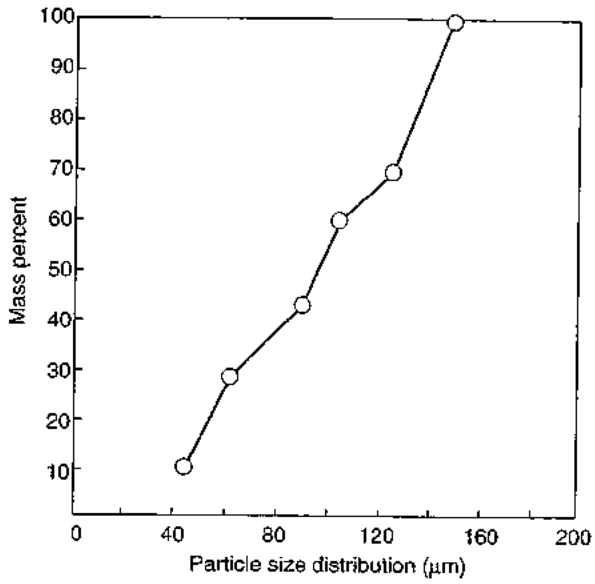

Fig. 5: Particle size distribution of PEG 4000 powder.

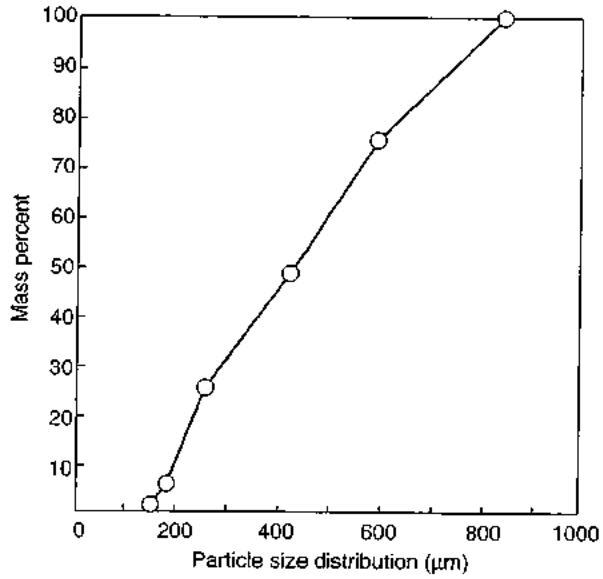

Fig. 6: Particle size distribution of PEG 6000 flakes.

13. Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14. Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[10-12] However, adverse reactions to polyethylene glycols have been reported and although of relatively low toxicity, any toxicity appears to be greatest with polyethylene glycols of low molecular weight.

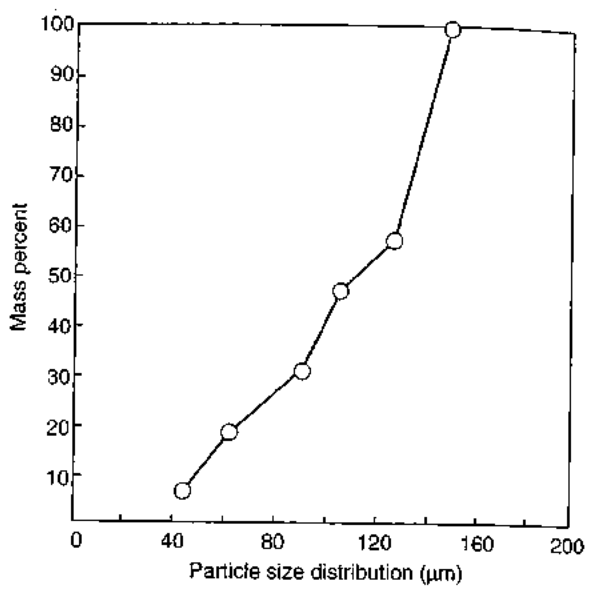

Fig. 7: Particle size distribution of PEG 6000 powder.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically, including urticaria and delayed allergic reactions, have also been reported.[13] However, the most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.[14] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high molecular weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[15]

Liquid polyethylene glycols may be absorbed when taken orally, but the higher molecular weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[16]

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v since hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data *see* Table V.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, ophthalmic preparations, oral

Table III: Specification for viscosity of polyethylene glycol of nominal molecular weight at 98.9°C ± 0.3°C from the USP.

Nominal average molecular weight	Viscosity range in mm^2/s (cSt)
200	3.9-4.8
300	5.4-6.4
400	6.8-8.0
500	8.3-9.6
600	9.9-11.3
700	11.5-13.0
800	12.5-14.5
900	15.0-17.0
1000	16.0-19.0
1100	18.0-22.0
1200	20.0-24.5
1300	22.0-27.5
1400	24-30
1450	25-32
1500	26-33
1600	28-36
1700	31-39
1800	33-42
1900	35-45
2000	38-49
2100	40-53
2200	43-56
2300	46-60
2400	49-65
2500	51-70
2600	54-74
2700	57-78
2800	60-83
2900	64-88
3000	67-93
3250	73-105
3350	76-110
3500	87-123
3750	99-140
4000	110-158
4250	123-177
4500	140-200
4750	155-228
5000	170-250
5500	206-315
6000	250-390
6500	295-480
7000	350-590
7500	405-735
8000	470-900

Table IV: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Grade	Viscosity in mm^2/s (cSt)	
	25°C	99°C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20 000 solid	6900	—

Table V: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[17]

PEG grade	LD_{50} in g/kg									
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (SC)	Rat (IP)	Rat (IV)	Rat (oral)	Rat (SC)
PEG 200	—	7.5	—	38.3	19.9	—	—	—	28.9	—
PEG 300	19.6	—	—	—	17.3	—	17	—	27.5	—
PEG 400	15.7	10.0	8.6	28.9	26.8	—	9.7	7.3	30.2	—
PEG 810	—	—	—	—	—	—	—	13	—	16
PEG 1000	22.5	20	—	—	—	—	—	—	42	—
PEG 1540	—	—	—	—	—	—	15.4	—	51.2	—
PEG 4000	50.9	—	16	—	76	18	11.6	—	50	—
PEG 6000	50	—	—	—	—	—	6.8	—	50	—

capsules, solutions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Polyethylene glycols are described in many pharmacopeias.

Some pharmacopeias, such as the US, have a single monograph describing various different grades; other pharmacopeias have individual monographs. The BP for example has separate monographs for PEG 300, PEG 400, PEG 1000, PEG 1500, PEG 3000, PEG 4000, PEG 6000, PEG 20 000, and PEG 35 000.

18. Related Substances

Polyoxyethylene alkyl ethers; polyoxyethylene sorbitan fatty acid esters; suppository bases.

19. Comments

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Yamaoka T, Tabata Y, Ikada Y. Distribution and tissue uptake of poly(ethylene glycol) with different molecular weights after intravenous administration to mice. *J Pharm Sci* 1994; 83: 601-606.

22. Authors

JC Price.

Exhibit C

Povidone

1. Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Polyvidonum
USP: Povidone

2. Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3. Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ 2500-3 000 000

The USP describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. The K-value is calculated using Fikentscher's equation[1] shown below:

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the K-value × 10^{-3}, and c is the concentration in % w/v.

Alternatively, the K-value may be determined from the following equation:

$$\text{K-value} = \sqrt{\frac{300\,c\log z+(c+1.5\,c\log z)^2+1.5}{0.15c+0.003c^2}}$$

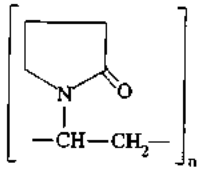
where z is the relative viscosity of the solution of concentration c, k is the K-value × 10^{-3}, and c is the concentration in % w/v.

Approximate molecular weights for different povidone grades are shown below:

K-value	Approximate molecular weight
12	2500
15	8000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5. Structural Formula



6. Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a disintegrant [4,5] and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[6-8] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations, *see* Section 14.

Use	Concentration (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

8. Description

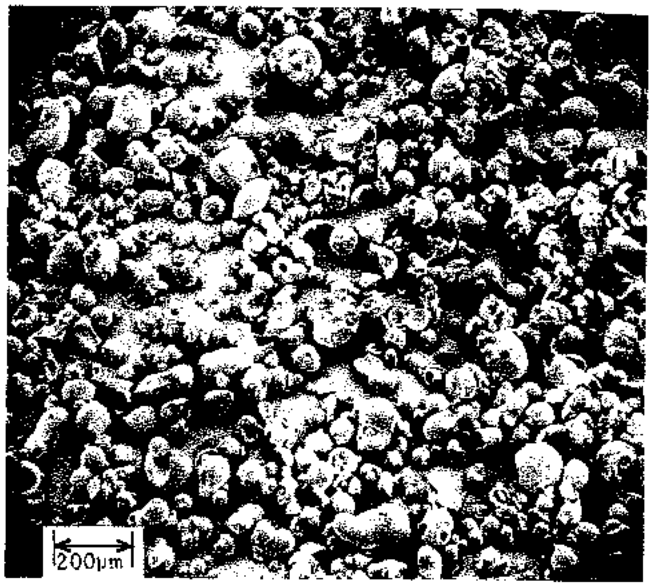
Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and exist as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and exist as plates.

9. Pharmacopeial Specifications

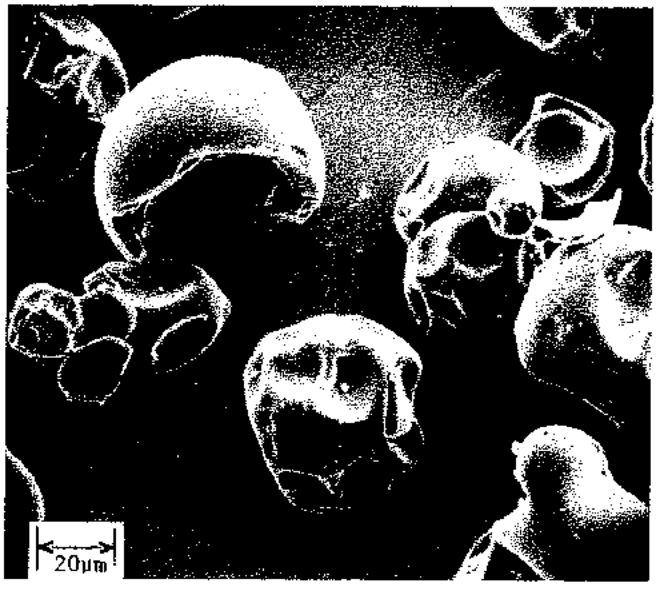
Test	JP	PhEur	USP
Identification	—	+	+
Characters	+	+	—
pH	—	—	3.0-7.0
K ≤ 30	3.0-5.0	3.0-5.0	—
K > 30	4.0-7.0	4.0-7.0	—
Appearance of solution	+	+	—
Water	≤ 5.0%	≤ 5.0%	≤ 5.0%
Residue on ignition	≤ 0.1%	—	≤ 0.1%
Sulfated ash	—	≤ 0.1%	—
Lead	—	—	≤ 10 ppm

SEM: 1
Excipient: Povidone K-15 (*Plasdone* K-15)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60×
Voltage: 5 kV

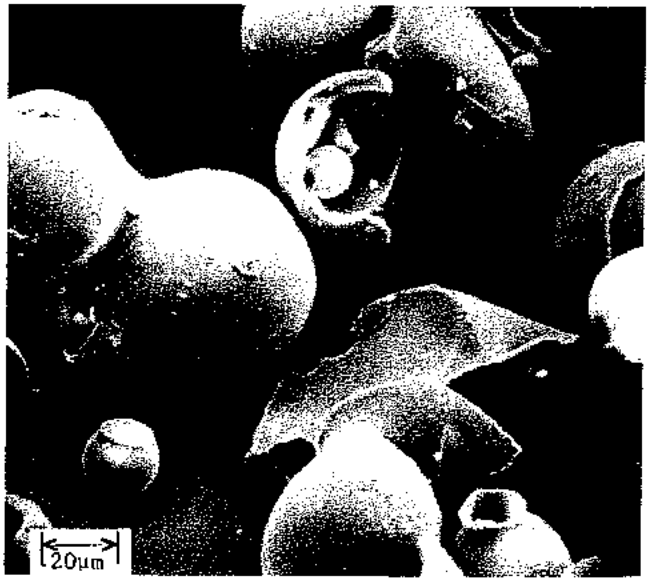
SEM: 3
Excipient: Povidone K-26/28 (*Plasdone* K-26/28)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60×
Voltage: 5 kV



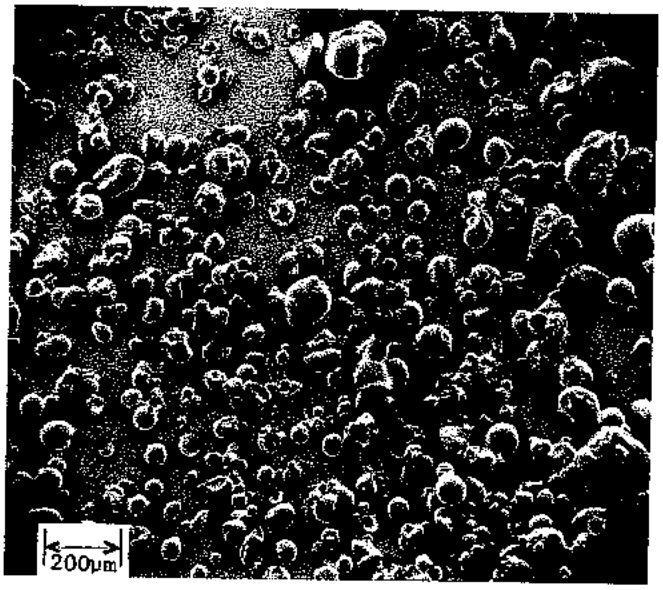
SEM: 2
Excipient: Povidone K-15 (*Plasdone* K-15)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600×
Voltage: 5 kV



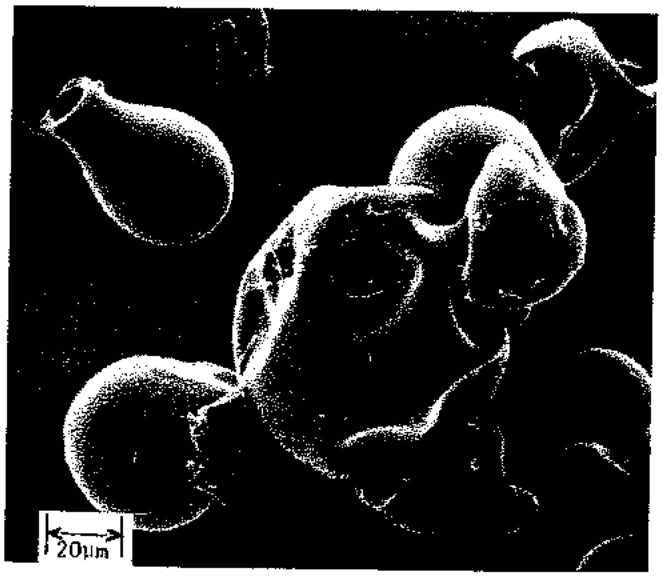
SEM: 4
Excipient: Povidone K-26/28 (*Plasdone* K-26/28)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600×
Voltage: 10 kV



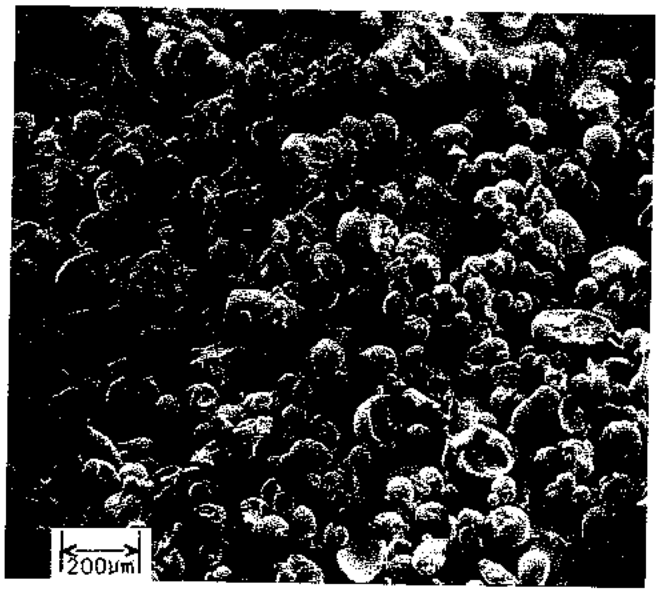
SEM: 5
Excipient: Povidone K-30 (*Plasdone* K-30)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60×
Voltage: 10 kV



SEM: 6
Excipient: Povidone K-30 (*Plasdone* K-30)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600×
Voltage: 10 kV



SEM: 7
Excipient: Povidone K-29/32 (*Plasdone* K-29/32)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone* K-29/32)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600×
Voltage: 10 kV

(Continued)

Test	JP	PhEur	USP
Aldehydes	≤ 500 ppm[a]	≤ 500 ppm[a]	≤ 0.05%
Hydrazine	≤ 1 ppm	≤ 1 ppm	≤ 1 ppm
Vinylpyrrolidinone	+	≤ 10 ppm	≤ 0.2%
Peroxides	≤ 400 ppm[b]	≤ 400 ppm[b]	—
K-value	25-90	—	—
≤ 15	90.0-108.0%	85.0-115.0%	85.0-115.0%
> 15	90.0-108.0%	90.0-108.0%	90.0-108.0%
Nitrogen content	11.5-12.8%	11.5-12.8%	11.5-12.8%
Heavy metals	≤ 10 ppm	≤ 10 ppm	—

[a] Expressed as acetaldahyde.

[b] Expressed as hydrogen peroxide.

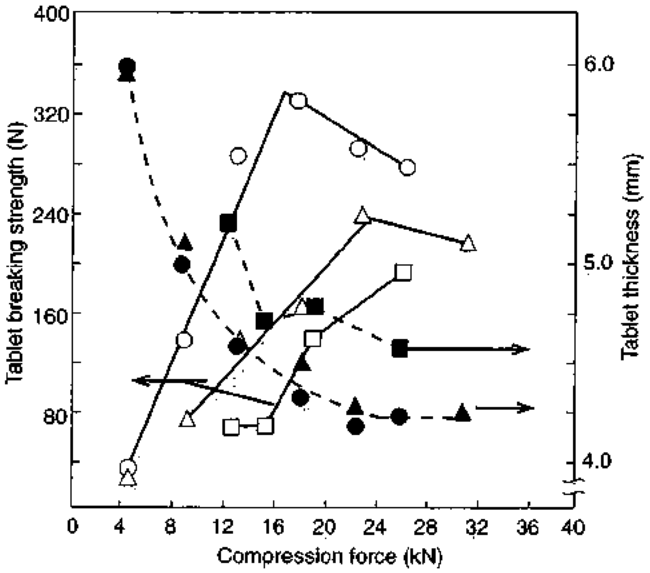


Fig. 1: Compression characteristics of povidone K-15 (Plasdone K-15).
○● : Unlubricated, Carver laboratory press
△▲ : Lubricated, Carver laboratory press
□■ : Lubricated, Instrumental Stokes model F-single punch press

10. Typical Properties

Acidity/alkalinity:
pH = 3.0-7.0 (5% w/v aqueous solution)

Compressibility: *See* Figs. 1-5.[a][b]

Density (bulk): 0.409 g/cm^3[b]

Density (tapped): 0.508 g/cm^3[b]

Density (true): 1.180 g/cm^3[b]

Flowability:
20 g/s for povidone K-15;
16 g/s for povidone K-29/32.

Hygroscopicity: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figs. 6,7, and 8.[a]

Melting point: softens at 150°C

Particle size distribution: 90% > 50 µm, 50% > 100 µm, 5% > 200 µm in size for *Kollidon 25/30*; 90% > 200 µm, 95% > 250 µm in size for *Kollidon 90*.[9]

Solubility: freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water the concentration of a solution is limited only by the viscosity of the resulting solution which is a function of the K-value.

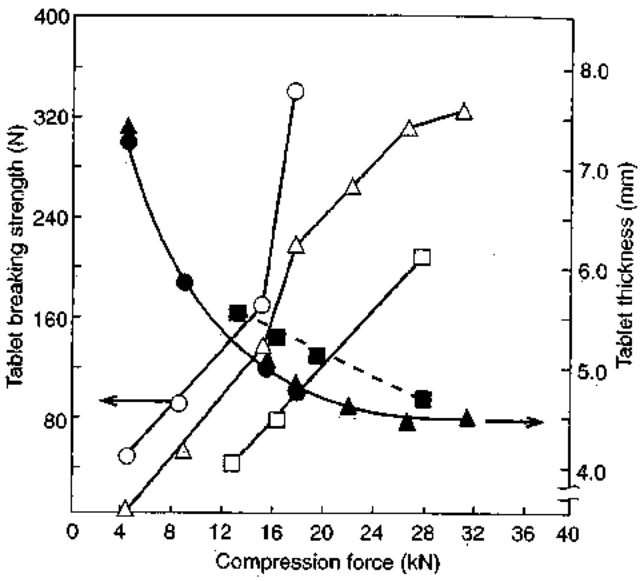


Fig. 2: Compression characteristics of povidone K-29/32 (Plasdone K-29/32.)[a]
○● : Unlubricated, Carver laboratory press
△▲ : Lubricated, Carver laboratory press
□■ : Lubricated, Instrumental Stokes model F-single punch press

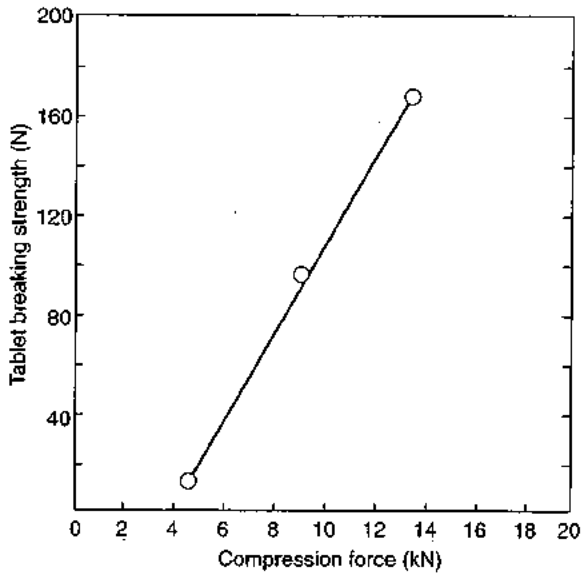


Fig. 3: Compression characteristics of povidone K-29/32 (Plasdone K 29/32).[a]
Tablet weight: 500 mg

Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and molecular weight of the polymer employed. *See* Tables I and II.[9]

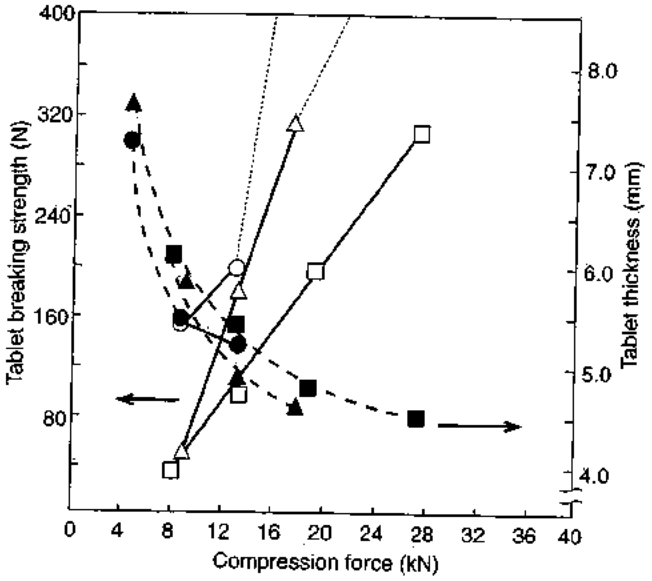


Fig. 4: Compression characteristics of povidone K-30 (*Plasdone K 30*).[a]
○● : Unlubricated, Carver laboratory press
△▲ : Lubricated, Carver laboratory press
□■ : Lubricated, Instrumental Stokes model F-single punch press

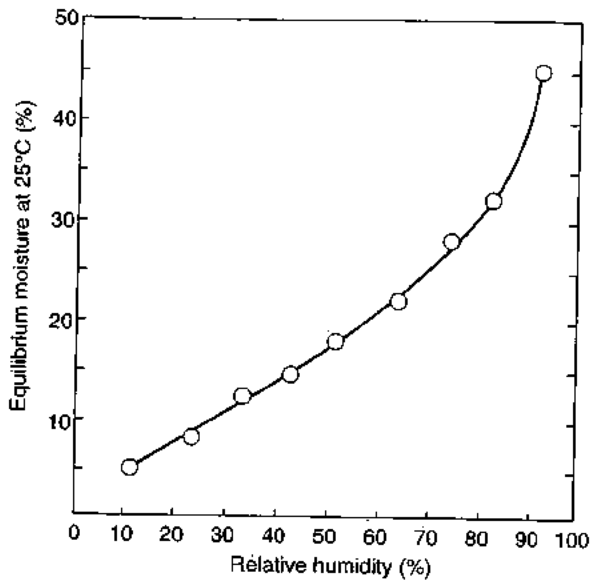


Fig. 6: Equilibrium moisture content of povidone (Plasdone).[a]

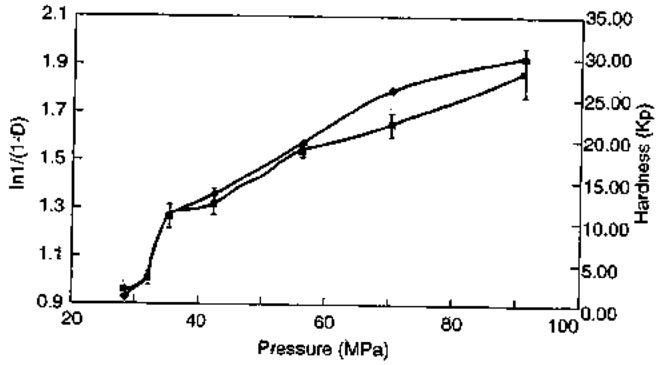


Fig. 5: Heckel plot for povidone.[b]
◆ : ln1/(1-D)
■ : Hardness

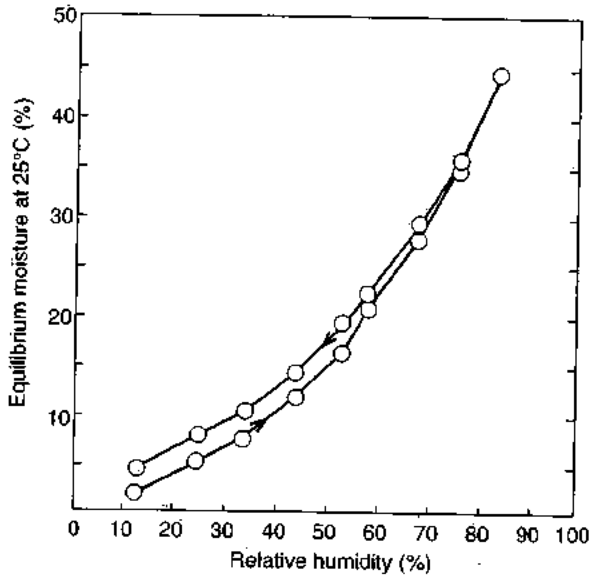


Fig. 7: Sorption-desorption isotherm of poivodne K-15 (*Plasdone K-15*).[a]

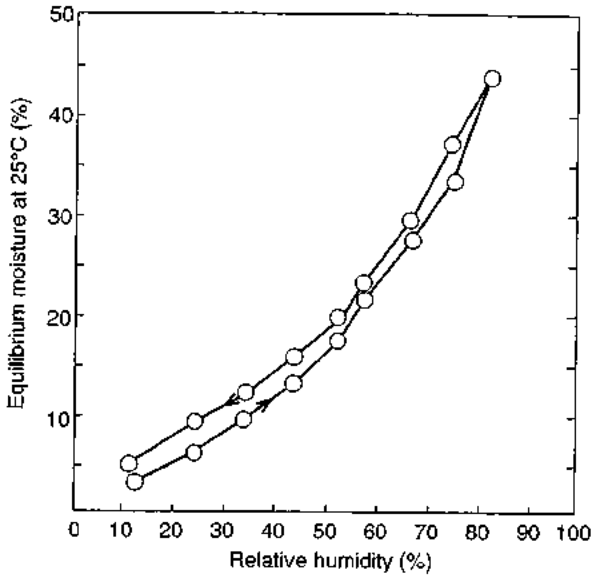


Fig 8: Sorption-desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).[a]

Table I: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[9]

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3-2.3
K-16/18	1.5-3.5
K-24/27	3.5-5.5
K-28/32	5.5-8.5
K-85/95	300-700

Table II: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol and propan-2-ol at 25°C.[9]

Grade	Dynamic viscosity (mPa s)	
	Ethanol	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

[a] *Handbook of Pharmaceutical Excipients*, First Edition.

[b] Results of laboratory project for third edition.

11. Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry, place.

12. Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds, *see* Section 19. The efficacy of some preservatives, e.g., thimerosal, may be adversely affected by the formation of complexes with povidone.

13. Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14. Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[10]

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[10] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[11] Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.[12]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[13]

LD_{50} (mouse, IP): 12 g/kg[14]
LD_{50} (mouse, IV): > 11 g/kg
LD_{50} (rat, oral): 8.25 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16. Regulatory Status

Accepted in Europe as a food additive in certain applications. Included in the FDA Inactive Ingredients Guide (IM and IV injections, ophthalmic preparations, oral capsules, drops, granules, suspensions and tablets, sublingual tablets, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Eur, Int, Jpn, Pol, and US.

18. Related Substances

Crospovidone.

19. Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms and parenteral formulations. Perhaps the best known example of povidone complex formation is povidone-iodine which is used as a topical disinfectant.

For accurate standardization of solutions the water content of the solid povidone must be determined before use and taken into account for any calculations.

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22. Authors

AH Kibbe.

Electronic Acknowledgement Receipt

EFS ID:	3235758
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Janis K. Fraser/Lisa Gray
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	06275-410US1
Receipt Date:	30-APR-2008
Filing Date:	27-JUL-2004
Time Stamp:	17:46:01
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		06275410US1amendment.pdf	1645727 ddae70897b28e3fe44ab2c669f9410cce5d4f291	yes	26

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment - After Non-Final Rejection	1	1
	Specification	2	2
	Claims	3	6
	Applicant Arguments/Remarks Made in an Amendment	7	26

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/502,685	07/27/2004	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 04/30/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0	X $ =		OR	X $50=	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $210=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TYWANA P. LOVELACE/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 04/28/2008

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
04/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Interview Summary	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	ALTON N. PRYOR	1616	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ALTON N. PRYOR*. (3)_____.

(2) *Attorney Fraser*. (4)_____.

Date of Interview: *23 April 2008*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *none*.

Identification of prior art discussed: *none*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Attorney Faser discussed 112 issues with the Examiner and has agreed to address 112 issues in her next response*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Alton N. Pryor/
Primary Examiner, Art Unit 1616
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

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