AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/21/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	WOCKHARDT BIO LTD., WOCKHARDT LTD., and WOCKHARDT USA, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/2/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	NANG KUANG PHARMACEUTICAL CO., LTD. and CANDA NK-1, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Dismissed Voluntarily — See Attached

CLERK	(BY) DEPUTY CLERK	DATE
~~John A Cerino, Clerk~~ United States District Court 844 N. King Street, Unit 18 ~~Wilmington, DE 19801~~		10/3/14

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-2095-GMS	9/18/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	ACCORD HEALTHCARE, INC. and INTAS PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,445,524	5/21/2013	CEPHALON, INC.
2	8,436,190	5/7/2013	CEPHALON, INC.
3	8,609,863	12/17/2013	CEPHALON, INC.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,791,270	7/29/2014	CEPHALON, INC.
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/2/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	SAGENT PHARMACEUTICALS, INC. and SAGENT AGILA LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	5/27/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	BRECKENRIDGE PHARMACEUTICAL, INC. and NATCO PHARMA LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DECISION/JUDGEMENT

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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-2095-GMS	12/26/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	ACCORD HEALTHCARE, INC. and INTAS PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,445,524	5/21/2013	CEPHALON, INC.
2	8,436,190	5/7/2013	CEPHALON, INC.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
4/9/2014	☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,609,863	12/17/2013	CEPHALON, INC.
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/14/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	SUN PHARMA GLOBAL FZE, SUN PHARMACEUTICAL INDUSTRIES LTD., and SUN PHARMACEUTICAL INDUSTRIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/14/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
2			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/719,379	12/17/2013	8609863	CEPH-4457/CP391B US	6187

46347 7590 11/26/2013

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

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):

Jason Edward Brittain, El Cajon, CA;
Joe Craig Franklin, Tulsa, OK;

Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
(use as many sheets as necessary)				**Examiner Name**	Soroush, Ali
Sheet	1	of	1	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PATENT APPLICATION DOCUMENTS				
Examiner Initials	Cite No.	Application Number	Fling Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**116**	13/719,409	12-19-2012	Cephalon, Inc.

U. S. PUBLICATION AND PATENT DOCUMENTS				
Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**117**	2013/0041003 A1	02-14-2013	~~Cephalon, Inc.~~ Brittain; Jason Edward ; et al.
/A.S./	**118**	8,436,190	05-07-2013	Brittain, J.E. et al.

Change(s) applied to document, /S.J.W.S./ 11/13/2013

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
/A.S./	**119**	Teagarden et al., "Practical aspects of lyophilization using non-aqueous co-solvent systems," European Journal of Pharmaceutical Sciences, March 2002, 15(2), 115-133	
/A.S./	**120**	Wittaya-Areekul et al., "Freeze-drying of tert-butyl alcohol/water cosolvent systems: Effects of formulation and process variables on residual solvents," Journal of Pharmaceutical Sciences, April 1998, 87(4), 491-495	

Examiner Signature	/Ali Soroush/	**Date Considered**	09/18/2013

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	2	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**25**	5,192,743	03-09-1993	Hsu et al.
	26	5,204,335	04-20-1993	Sauerbier et al.
	27	5,227,373	07-13-1993	Alexander et al.
	28	5,227,374	07-13-1993	Alexander et al.
	29	5,268,368	12-07-1993	Palepu
	30	5,413,995	05-09-1995	Alexander et al.
	31	5,418,223	05-23-1995	Palepu et al.
	32	5,750,131	05-12-1998	Wichert et al.
	33	5,770,230	06-23-1998	Teagarden et al.
	34	5,776,456	07-07-1998	Anderson et al.
	35	5,955,504	09-21-1999	Wechter et al.
	36	5,972,912	10-26-1999	Marek et al.
Change(s) applied to document, /C.C.B./ 11/20/2013	**37**	6,034,256	03-07-2000	~~Masferrer~~ Carter et al.
	38	6,077,850	06-20-2000	~~Masferrer~~ Carter et al.
	39	6,090,365	07-18-2000	Kaminski et al.
	40	6,271,253	08-07-2001	~~Masferrer~~ Carter et al.
	41	6,380,210	04-30-2002	Desimone et al.
	42	6,492,390	12-12-2002	~~Masferrer~~ Carter et al.
	43	6,545,034	04-08-2003	Carson et al.
	44	6,569,402	05-27-2003	Cheesman et al.
	45	6,573,292	06-03-2003	Nardella
	46	6,613,927	09-02-2003	Kwok

Examiner Signature	/Ali Soroush/	**Date Considered**	02/25/2013

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.
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US	6187

46347 7590 11/18/2013

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
11/18/2013	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):

eofficemonitor@woodcock.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.
13/719,379	19 December, 2012	BRITTAIN ET AL.	CEPH-4457/CP391B US

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

EXAMINER	
RICHARD ELLIS	
ART UNIT	PAPER
OPIM	A-82087

DATE MAILED:

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

Commissioner for Patents

The attached addendum forms part of the previously mailed PTOL-85 (Notice of Allowance and Fees Due). This addendum does NOT change the time period set in the PTOL-85 for payment of the issue fee.

ANY QUESTIONS REGARDING THIS COMMUNICATION SHOULD BE DIRECTED TO THE OFFICE OF PATENT LEGAL ADMINISTRATION AT (571) 272-7701.

PTO-90C (Rev.04-03)

Notices of Allowance and Fee(s) Due mailed between October 1, 2013 and December 31, 2013

(Addendum to PTOL-85)

If the "Notice of Allowance and Fee(s) Due" has a mailing date on or after October 1, 2013 and before January 1, 2014, the following information is applicable to this application.

If the issue fee is being timely paid on or after January 1, 2014, the amount due is the issue fee and publication fee in effect January 1, 2014. On January 1, 2014, the issue fees set forth in 37 CFR 1.18 decrease significantly and the publication fee set forth in 37 CFR 1.18(d)(1) decreases to $0.

If an issue fee or publication fee has been previously paid in this application, applicant is not entitled to a refund of the difference between the amount paid and the amount in effect on January 1, 2014.

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)

46347 7590 10/02/2013
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

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.
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US	6187

TITLE OF INVENTION: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	01/02/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, ALI	1617	548-304700

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 Woodcock Washburn LLP
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: Cephalon, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Frazer, Pennsylvania

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 233050 (enclose an extra copy of this form).

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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 /Stephanie A. Lodise/ Date November 5, 2013

Typed or printed name Stephanie A. Lodise Registration No. 51430

Electronic Patent Application Fee Transmittal

Application Number:	13719379
Filing Date:	19-Dec-2012
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Filer:	Stephanie A. Lodise/Danielle Langdon
Attorney Docket Number:	CEPH-4457/CP391B US

Filed as Large Entity

Utility under 35 USC 111(a) 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	1780	1780
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1780**

Electronic Acknowledgement Receipt

EFS ID:	17318914
Application Number:	13719379
International Application Number:	
Confirmation Number:	6187
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Lodise/Danielle Langdon
Filer Authorized By:	Stephanie A. Lodise
Attorney Docket Number:	CEPH-4457/CP391B US
Receipt Date:	05-NOV-2013
Filing Date:	19-DEC-2012
Time Stamp:	15:19:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1780
RAM confirmation Number	1905
Deposit Account	233050
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 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	Issue Fee Payment (PTO-85B)	Issue_fee_transmittal.PDF	112286 d91687d6be8949529ce93463cae58e6bc9dcfb6e	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30204 0fdaee13caed625061ad7161f9c7602481c4cc1d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	142490		

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

46347 7590 10/02/2013
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/02/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US	6187

TITLE OF INVENTION: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	01/02/2014

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 ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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.

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)

46347 7590 10/02/2013
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

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.
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US	6187

TITLE OF INVENTION: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	01/02/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, ALI	1617	548-304700

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)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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.

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.
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US	6187

46347 7590 10/02/2013

WOODCOCK WASHBURN LLP
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2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/02/2013

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.

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.

Notice of Allowability	Application No. 13/719,379	Applicant(s) BRITTAIN ET AL.	
	Examiner ALI SOROUSH	Art Unit 1617	AIA (First Inventor to File) Status No

-- 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 *response filed on 06/03/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-4*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   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.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ 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. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 06032013
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Acknowledgement of Receipt

Applicant's response filed on 06/03/2013 to the Office Action mailed on 03/01/2013 is acknowledged.

Claim Status

Claims 1-4 are pending.

Claims 1-4 have been examined.

Claims 1-4 are allowed.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 06/03/2013 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Withdrawn Claim Rejections – 35 USC § 102

Response to Applicant's Arguments

The rejection of claim 4 of under 35 U.S.C. 102(a) as being anticipated by Kanekal et al. (SDX-105(TREANDA) Enhances the Tumor Growth Inhibitory Effect of Rituximab in Daudi Lymphoma Xenografts, Published 2004) as evidenced by RxList (Treanda, Published 2013) in view of Applicant's declaration under 37 C.F.R. sec.

1.131, indicating that the Applicant did invent the instant subject matter prior to the Kanekal et al. publication date, is withdrawn.

Withdrawn Claim Rejections - 35 USC § 103

Response to Applicant's Arguments

The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Oltoff et al. (DE 159289, Published 06/01/1981) in view of Ni et al. (Use of pure t-butanol as a solvent for freeze-drying: a case study, Published 2001)is withdrawn in view of Applicant's arguments.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: While the prior art teaches a composition that maybe reconstituted comprising bendamustine hydrochloride and mannitol (third party prior art submission filed on 08/12/2013 in Co-Pending Application 13/719409), the instantly claimed ratio is not taught. Applicant however has found unexpectedly that the instant ratio allows for the maintenance of a well formed cake resistant to breakage during handling (page 46, lines 17-27 of the instant specification). Therefore, claims 1-4 are allowed.

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."

Conclusion

Claims 1-4 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached on M-F (9am-6pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on (571)272-3311. 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.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

September 18, 2013

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13719379	BRITTAIN ET AL.
	Examiner	**Art Unit**
	ALI SOROUSH	1617

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	4	
/ALI SOROUSH/ Primary Examiner.Art Unit 1617	09/18/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13719379	BRITTAIN ET AL.
	Examiner	**Art Unit**
	ALI SOROUSH	1617

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
548	304.7	C	0	7	D	235 / 04 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
34	284				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	4	
/ALI SOROUSH/ Primary Examiner.Art Unit 1617	09/18/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13719379	BRITTAIN ET AL.
	Examiner	**Art Unit**
	ALI SOROUSH	1617

☒ 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	1														
2	2														
3	3														
4	4														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 4	
/ALI SOROUSH/ Primary Examiner.Art Unit 1617 (Primary Examiner)	09/18/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
				Examiner Name	Soroush, Ali
Sheet	1	of	1	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PATENT APPLICATION DOCUMENTS

Examiner Initials	Cite No.	Application Number	Fling Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**116**	13/719,409	12-19-2012	Cephalon, Inc.

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**117**	2013/0041003 A1	02-14-2013	Cephalon, Inc.
/A.S./	**118**	8,436,190	05-07-2013	Brittain, J.E. et al.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
/A.S./	**119**	Teagarden et al., "Practical aspects of lyophilization using non-aqueous co-solvent systems," European Journal of Pharmaceutical Sciences, March 2002, 15(2), 115-133	
/A.S./	**120**	Wittaya-Areekul et al., "Freeze-drying of tert-butyl alcohol/water cosolvent systems: Effects of formulation and process variables on residual solvents," Journal of Pharmaceutical Sciences, April 1998, 87(4), 491-495	

Examiner Signature	/Ali Soroush/	**Date Considered**	09/18/2013

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	(548/304.7.ccls. 34/284.ccls.) and bendamustine.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/09/18 16:07
L2	1000	(548/304.7.ccls. 34/284.ccls.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/09/18 16:07
S1	1337	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:38
S2	173689	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:39
S3	175501	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol mannite (manna adj sugar)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:39
S4	19	S1 near5 S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:40
S5	23	S1 with S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:40
S6	1337	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:28
S7	1337	S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:28
S8	175501	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol mannite (manna adj sugar)	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	OFF	2013/02/14 16:29

			JPO; DERWENT; IBM_TDB			
S9	47	S7 same S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:29
S10	24	S7 same lyophilized	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:29
S11	445	S7 and lyophilized	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:29
S12	97	S6.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:30
S13	97	cyclophosphamide with mannitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:40
S14	5	S13 same lyophilization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:40
S15	0	cyclophosphamide with (butyl$1alcohol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:42
S16	0	cyclophosphamide with ($9butyl adj alcohol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:42
S17	1337	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:56
S18	8	S17 and Astellas.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:56
S19	173689	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:57
S20	40	S17 same S19	US-PGPUB; USPAT; USOCR;	OR	OFF	2013/02/14 16:57

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S21	163	ribomustin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:00
S22	40	S21 and @PD<="20051301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:01
S23	19	bendamustine near5 mannitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:05
S24	40	S19 same S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:05
S25	0	S24 and @PD<="20051301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:05
S26	1287	lundbeck.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:30
S27	0	S26 and S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:30
S28	2	"8349613".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 11:42
S29	2270	bendamustine sarcnu	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:26
S30	5	bendamustine with sarcnu	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:26
S31	37	bendamustine with nitrosurea	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:26
S32	37	bendamustine and @pd<="20051301"	US-PGPUB; USPAT; USOCR;	OR	OFF	2013/02/19 15:27

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S33	11	S32 and (lyophilize lyophilization lyophilized "freeze-dry" "feeze-dried" "freeze-drying")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:28
S34	0	bendamustine with (ascrobic adj acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:37
S35	19	bendamustine with (ascorbic adj acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:37
S36	0	(alkylating adj agent) with lyophilize	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:47
S37	0	(alkylating adj agent) same lyophilize	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:47
S38	40337	(alkylating adj agent)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:47
S39	8	S38 same (lyophilize lyophilization)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:48
S40	1398	(lyophilize lyophilization) with mannitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:50
S41	1339	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:28
S42	1339	S41	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:28
S43	27	S42 with (lyophilize lyophilized lyophilization lyophilisate "freeze-dry" "freeze-dried" "freeze-drying")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:28
S44	32	S42 same (lyophilize lyophilized	US-PGPUB;	OR	OFF	2013/02/19

		lyophilization lyophilisate "freeze-dry" "freeze-dried" "freeze-drying")	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			18:29
S45	5	"09323915"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:28
S46	12	"3223206"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:30
S47	0	3-223206	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:30
S48	36	"386812"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:31

9/ 18/ 2013 4:07:56 PM
C:\ Users\ asoroush\ Documents\ EAST\ Workspaces\ 13719379.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13719379	BRITTAIN ET AL.
	Examiner	Art Unit
	ALI SOROUSH	1617

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
34	284	09/18/2013	AS
548	304.7	09/18/2013	AS

SEARCH NOTES		
Search Notes	Date	Examiner
See search history printouts	09/18/2013	AS
Inventor/Assignee search EAST/PALM (Jason Edward Brittain, Joe Craig Franklin)	09/18/2013	AS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
34	384	09/18/2013	AS
548	304.7	09/18/2013	AS

/ALI SOROUSH/ Primary Examiner.Art Unit 1617	

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. 6187

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/719,379	12/19/2012	548	1617	CEPH-4457/CP391B US

APPLICANTS

Jason Edward Brittain, El Cajon, CA;
Joe Craig Franklin, Tulsa, OK;

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

This application is a CON of 13/654,898 10/18/2012 PAT 8461350
which is a CON of 11/330,868 01/12/2006 PAT 8436190
which claims benefit of 60/644,354 01/14/2005

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

02/01/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /ALI SOROUSH/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	6	4	2

ADDRESS

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891
UNITED STATES

TITLE

Bendamustine Pharmaceutical Compositions

FILING FEE RECEIVED		
1560	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

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/719,379	BRITTAIN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 6/3/13	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

ANDRE ROBINSON

2 TDS WERE APPRVD.

U.S. Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Jason Edward Brittain**	Confirmation No.: **6187**
Application No.: **13/719,379**	Group Art Unit: **1617**
Filing Date: **December 19, 2012**	Examiner: **Ali Soroush**

For: **BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS**

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

Dear Commissioner:

REPLY PURSUANT TO 37 CFR § 1.111

In response to the Official Action dated **March 1, 2013**, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

☐ **Amendments to the Specification** begin on page of this paper.

☒ **Amendments to the Claims** are reflected in the listing of the claims which begins on page 2 of this paper.

☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet.

☒ **Remarks** begin on page 3 of this paper.

☒ The Commissioner is hereby authorized to charge any fee deficiency, charge any additional fees, or credit any overpayment of fees, associated with this application in connection with this filing, or any future filing, submitted to the U.S. Patent and Trademark Office during the pendency of this application, to Deposit Account No. 23-3050.

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Original) A stable lyophilized preparation comprising bendamustine hydrochloride, mannitol, and a trace amount of tertiary-butyl alcohol (TBA), wherein the ratio by weight of bendamustine hydrochloride to mannitol is 15:25.5.

2. (Original) The stable lyophilized preparation of claim 1 in a vial containing 25 mg bendamustine hydrochloride.

3. (Original) The stable lyophilized preparation of claim 1 in a vial containing 100 mg bendamustine hydrochloride.

4. (Original) A stable lyophilized preparation comprising bendamustine hydrochloride and mannitol in a ratio by weight of about 15:25.5, wherein the preparation is obtained by a process comprising:

a) preparing a composition comprising bendamustine hydrochloride, mannitol, tertiary-butyl alcohol and water, wherein the bendamustine hydrochloride and mannitol are present in the ratio by weight of about 15:25.5, and

b) lyophilizing the composition from step a) to obtain the preparation.

REMARKS

Claims 1-4 are pending and no claim amendments have been made.

35 U.S.C. § 102

The Office alleges that claim 4 is not novel in view of Kanekal et al., SDX-105 (Treanda) Enhances the Tumor Growth Inhibitory Effect of Rituximab in Daudi Lymphoma Xenografts, *Blood* (ASH Annual Meeting Abstracts) 2004 104: Abstract 4580 ("Kanekal") as evidenced by RxList (Treanda) published 2013. Applicants note that according to *Blood*, Kanekal was published on November 16, 2004. Applicants also note that RxList was published well after the filing date of the present application and fails to provide any information about the composition of "Treanda" at the time Kanekal published. Nevertheless, and while not conceding to the propriety of the alleged rejection, the claimed invention was conceived and reduced to practice prior to November 16, 2004. Kanekal does not anticipate the claimed invention and Applicants request reconsideration and withdrawal of the rejection.

Accompanying this response is the Declaration Pursuant To 37 C.F.R. 1.131 of Jason E. Brittain ("Brittain Declaration"), one of the inventors of the present application.[1] In his Declaration, Dr. Brittain states that the claimed invention was reduced to practice prior to November 16, 2004. Brittain Declaration at ¶¶8-11. This prior invention is evidenced by the Formulation Development Report attached to the Brittain Declaration as Exhibit A. *See, e.g.,* Brittain Declaration, Exhibit A at Sections 3.3.2.3; 3.3.3; 4.3; 4.5; and 5; Figures 2, 3, and 4.

The evidence demonstrates that the claimed invention was reduced to practice prior to November 16, 2004. As a result, Kanekal is not prior art to the present invention. Applicants request reconsideration and withdrawal of the rejection.

35 U.S.C. § 103

The Office alleges that claims 1-4 are obvious over DE 159289 in view of Ni et al, Use of pure t-butanol as a solvent for freeze-drying: a case study, 2001 ("Ni"). A copy of the English

[1] Joe Craig Franklin, the other inventor of the claimed subject matter, is deceased. Brittain Declaration at ¶2.

translation of DE 159289, submitted in the Information disclosure statement filed on January 28, 2013, accompanies this response. Applicants request withdrawal of the rejection because the combination of cited art fails to teach or suggest the claimed invention. Indeed, DE 159289 teaches away from the claimed invention.

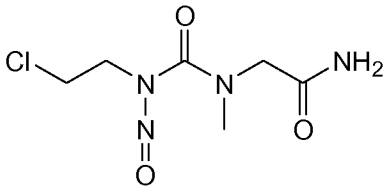
DE 159289

In contrast to the claimed invention which comprises, among other things, stable lyophilized preparations comprising bendamustine hydrochloride, mannitol, and a trace amount of tertiary-butyl alcohol, DE 159289 is directed to ***liquid*** formulations, wherein bendamustine is dissolved in an anhydrous solvent. Prior to injection, this solution is diluted with an aqueous medium.

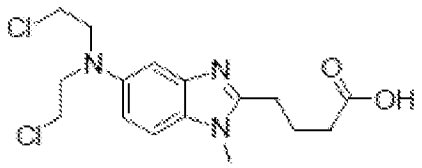
In addition, DE 159289 describes that the lyophilized preparations known prior to the present invention were undesirable. DE 159289 notes that "the lyophilisate obtained (25 mg/ampoule) has significant disadvantages for a technological production process. In particular, the technological realization is complicated even more by the extreme hygroscopicity and the fact that the process takes place under inert gas. Moreover, during the production of the [lyophilisate], clear signs for decomposition of 5 to 10% of the active substance were observed. It is furthermore unsatisfying that high amounts of micro particles were found after the dissolution of the lyophilisate, which indicate a further instability of the system." DE 159289 English translation at 3-4. DE 159289 advises that the lyophilized form should be avoided in favor of the liquid formulations described therein. *Id.* at 4.

Ni

Ni describes that tertiary-butanol is useful in lyophilizing SarCNU:



SarCNU



bendamustine

As the skilled person readily recognizes, SarCNU and bendamustine have different physicochemical properties such that one skilled in the art cannot predict whether formulations

effectively used for SarCNU can be successfully applied to bendamustine, and *vice versa*. Ni provides no suggestion that a predictable result would be obtained by using tertiary butanol for lyophilizing bendamustine. Nevertheless, the Office alleges that "one of skill in the art at the time of the instant invention [would have used] t-butanol in the lyophilisate of [DE 159289] and have a reasonable expectation of success. One would have been motivated to do so to improve the solubility and stability of bendamustine hydrochloride." Action at 5. The Office's statements have no support in the cited art or the field of art and are the result of improper hindsight.

The invention is non-obvious in view of the combination of DE 159289 and Ni

DE 159289 clearly states that a lyophilized bendamustine product should be avoided because bendamustine degrades during lyophilization. Moreover, DE 159289 states that a reconstituted, lyophilized bendamustine product has micro-particles. As those in the art readily appreciate, micro-particle-containing solutions are not suitable for injection into patients. DE 159289 instructs that *liquid formulations* of bendamustine, *not lyophilized formulations*, should be used.

Because DE 159289 *teaches away* from using a lyophilized form of bendamustine, the skilled person would not have combined the reference with Ni in order to produce a lyophilized bendamustine product. Moreover, there is nothing in the cited art that suggests that methods of lyophilizing SarCNU can be predictably and successfully applied to bendamustine. Furthermore, Ni provides no suggestions for eliminating micro-particles in a reconstituted solution. The Offices' allegations are speculative and cannot support a *prima facie* case of obviousness. Applicants request withdrawal of the rejection.

Applicants also submit herewith Terminal Disclaimers over a patent from which the present application claims priority (*i.e.*, U.S. Patent No. 8,436,190) and co-pending, related Application No. 13/719,409. Applicants submit these Terminal Disclaimers to obviate any possible contention that the pending claims would have been obvious in view of a claim of the disclaimed patent and patent application. The submission of these Terminal Disclaimers is not,

nor should it be construed as, an admission that Applicants consider any claim of the instant application to be patentably indistinct over any claim in the disclaimed patent and/or application.

Claims 1-4 are patentable over the cited art. An early notice to that effect is, therefore, earnestly solicited.

Date: June 3, 2013

/Stephanie A. Barbosa/
Stephanie A. Barbosa
Registration No. 51,430

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jason Edward Brittain

Confirmation No.: **6187**

Application No.: **13/719,379**

Group Art Unit: **1617**

Filing Date: **December 19, 2012**

Examiner: **Ali Soroush**

For: **Bendamustine Pharmaceutical Compositions**

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

Dear Commissioner:

DECLARATION PURSUANT TO 37 CFR § 1.131

I, Jason E. Brittain, hereby declare as follows:

1. I am one of the named inventors of the invention described and claimed in U.S. Application No. 13/719,379 ("the present application), which was filed with the United States Patent and Trademark Office ("the USPTO") on December 19, 2012.

2. Joe Craig Franklin, the other named inventor of the present application, is deceased.

3. As an inventor, I am familiar with the present application. I understand that the application traces its priority to U.S. Provisional Application No. 60/644,354, filed January 14, 2005.

4. I have reviewed the Office Action dated March 1, 2013 and the associated rejections alleged therein. I have also reviewed a reference cited in that Office Action – Kanekal et al., SDX-105 (Treanda™) Enhances the Tumor Growth Inhibitory Effect of Rituximab in Daudi Lymphoma Xenografts, Blood (ASH Annual Meeting Abstracts) 2004 104: Abstract 4580 ("the Kanekal reference"). I understand that the USPTO rejected claim 4 as allegedly not novel in view of the Kanekal reference.

5. I understand that the Kanekal reference has a publication date of November 16, 2004.

6. In accordance with 37 C.F.R. § 1.131, as an inventor of the subject matter of the allegedly rejected claim, and without conceding the propriety of the rejection, I hereby declare that Joe Craig Franklin and I invented the subject matter of claim 4 prior to November 16, 2004.

7. The inventions described and claimed in the present application were conceived and reduced to practice before the Kanekal reference published.

8. Exhibit A, attached to this declaration, is a redacted copy of a Formulation Development Report that summarizes research efforts and technical information related to an alternative formulation for bendamustine hydrochloride. I was the primary author of this report. Although the date of the Formulation Development Report has been redacted for purposes of this Declaration, I hereby declare that the document was prepared and signed by me prior to November 16, 2004.

9. The Formulation Development Report describes various experiments that were performed during the continued development of bendamustine hydrochloride. These experiments were performed by Joe Craig Franklin and me, or were performed under our direction and control.

10. The Formulation Development Report describes, among other things, a stable lyophilized preparation comprising bendamustine hydrochloride and mannitol in a ratio by weight of about 15:25.5, wherein the preparation is obtained by a process comprising preparing a composition comprising bendamustine hydrochloride, mannitol, tertiary-butyl alcohol and water, wherein the bendamustine hydrochloride and mannitol are present in the ratio by weight of about 15:25.5, and lyophilizing the composition under particular conditions to obtain the preparation. *See, e.g.,* Sections 3.3.2.3; 3.3.3; 4.3; 4.5; and 5; Figures 2, 3, and 4.

11. The Formulation Development Report shows that the subject matter claimed in the present application was invented prior to November 16, 2004.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or by imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

21 May 2013
Date

Jason E. Brittain

EXHIBIT A

Formulation Development Report for
SDX-105 (Bendamustine HCl) for Injection

1. Objective

To summarize and provide technical information for an alternative to the Ribomustine® formulation of Bendamustine HCl.

2. Introduction & History

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Ribomustine® is reconstituted with Water for Injection and subsequently diluted into normal saline. Reports from the clinic indicate that reconstitution can require as long as an hour with reconstitution rarely requiring less than 15 min. Bendamustine is unstable during admixture preparation primarily because of the lengthy reconstitution period resulting in significant potency loss with impurity attendant formation.

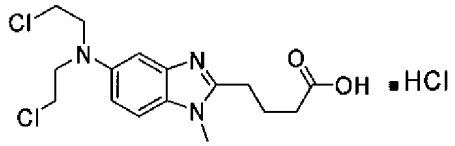
A work effort was initiated at Salmedix to further develop and optimize the drug product formulation and optimize the fill/finish process. The goals were to:

- Simplify the compounding procedure
- Stabilize bendamustine in solution to increase the permissible filling time
- Decrease lyophilization cycle time
- Decrease the amount of time for reconstitution
- Decrease the size of the vial to accommodate smaller lyophilizer chambers that are more commonly used in the industry.

3. Experimental

3.1. Materials

Bendamustine HCl, (Degussa, Lot # 0206005 and 0206007)



Mannitol, NF or equivalent (Mallinckrodt)
Ethyl Alcohol Dehydrated (200 proof), USP or equivalent (Spectrum)
Tertiary-butyl alcohol[1], Catalog #BX1805-1 (EM Science)
Methanol (Spectrum and EMD)
Propanol (Spectrum)
Iso-propanol (Spectrum)
Butanol (Spectrum)
Water, HPLC grade or equivalent (EMD)
Acetonitrile, HPLC grade or equivalent (EMD)
Trifluoroacetic Acid, J.T. Baker

3.2. Equipment

Waters 2695 Alliance HPLC system with photodiode array detector (ID #1066)
Waters 2795 Alliance HPLC system with dual wavelength detector (ID #1128)
Analytical Balance (Mettler AG285, ID #1028) and (Mettler XS205, ID #1097)
VirTis Lyophilizer AdVantage (ID #1088)

3.3 Procedure:

3.3.1 Solubility

The solubility of bendamustine HCl (bendamustine) in water (alone) and in co-solvent systems with varying amounts of methanol, ethanol, propanol, isopropanol, butanol and tertiary-butyl alcohol (TBA) was determined by visual inspection. Aliquots of bendamustine at 15 mg/mL, mannitol at 25.5 mg/mL were prepared in 10 mL of the indicated alcohol solutions at room temperature. Samples were then refrigerated at 5°C and inspected after 0, 3, 6 and 24 hours for the presence of particulates and/or precipitates.

The solubility of bendamustine was determined in 20% (v/v) TBA containing 25.5 mg/mL mannitol in water, 30% (v/v) TBA containing 25.5 mg/mL mannitol in water, REDACTED Bendamustine was added to 4 mL of each solution while mixing until bendamustine would no longer dissolve. The saturated solutions were allowed to mix for 1 hour at -8°C, 0°C, 5°C, or 25°C. The samples were centrifuged and placed back at the original temperature for a minimum of 30 minutes. The -8°C sample was placed into an ice bath containing sodium chloride which lowers the temperature of the ice bath

[1] Tertiary-butyl alcohol should be pharmaceutical grade and suitable for use in GMP manufacturing.

and the temperature was measured when the sample was pulled for analysis. An aliquot of each sample was taken and prepared for HPLC analysis.

3.3.2 Stability

3.3.2.1 Water

Solutions of bendamustine (15 mg/mL), mannitol (25.5 mg/mL) prepared in water at room temperature were immediately placed an ice bath (to lower the temperature quickly and close to 5°C) for 10 minutes and then refrigerated at 5°C. A sample of each formulation was analyzed by HPLC after 0, 3, 6 and 24 hours following storage at 5°C.

3.3.2.2 Ethyl alcohol

Solutions containing 15 mg/mL bendamustine, 25.5 mg/mL mannitol, REDAC REDACTED 5%, 10%, 20% or 30% (v/v) ethyl alcohol in water were prepared at room temperature, placed into an ice bath for 10 minutes and then refrigerated at 5°C. A sample of each formulation was analyzed by HPLC after 0, 3, 6 and 24 hours following storage at 5°C.

3.3.2.3 TBA, Methanol, Propanol, Iso-propanol, Butanol

Solution containing 15 mg/mL bendamustine, 25.5 mg/mL mannitol, and 5%, 10%, 20% or 30% (v/v) TBA, methanol, propanol, iso-propanol, or butanol in water were prepared at room temperature, placed into an ice bath for 10 minutes and then refrigerated at 5°C. A sample of each formulation was analyzed by HPLC after 0, 3, 6 and 24 hours following storage at 5°C.

3.3.3 Lyophilization Cycle Development

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activities. Different formulations were prepared at various concentrations of bendamustine, mannitol, ethanol, and TBA in water. The cycle parameters were changed and optimized at each step for freezing (fast vs. slow), primary drying (both temperature and pressure), and secondary drying.

3.4 Test methods description:

3.4.1 Appearance: The appearance was visually inspected for color and clarity.

3.4.2 Assay: Refer to development report REDACTED

3.4.3 Related Substances: Refer to development report REDACTED

4. Results

4.1 Solubility

The experiment summarized in Table 1 evaluated the effect of various alcohols, commonly used in lyophilization, on the stability of pharmaceutical formulations of

bendamustine as evaluated by visual appearance. The experimental solutions used varying concentrations of alcohols with 15 mg/mL bendamustine and 25.5 mg/mL mannitol. The indicated solutions were prepared at room temperature, refrigerated at 5°C, and visually inspected periodically over the following 24 hours.

Results summarized in Table 1 indicate that bendamustine solubility is dependent on time, temperature and the amount of alcohol in aqueous solutions. For the alcohols tested (excluding n-butanol), the solubility of bendamustine increased as the concentration of alcohol increased. Bendamustine did not precipitate immediately with any alcohol, but crystallized after storage at 5°C. Alcohols varied in their effect on bendamustine solubility. Smaller alcohols such as methanol and ethanol have less of an effect on solubility as compared with larger alcohols (t-butanol and n-butanol). However, the configuration of the alcohol was also important. For example n-propanol was much better than iso-propanol in preventing precipitation in this system. Bendamustine was most soluble in n-propanol and t-butanol.

Table 1. Physical Appearance over the 24 hour period in the various alcohols when stored at 5°C.

	Zero Time	3 Hours	6 Hours	24 Hours
Methanol				
0% (Water Only)	CCS	CCS	Precipitate	Precipitate
5%	CCS	CCS	Precipitate	Precipitate
10%	CCS	CCS	CCS	Precipitate
20%	CCS	CCS	CCS	Precipitate
30%	CCS	CCS	CCS	CCS
Ethanol				
1.9% (1.5% w/w)	CCS	CCS	Precipitate	Precipitate
5%	CCS	CCS	Precipitate	Precipitate
10%	CCS	CCS	CCS	Precipitate
20%	CCS	CCS	CCS	CCS
30%	CCS	CCS	CCS	CCS
Propanol				
5%	CCS	CCS	CCS	Precipitate
10%	CCS	CCS	CCS	CCS
20%	CCS	CCS	CCS	CCS
30%	CCS	CCS	CCS	CCS
Iso-propanol				
5%	CCS	Precipitate	Precipitate	Precipitate
10%	CCS	CCS	CCS	CCS
20%	CCS	CCS	CCS	CCS
30%	CCS	CCS	CCS	CCS
Butanol				
5%	CCS	CCS	CCS	CCS
10%	CCS	CCS	CCS	CCS
20%	2 layers	2 layers	2 layers	2 layers
30%	2 layers	2 layers	2 layers	2 layers
Tert-Butanol				
5%	CCS	CCS	CCS	Precipitate
10%	CCS	CCS	CCS	Precipitate
20%	CCS	CCS	CCS	CCS
30%	CCS	CCS	CCS	CCS

CCS-Clear, colorless solution

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REDACTED Experiments to quantitatively determine the solubility of bendamustine at various temperatures for three different co-solvent systems are summarized in Table 2 and Figure 1. The amount of TBA, 20% (v/v) and 30% (v/v), used in the experiment was based on stability studies (results described below). REDACTED
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Table 2. Solubility limit for three different co-solvent systems at various temperatures.

Formulation	Temperature			
	-8°C	0°C	5°C	25°C
20% (v/v) TBA 25.5 mg/mL mannitol Water, q.s. to volume	14 mg/mL	11 mg/mL	17 mg/mL	47 mg/mL
30% (v/v) TBA 25.5 mg/mL mannitol Water, q.s. to volume	20 mg/mL	18 mg/mL	27 mg/mL	65 mg/mL

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Figure 1.

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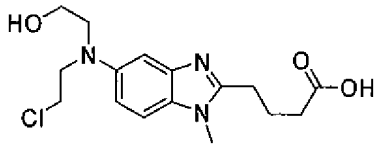
For all three solutions, the solubility of bendamustine decreased linearity with temperatures from 25°C to 0°C. This experiment confirms the observations made in the preceding experiment and discriminates the difference in bendamustine solubility for 20% and 30% TBA solutions.

4.2 Stability

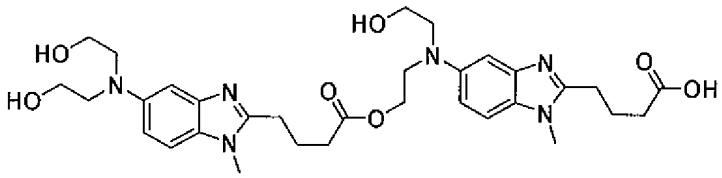
Bendamustine requires lyophilization because of its instability in aqueous solutions. However, during manufacturing of lyophilized drug products, aqueous solutions are commonly used during the process of filling, prior to lyophilization. Consequently, degradation of bendamustine occurs during filling of Ribomustine®. The effect of various co-solvent alcohol systems on stability was therefore evaluated.

Table 3 (refer to Appendix 1) shows the stability results of bendamustine in water without alcohol over a 24 hour period at 5°C. Bendamustine degrades rapidly in water alone and forms predominantly the hydrolysis product, HP1 (monhydroxy bendamustine).



Monohydroxyl bendamustine (HP1)

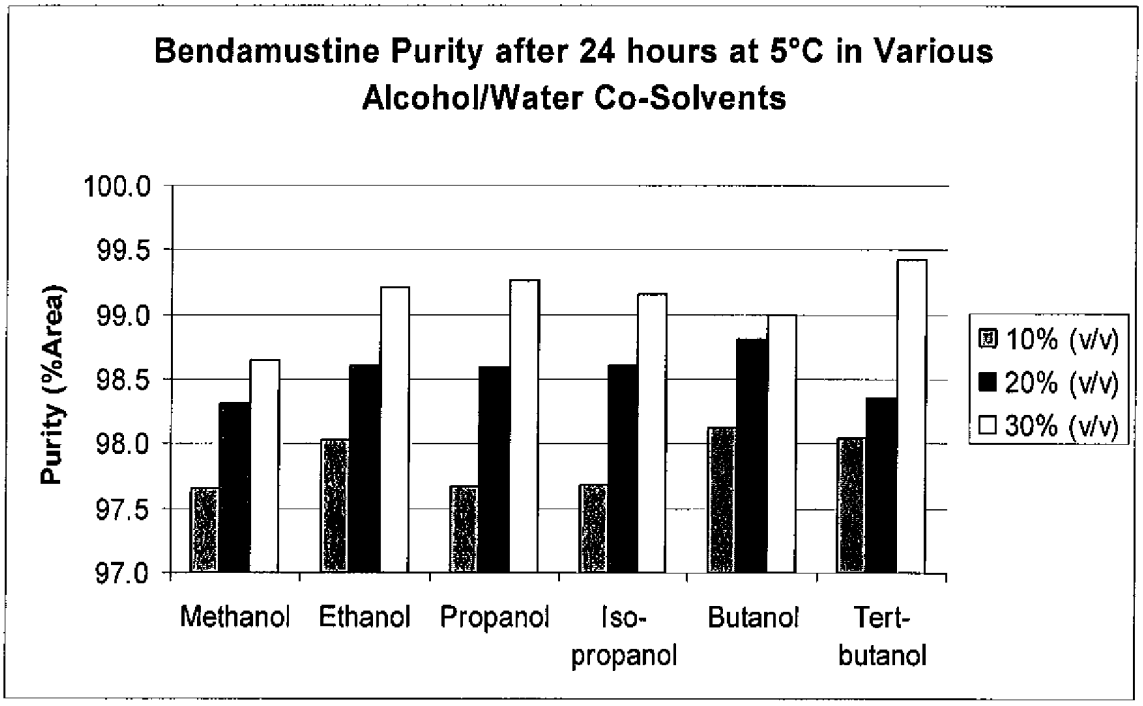
The other degradant observed during this study and longer term formal stability studies is the dimer of bendamustine.



Bendamustine Dimmer (BM1 Dimer)

Figure 2 summarizes the purity results of the HPLC analysis after incubating bendamustine in various alcohols for 24 hours at 5°C. Results are presented as the area percent of the bendamustine peak. The purity was highest in solutions containing higher concentration of alcohols, regardless of the alcohol. Of the alcohols evaluated, bendamustine degraded the least in a solution containing 30% (v/v) TBA. While in 10% and 20 % alcohol solutions, n-butanol was superior (Note: 20% and 30% (v/v) n-butanol aqueous solutions form two layers due to the insolubility in water).

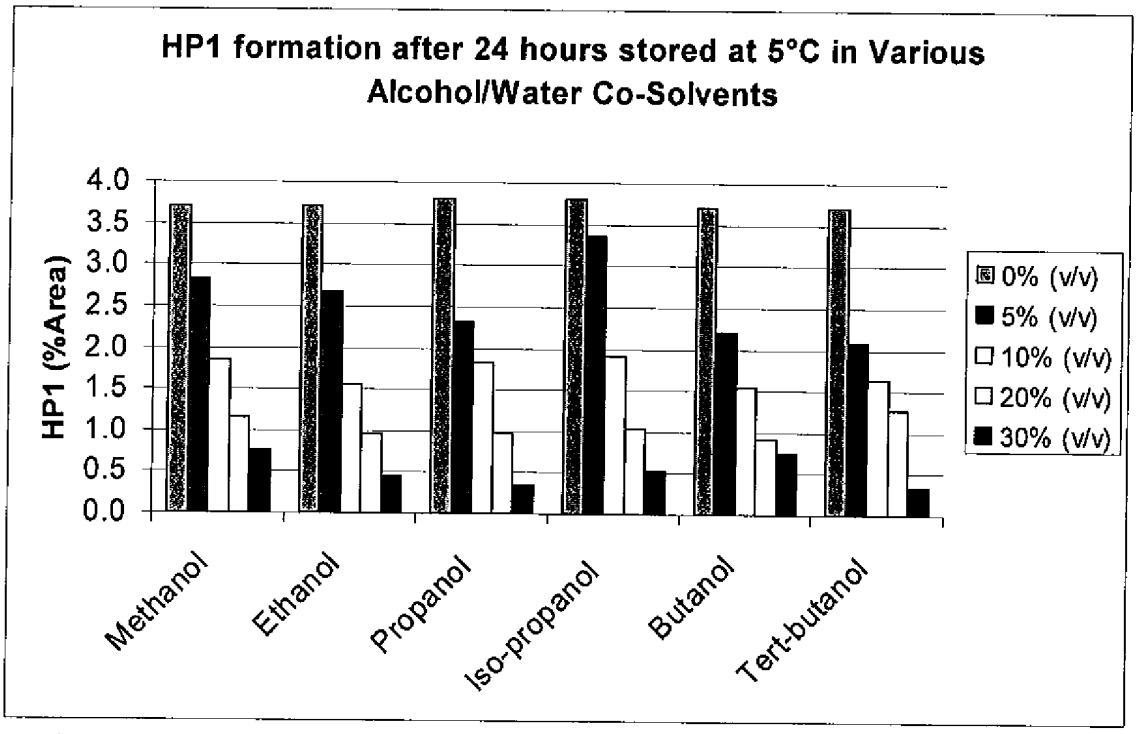
Figure 2.



The numerical values for Figure 2 are provided in Tables 3-9 in Appendix 1.

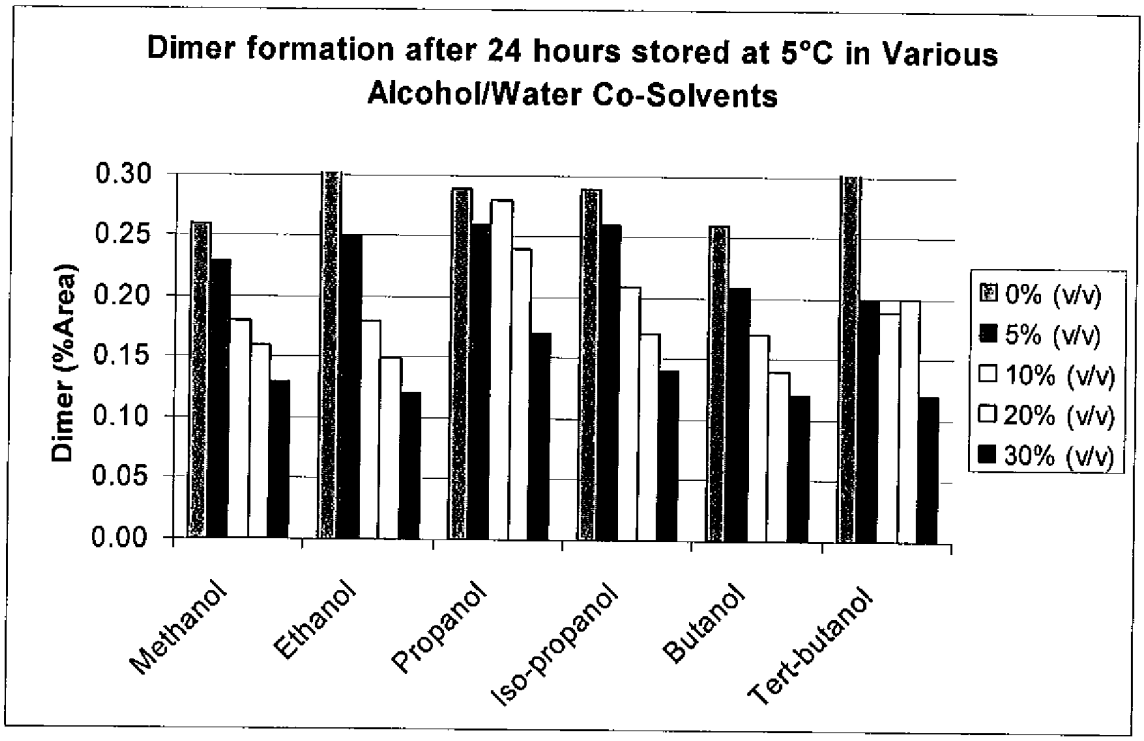
Figures 3 and 4 plots the amount of the only two observed degradants, HP1 and Dimer, detected after 24 hours in various alcohol/water co-solvent systems. The chromatographic peaks increased as the amount of alcohol concentration decreased regardless of the alcohol. In general, stability of bendamustine increased with increased alcohol in the co-solvent systems. T-butanol and n-butanol appeared superior to other alcohols. This increase in impurities was time dependent (refer to Tables 3-9 in Appendix 1 for data). An additional experiment was performed that showed mannitol had no effect on the stabilization of bendamustine with TBA.

Figure 3.



The numerical values for Figure 3 are provided in Tables 3-9 in Appendix 1.

Figure 4.



The numerical values for Figure 4 are provided in Tables 3-9 in Appendix 1.

4.3 Formulation Optimization

After the solubility and stability of bendamustine was determined in the previously described experiments, the formulation was optimized for lyophilization. Since the solubility of bendamustine is higher in a 30% TBA/water saturated solution as compared REDACTED REDACTED the fill volume containing 100 mg of bendamustine can be decreased. Although a saturated solution contains 18 mg/mL at 0°C, a concentration of 15 mg/mL was selected for the formulation to compensate for slight differences in API solubility. A concentration of 15 mg/mL bendamustine requires 6.67 mL to fill 100 mg of bendamustine per vial REDACTED REDACTED REDACTED

The surface (sublimation) area to volume ratio is critical to producing a lyophilized product with good appearance that freeze dries quickly. Generally, lyophilized products occupy between 30% to 50% of the vial volume. A 20 mL vial with 6.67 mL contains about 30% of its capacity and has a surface area ratio of 0.796 cm^2/mL. REDACTED REDACTED

Mannitol was again selected as the bulking agent in order to maintain a formulation similar to that of Ribomustine®. Studies were performed to evaluate the effect of mannitol on bendamustine solubility and appearance of the product. Mannitol decreases the solubility of bendamustine (at 15 mg/mL) in both ethanol and TBA aqueous solutions. For example, solutions containing 5% and 10% ethanol and TBA without mannitol did not precipitate over 24 hours. However, for samples with mannitol (Table 1) precipitate was observed within 24 hours. There was no precipitate with aqueous solutions containing 30% (v/v) TBA, 15 mg/mL bendamustine, and 25.5 mg/mL mannitol. In order to maintain a well formed cake resistant to breakage during handling, 134 to 200 mg/vial of mannitol proved optimal.

All alcohols tested increased the stability and solubility of bendamustine. However, a significant mole fraction was required to stabilize the filling solution and enhance ease of manufacturing. Smaller alcohols have the undesirable effect of lowering the freezing point of the bulk solution, thus requiring long lyophilization cycles at lower temperatures. Higher concentrations of methanol and ethanol resulted in unattractive cakes that were difficult to reconstitute. The fill solutions containing 10% ethanol, 20% ethanol, 10% iso-propanol, or 20% iso-propanol co-solvent produced either a collapsed cake or a film residue post lyophilization. The only co-solvent system producing an acceptable cake was 30% TBA. Reconstitution of 10% ethanol, 20% ethanol, 10% iso-propanol, 20% iso-propanol lyophilized vials were difficult and did not fully dissolve until >45 minutes. Reconstitution from the 30% TBA co-solvent lyophiliate was much easier.

At lower concentrations of ethanol, methanol, isopropanol and n-propanol, which would produce acceptable lyophiliate cake appearance, a more dilute solution (due to solubility) of bendamustine is required. Consequently, to allow a vial containing bendamustine with 100 mg, a larger vial would be required. Stability studies also indicated that at the lower alcohol concentration, the chemical stability was not sufficient for allow for acceptable filling times using methanol, ethanol, propanol, iso-propanol, or n-butanol.

TBA is a commonly used co-solvent for lyophilization[2] REDACTED
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One of the factors affecting ease of reconstitution is the porosity of the lyophiliate. In general, amorphously precipitated solids with little surface area are more difficult to solubilize. Most lyophiliates containing mannitol will reconstitute within 3-5 minutes as long as there no is precipitate, frequently caused by evaporation of a liquid (melt back). Based on our experience with several lyophilization co-solvent systems, we believe the problems associated with Ribomustine® reconstitution are associated with precipitation caused by melt back during lyophilization. Most organic solvents do not lyophilize efficiently and cause melt back because of their low melting point. TBA has a high melting point and a vapor pressure similar to that of water. TBA is removed by sublimation, not evaporation, at about the same rate as water. Bendamustine lyophiliates produced with 30% (v/v) TBA reconstitute within 3-5 minutes following addition of Water for Injection as compared to 30-45 minutes for Ribomustine®.

Based upon all of the information detailed above regarding bendamustine solubility, stability, and ease of lyophilization, the final formulation selected is:

Ingredients	Concentration
Bendamustine HCl	15 mg/mL
Mannitol	25.5 mg/mL
Tertiary-butyl alcohol	30% (v/v)
Water, q.s. to	1 mL

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1) Add ~65% total volume with water
2) Add mannitol and mix until dissolved
3) Add TBA and mix until homogenous
4) Add bendamustine and mix until dissolved
5) q.s. with water,
6) Cool solution to 5°C

4.4 Impurity assessment

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With the use of a 30% TBA aqueous filling solution, the possibility of forming the analogous tert-butyl ester exists and consequently was investigated.

[2] Teagarden, D., Baker, D. 2002. Practical aspects of lyophilization using non-aqueous co-solvent systems. European Journal of Pharmaceutical 15. 2002. p 115-133

The reaction conditions required for the formation of tert-butyl ester of bendamustine were explored. Bendamustine was heated in 60°C TBA with HCl for 20 hours. No esterification was observed. This result indicated that it would be very difficult to form the tert-butyl ester of bendamustine during drug product manufacturing.

Another attempt to make tert-butyl ester was carried out by formation of bendamustine acyl chloride. A suspension of bendamustine in methylene chloride was treated with oxalyl chloride and N,N-dimethylformamide. After acyl chloride was formed, the solvent was concentrated. The residue was added to methylene chloride, tert-butanol, triethylamine, and 4-dimethylaminopyridine and the mixture was stirred at room temperature overnight. After work-up and purification, an unknown compound was obtained. The LC-MS did not match the molecular weight of bendamustine tert-butyl ester and the proton NMR did not showed the peak for tert-butyl. Therefore, this attempt also failed to produce the bendamustine tert-butyl ester. REDACTED
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4.5 Lyophilization Cycle Development

Numerous lyophilization cycles were performed to evaluate the critical stages of lyophilization and achieve the most efficient drying cycle. Experiments were performed to evaluate the effect of the freezing rate, primary drying temperature, time, and pressure on product quality.

4.5.1 Freezing Rate

The literature[3] reports that TBA adopts different crystal forms depending on the freeze rate. In some TBA solutions, the slower the product froze, the quicker it dried. Larger crystals formed during slow freezing producing bigger pores allowing more efficient sublimation. During studies with bendamustine, freezing rate was not found to be a critical processing parameter.

4.5.2 Primary and Secondary Drying

During the first attempts to lyophilize from 30% TBA solutions, the lyophilized cake fractured and powder was ejected from the vial. These cakes appeared to contain amorphous particles within the lyophiliate, an indication of melt back. This phenomenon was reproducible and occurred when the product reached about -10°C independent of the warming rate. Several variables were tested to determine the cause and solution to the problem of the powder ejection. The pressure was raised from 50 μm to 150 μm during primary drying, but powder ejection was still observed but to a lesser extent (JB039-82). Experiment JB039-82 was repeated except the freezing rate was extended to 8 hours from 2 hours. This change had no effect. The length of primary drying was evaluated as follows for a very slow freeze drying cycle:

[3] Wittaya-Areekul, S., Nail, S.L. 1998. Freeze-Drying of tert-Butyl Alcohol/Water Cosolvent Systems: Effects of Formulation and Process Variables on Residual Solvents. Journal of Pharmaceutical Sciences. 87 (4) April 1998. p 491-495

1) Freezing from +25°C to -50°C over eight hours
2) Holding at -50°C for 5 hours
3) Warming and drying from -50°C to -25°C over 7 hours, a chamber pressure of 150 μm
4) Holding for 20 hours at -25°C, a chamber pressure of 150 μm
5) Warming and drying from -25°C to -15°C over 2 hours, a chamber pressure of 150 μm
6) Holding for 20 hours at -15°C, a chamber pressure of 150 μm
7) Warming and drying from -15°C to 40°C over 6 hours, a chamber pressure of 150 μm
8) Holding for 20 hours at 40°C, a chamber pressure of 150 μm
9) Cooling to 20°C for unloading the vials

Using this modified lyophilization scheme, no powder ejection (refer to Attachment II) was observed. The secondary drying did not require drying for the entire 20 hours because the main result of no powder ejection occurred and a new cycle was going to be initiated. This modified cycle resulted in a well formed cake without fracture that reconstituted readily. We believe that the problems with powder ejection and difficulty with reconstitution are the result of drying the lyophiliate too fast, thus resulting in strong vapor flow out of the cake and melt back. With the use of a less aggressive drying cycle an aesthetic, stable, and easy to reconstitute cake was reproducibly formed. The lyophilization cycle was further optimized under these gentle conditions (refer to Attachment III).

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4.6 Safety

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5. Conclusions

Solubility

The solubility of bendamustine is temperature dependent whether it is dissolved in water alone or with an alcohol co-solvent. 20% (v/v) TBA is most likely the lower limit required for efficient and robust pharmaceutical manufacturing due to the stability and solubility of bendamustine. A filling solution of 15 mg/mL bendamustine is less than the saturation limit of 17.2 mg/mL bendamustine in 20% (v/v) TBA at 5°C but higher than the limit at 0°C which could create problems during reconstitution due to precipitation of bendamustine. 30% (v/v) TBA is therefore the recommended concentration of TBA for

the final formulation and is well within the solubility across the range of temperatures used in the manufacturing process.

Stability

Bendamustine degrades quickly in water but the stability of bendamustine increases with increasing alcohol concentrations. Although alcohols are frequently used in lyophilization to aid in solubility, the effect of alcohols on bendamustine stability is unique, unexpected and useful in manufacturing bendamustine with fewer impurities. TBA was found to be the best stabilizer of the six alcohols tested. All alcohols at 30% (v/v) reduced the formation of impurities HP1 and Dimer at 5°C for up to 24 hours. With respect to TBA, HP1 reaches only about 0.4% when stored at 5°C for up to 24 hours. This is well within the product specification that allows for up to 3.3%. Lower concentrations of TBA are not practical, when formulated at 15 mg/mL and stored at 5°C due to bendamustine precipitation and impurity formation.

Formulation

Based upon the solubility, stability, ease of reconstitution and manufacturing considerations, the following bulk formulation process is recommended:

1) Add ~65% total volume with water
2) Add mannitol and mix until dissolved
3) Add TBA and mix until homogenous
4) Add bendamustine and mix until dissolved
5) q.s. with water,
6) Cool solution to 5°C

The bulk formulation is then filled at 5°C using 6.67 mL in an amber 20 mL, 20 mm vial and partially stoppered with a bromobutyl stopper and loaded into a pre-chilled lyophilizer.

Lyophilization cycle.

The VirTis Advantage XL is a small laboratory scale lyophilizer that operates much different than production lyophilizers. In this lyophilizer, this formulation required a less aggressive cycle. It was important to control the pressure at ~150 μm, maintaining the temperature below -10°C to remove the majority of the water and residual t-butanol. Product in the VirTis Advantage XL lyophilizer is about 15°C warmer than the shelf under colder temperatures. Production lyophilizer should display fewer differences between the product and shelf temperature and this will need to be evaluated. The secondary drying was not fully optimized in this study. The length of time for the secondary drying could be reduced with studies following the removal of volatiles over time.

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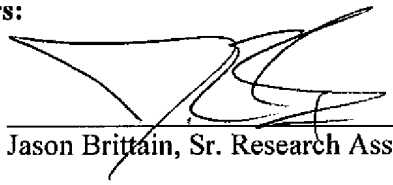
Authors:



REDACTED

Jason Brittain, Sr. Research Associate Pharmaceutical Sciences

Approval:

REDACTED

Gary Elliott, VP Product Development

Appendix 1.

Table 3. Bendamustine stability results for water alone solutions over a 24 hour period.

	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
0% Alcohol or Water Alone	0 hours	99.11	0.60	0.11
	3 hours	98.83	0.86	0.13
	6 hours	98.44	1.22	0.17
	24 hours	95.67	3.81	0.29

Table 4. Bendamustine stability results for various ethyl alcohol co-solvent concentrations over a 24 hour period.

Co-Solvent	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
1.5% Ethanol/H_2O (1.9% v/v)	0 hours	99.11	0.64	0.12
	3 hours	98.83	0.90	0.14
	6 hours	98.60	1.12	0.15
	24 hours	96.16	3.41	0.27
5% Ethanol/H_2O	0 hours	99.31	0.44	0.12
	3 hours	99.10	0.64	0.13
	6 hours	98.87	0.86	0.14
	24 hours	96.89	2.68	0.25
10% Ethanol/H_2O	0 hours	99.44	0.33	0.11
	3 hours	99.28	0.48	0.12
	6 hours	99.10	0.65	0.12
	24 hours	98.03	1.57	0.18
20% Ethanol/H_2O	0 hours	99.54	0.22	0.10
	3 hours	99.45	0.30	0.11
	6 hours	99.36	0.39	0.11
	24 hours	98.61	0.96	0.15
30% Ethanol/H_2O	0 hours	99.62	0.15	0.10
	3 hours	99.56	0.21	0.11
	6 hours	99.52	0.24	0.12
	24 hours	99.21	0.45	0.12

Table 5. Bendamustine stability results for various tert-butyl alcohol co-solvent concentrations over a 24 hour period.

Co-Solvent	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
5% Tert-butanol/H_2O	0 hours	99.34	0.41	0.12
	3 hours	99.10	0.64	0.14
	6 hours	98.85	0.88	0.13
	24 hours	97.58	2.09	0.20
10% Tert-butanol/H_2O	0 hours	99.46	0.30	0.11
	3 hours	99.26	0.48	0.12
	6 hours	99.05	0.69	0.13
	24 hours	98.04	1.64	0.19
20% Tert-butanol/H_2O	0 hours	99.59	0.17	0.11
	3 hours	99.48	0.29	0.11
	6 hours	99.35	0.40	0.12
	24 hours	98.35	1.27	0.20
30% Tert-butanol/H_2O	0 hours	99.63	0.13	0.10
	3 hours	99.60	0.16	0.10
	6 hours	99.58	0.18	0.11
	24 hours	99.42	0.34	0.12

Table 6. Bendamustine stability results for various propyl alcohol co-solvent concentrations over a 24 hour period.

Co-Solvent	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
5% Propanol/H_2O	0 hours	99.25	0.43	0.13
	3 hours	99.00	0.66	0.15
	6 hours	98.72	0.94	0.16
	24 hours	97.24	2.33	0.26
10% Propanol/H_2O	0 hours	99.34	0.33	0.15
	3 hours	99.17	0.48	0.14
	6 hours	98.92	0.70	0.16
	24 hours	97.67	1.83	0.28
20% Propanol/H_2O	0 hours	99.45	0.33	0.13
	3 hours	99.42	0.26	0.13
	6 hours	99.29	0.39	0.14
	24 hours	98.60	0.97	0.24
30% Propanol/H_2O	0 hours	99.53	0.15	0.13
	3 hours	99.51	0.15	0.15
	6 hours	99.44	0.20	0.11
	24 hours	99.27	0.36	0.17

Table 7. Bendamustine stability results for various iso-propyl alcohol co-solvent concentrations over a 24 hour period.

Co-Solvent	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
5% Iso-propanol/H_2O	0 hours	99.21	0.48	0.13
	3 hours	98.65	0.72	0.14
	6 hours	98.56	1.02	0.14
	24 hours	96.14	3.35	0.26
10% Iso-propanol/H_2O	0 hours	99.32	0.37	0.12
	3 hours	99.11	0.55	0.14
	6 hours	98.85	0.75	0.16
	24 hours	97.68	1.92	0.21
20% Iso-propanol/H_2O	0 hours	99.49	0.21	0.11
	3 hours	99.39	0.31	0.12
	6 hours	99.22	0.42	0.13
	24 hours	98.61	1.04	0.17
30% Iso-propanol/H_2O	0 hours	99.56	0.15	0.10
	3 hours	99.47	0.20	0.12
	6 hours	99.40	0.24	0.11
	24 hours	99.15	0.52	0.14

Table 8. Bendamustine stability results for various methyl alcohol co-solvent concentrations over a 24 hour period.

Co-Solvent	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
5% Methanol/H_2O	0 hours	99.35	0.40	0.12
	3 hours	98.97	0.70	0.14
	6 hours	98.66	0.95	0.14
	24 hours	96.65	2.83	0.23
10% Methanol/H_2O	0 hours	99.42	0.34	0.11
	3 hours	99.01	0.59	0.12
	6 hours	98.86	0.80	0.12
	24 hours	97.65	1.85	0.18
20% Methanol/H_2O	0 hours	99.56	0.22	0.11
	3 hours	99.31	0.38	0.11
	6 hours	98.99	0.50	0.12
	24 hours	98.31	1.15	0.16
30% Methanol/H_2O	0 hours	99.59	0.18	0.10
	3 hours	99.43	0.27	0.11
	6 hours	99.25	0.34	0.11
	24 hours	98.65	0.76	0.13

Table 9. Bendamustine stability results for various butyl alcohol co-solvent concentrations over a 24 hour period.

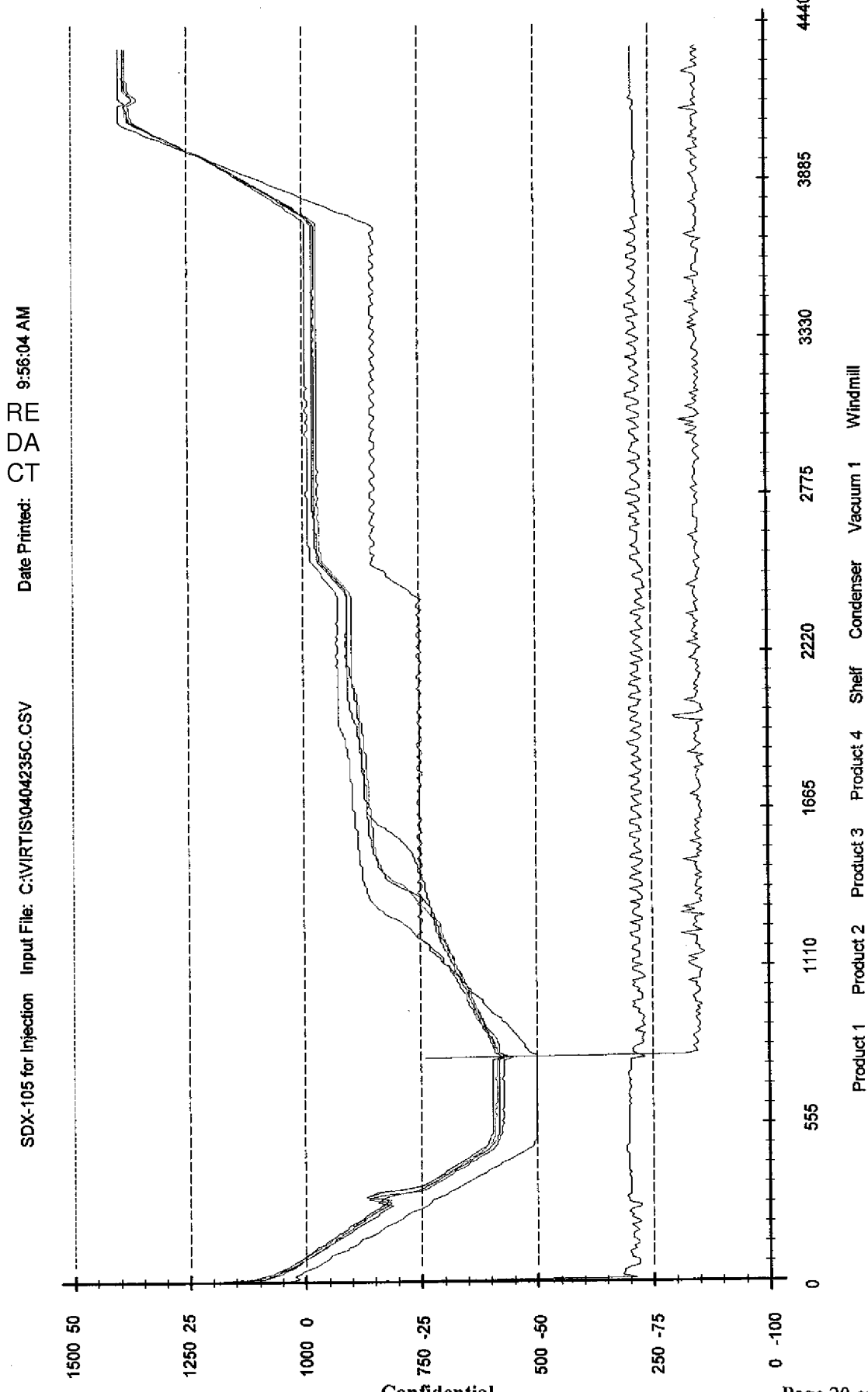
Co-Solvent	Hold Time	Purity (%Area)	Related Substances	
			HP1 (%)	Dimer (%)
5% Butanol/H_2O	0 hours	99.25	0.49	0.13
	3 hours	98.94	0.73	0.14
	6 hours	98.76	0.91	0.14
	24 hours	97.46	2.20	0.21
10% Butanol/H_2O	0 hours	99.44	0.30	0.11
	3 hours	99.18	0.49	0.12
	6 hours	99.03	0.64	0.12
	24 hours	98.13	1.55	0.17
20% Butanol/H_2O [a]	0 hours	99.54	0.23	0.10
	3 hours	99.45	0.31	0.11
	6 hours	99.30	0.40	0.11
	24 hours	98.81	0.91	0.14
30% Butanol/H_2O [a]	0 hours	99.55	0.24	0.10
	3 hours	99.40	0.29	0.10
	6 hours	99.40	0.37	0.11
	24 hours	99.00	0.74	0.12

a – Both solutions had 2 layers/phases of liquids in the vial. Solutions were vortexed prior to sample preparation.

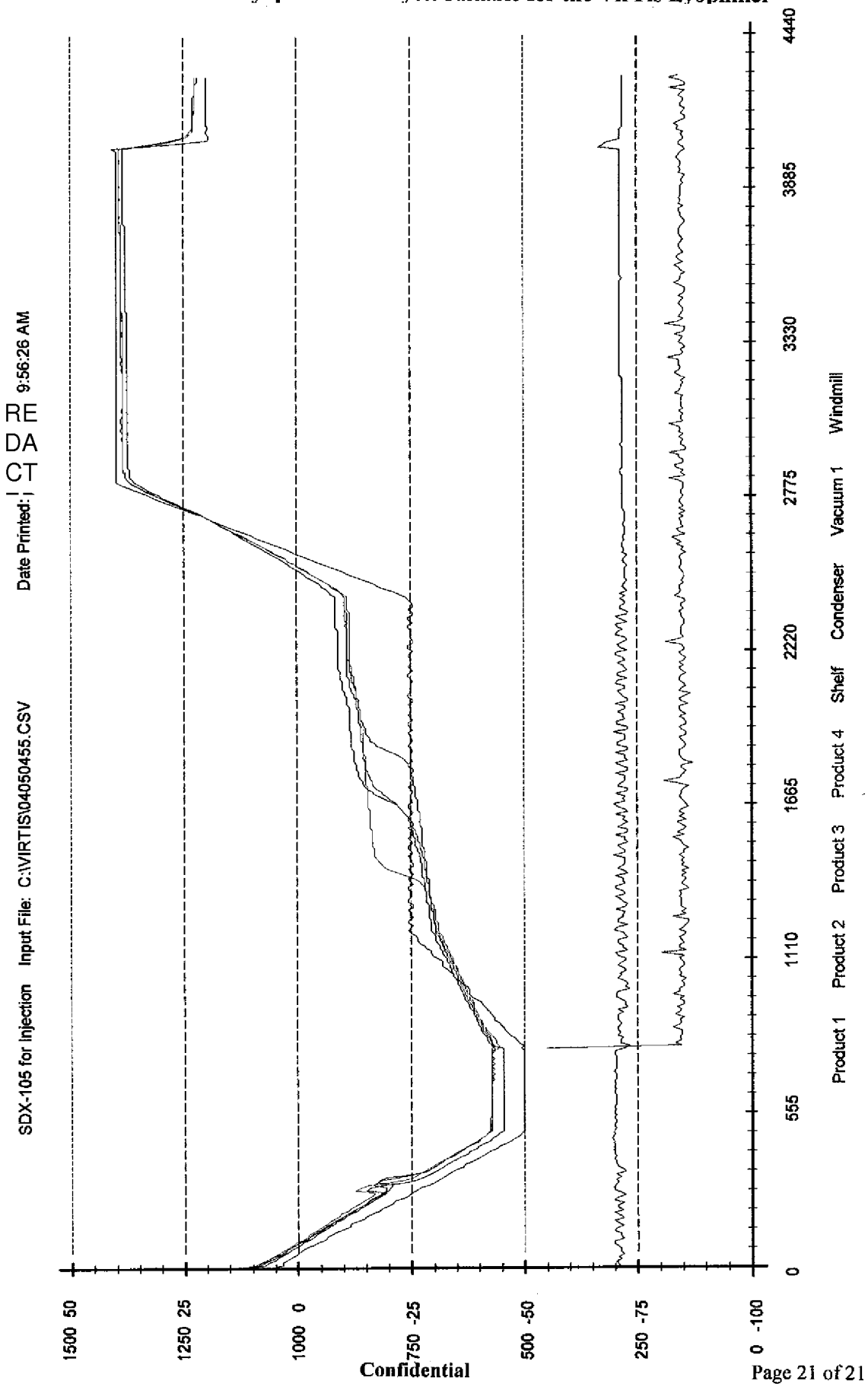
Attachment I. REDACTED

REDACTED

Attachment II. Lyophilization Cycle suitable for the VirTis Lyophilier



Attachment III. Modified Lyophilization Cycle suitable for the VirTis Lyophilier



Abstract: The invention relates to a method for producing stable injection solutions which can be used for medical treatment. It is the objective to produce a ready to use, stable injection solution of N-mustard compounds, avoiding the technical solution of a dry ampoule. According to the invention, the N-mustard compounds are used in concentrations of 25 mg/ ml to 100 mg/ ml, dissolved in an anhydrous monovalent or polyvalent alcohol (polyol), wherein the solution is dissolved, filled and stored under inert gas. Before the injection, the solutions are diluted by means of an aqueous injection medium in order to achieve the desired concentration.

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(54) VERFAHREN ZUR HERSTELLUNG STABILER INJEKTIONSLOESUNGEN VON N-LOSTVERBINDUNGEN

(57) Die Erfindung beinhaltet ein Verfahren zur Herstellung von zur medizinischen Behandlung verwendbaren Injektionslösungen. Ziel ist die Herstellung einer stabilen und gebrauchsfertigen Injektionslösung von N-Lostverbindungen unter Umgehung der technischen Lösung als Trockenampulle. Die N-Lostderivate werden erfindungsgemäß in Konzentrationen von 25 mg/ml bis zu 100 mg/ml in einem ein- oder mehrwertigen Alkohol, insbesondere 1,2-Propylenglykol, gelöst wobei das Lösen, Abfüllen und Aufbewahren der Lösungu unter Inertgas erfolgt. Vor der Injektion werden die Lösungen mit einem wäßrigen Injektionsträger auf die gewünschte Konzentration verdünnt.

9 Seiten

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bei der chronischen Lymphadenose, der Lymphoretikulose, der Lyphogranulomatose und bei Retikulosen eingeführt.

Bendamustinhydrochlorid ist eine relativ instabile Verbindung. In wäßrigen Lösungen erfolgt nach kurzer Zeit eine nahezu vollständige Hydrolyse der Lost-Halogengruppen. Deshalb ist die Herstellung der Injektionslösungen erst kurz vor der Injektion möglich. Die kinetischen Untersuchungen zur Chloridhydrolyse der N-Lostgruppe des Bendamustinhydrochlorids ergaben in sauren und neutralen Lösungen einen Reaktionsablauf, der sich nach pseudoerster Reaktionsordnung für eine Folgereaktion der symmetrischen Dihalogenidverbindung berechnen ließ (U. OLTHOFF, Abstr. Congr. Pharm. Hung. VI, Budapest 1974, S. 72). Die Chlorid- und Protonenabspaltung aus den ß-Chlorethylgruppen erfolgt unabhängig vom pH-Wert und von eingesetzten Puffersystemen vollständig und mit sehr großer Geschwindigkeit. Dabei übertrifft Bendamustinhydrochlorid sogar die besonders reaktionsfähigen Loste N-Methyl-Lost, Chlorambucil und Uracil-Lost. Diese Angaben begründen die besondere Schwierigkeiten, die sich der Herstellung stabiler medizinischer Zubereitungen des Bendamustinhydrochlorids entgegenstellen.

Nach der DDR-Patentschrift WP 80 967 muß das N-Lostderivat Bendamustinhydrochlorid steril, schwebstofffrei und in einer für die schnelle Auflösung geeigneten Kristallform hergestellt werden. Die Zubereitungsform ist eine Trockenampulle, die eine Mischung von 25 mg Bendamustinhydrochlorid und 175 mg Ascorbinsäure enthält. Vor der Anwendung ist der Ampulleninhalt in Wasser zur Injektion aufzulösen. Die Ascorbinsäure hat die Aufgaben, ein abfüllfähiges Pulvergemisch herzustellen, sowie die Haltbarkeit und den pH-Wert der Injektionslösung zu sichern. Außerdem soll auch die Lagerfähigkeit des trockenen Gemisches erreicht werden. Die Hydrolysegeschwindigkeit wird nach vorliegenden Versuchsergebnissen durch den Ascorbinsäurezusatz nicht beeinflußt.

Der pH-Wert einer Bendamustinhydrochlorid-Lösung, der im Bereich von 2,4 bis 3,0 liegt, wird durch den Ascorbinsäurezusatz nicht wesentlich verändert. Der Ascorbinsäurezusatz erfüllt demnach nicht die an einen Stabilisator zu stellenden Anforderungen. Bendamustinhydrochlorid zeigt als Festsubstanz nach einiger Lagerungszeit eine rosa bis braunrote Verfärbung, die von der Substanzoberfläche ausgeht und nach längerer Zeit die gesamte Substanz für die Herstellung von pharmazeutischen Zubereitungen ungeeignet macht. Auch die Mischung mit Ascorbinsäure zeigt diesen Effekt.

Weiterhin wurde vorgeschlagen, die wäßrige Lösung der Substanz Bendamustinhydrochlorid zu lyophilisieren und vor der Anwendung in Wasser oder Natriumchloridlösung aufzulösen (Herstellungsverfahren des ZIMET, Pharmazeutisches Gutachten IfAr/Nr. 180/80). Das erhaltene Lyophilisat (25 mg/Ampulle) weist erhebliche Nachteile für einen technologischen Herstellungsprozeß auf. Insbesondere die extreme Hygroskopizität und die Durchführung des Prozesses unter Inertgas erschweren die technologische Realisierbarkeit. Außerdem wurden während der Herstellung des Präparates deutliche Zersetzungserscheinungen im Bereich von 5 bis 10 % des Wirkstoffes nachgewiesen. Unbefriedigend ist auch die Feststellung großer Mengen von Mikropartikeln nach Auflösen des Lyophilisats, die auf eine weitere Instabilität des Systems hinweisen.

Der Nachteil der extremen Hygroskopizität des Lyophilisats kann durch Zusätze von bei Raumtemperatur festen Polyolen, insbesondere von Mannitol, behoben werden. Neben dem hohen technologischen Aufwand sind jedoch weiterhin die Nachteile einer erheblichen Zersetzung und des Auftretens von ungelösten Mikropartikeln gegeben.

Ziel der Erfindung

Ziel der Erfindung ist die Herstellung einer stabilen und gebrauchsfertigen Injektionslösung von N-Lostverbindungen unter Umgehung der technischen Lösung als Trockenampulle.

Darlegung des Wesens der Erfindung

Die bisher bekannten technischen Lösungen realisierten das Injektionspräparat entweder als Pulverabfüllung unter Zugabe eines Stabilisators bzw. andersartiger Hilfsstoffe, oder als Lyophilisat, ggf. unter Zusatz von Hilfsstoffen. Durch diese Maßnahmen gelingt es nicht bzw. nur mit erheblichen Nachteilen, ein geeignetes Injektionspräparat herzustellen. Die so erhaltenen Trockenabfüllungen sind durch mangelhafte chemische und physikalische Stabilität gekennzeichnet. Außerdem stellt die Lyophilisierung einen erheblichen technischen Mehraufwand dar, der sich als kapazitätsbegrenzend erweisen kann.

Überraschend wurde nunmehr gefunden, daß der Wirkstoff Bendamustinhydrochlorid in einwertigen Alkoholen, Glykolen und anderen mehrwertigen Alkoholen eine zur Herstellung von Injektionslösungen ausreichende Löslichkeit und vor allem eine auffällig hohe chemische Stabilität aufweist. Die Stabilität der erfindungsgemäß hergestellten Lösungen ist unerwartet, weil Verbindungen mit extremer Hydrolyseempfindlichkeit in der Regel auch empfindlich gegenüber anderen OH-Gruppen enthaltenden Lösungsmitteln sind. Im Falle von Alkoholen oder Polyolen sind derartige Reaktionen als Alkoholyse bekannt.

Es wurde nunmehr gefunden, daß N-Lostverbindungen vom Typ des Bendamustinhydrochlorids keine Alkoholysereaktion eingehen. Voraussetzung ist die Verwendung wasserfreier Lösungsmittel, um Zersetzungen durch die angegebene große Hydrolyseempfindlichkeit zu vermeiden. Unter diesen Voraussetzungen ist z. B. Bendamustinhydrochlorid über lange Zeiträume in der genannten Gruppe von Lösungsmitteln chemisch stabil und bildet nicht die aus wäßrigen Lösungen bekannten Mono- und Dihydroxy- bzw. -alkoxyderivate.

Zur Untersuchung der Stabilität wurde Bendamustinhydrochlorid in einer Konzentration von 25 mg/ml in Ethanol und 1,2-Propylenglykol gelöst und die Lösung bei Raumtemperatur, sowie erhöhten Temperaturen (50 °C, 75 °C, 130 °C) aufbe-

mittels eines spezifischen dünnschichtchromatographischen Verfahrens (Auftragmenge entspr. 0,025 mg Bendamustinhydrochlorid, Kieselgel G, Laufmittel: Butanol/Essigsäure/Wasser 4:1:5, Detektion UV 360 nm bzw. Dragendorff-Reagenz) auf die Bildung von Spaltprodukten hin untersucht, Befunde:

Bildung von Abbauprodukten in:

Zeit	Ethanol-Lösung		Propylenglykol-Lösung		
	25 °C	50 °C	25 °C	75 °C	130 °C
0,5 h	–	–	–	–	(Spuren)
1 h	–	–	–	ohne	–
1,5 h	–	–	–	–	(Spuren)
2 h	–	–	–	ohne	geringe Zersetzung
5 h	ohne	ohne	–	ohne	–
7 h	ohne	ohne	–	–	–
24 h	ohne	–	–	–	–
8 Wochen	ohne	–	ohne	–	–

Aus pharmakologischen und fertigungstechnischen Gründen sind einwertige Alkohole zur Herstellung von Injektionslösungen wenig geeignet. Häufiger verwendet wird 1,2-Propylenglykol. Die erzielbaren Löslichkeiten von Bendamustinhydrochlorid in einigen der benutzten Lösungsmittel betragen bei 25 °C etwa

Ethanol abs.	ca.	50 mg/ml
Propylenglykol	ca.	125 mg/ml und
Glycerol	ca.	50 mg/ml.

In den bisher bekannten Injektionsformen des Bendamustinhydrochlorids werden 25 mg Wirkstoff in 10 ml Lösungsmittel eingesetzt. Es wird nunmehr vorgeschlagen, zur Gewährleistung einer vereinfachten Herstellungstechnologie, einer verbesserten Wirkstoffstabilität bei der Herstellung der Lösungen und deren Aufbewahrung sowie einer vereinfachten Handhabung bei der Herstellung der injektionsfertigen Lösung den Wirkstoff in Polyolen, insbesondere in 1,2-Propylenglykol zu lösen und in Ampullen abzufüllen. Unmittelbar vor der vorgesehenen Injektion wird die Polyollösung durch

den Zusatz eines geeigneten wäßrigen Verdünnungsmittels (Natriumchloridlösung oder Wasser zur Injektion) so verdünnt, daß die zur Anwendung kommende Lösung nur noch ca. 10 % Polyol, ggf. auch weniger enthält. Die Polyollösungen sind mit den angegebenen Verdünnungsmitteln ohne Nachteil für den Wirkstoff beliebig verdünnbar. Durch die breite Variationsmöglichkeit des Polyolanteils und der Verdünnung ergeben sich weitere Vorteile für die Auswahl einer optimalen, besonders gut verträglichen Injektionszubereitung. Neben der Hydrolyseempfindlichkeit sind als weitere Stabilitätsfaktoren die Einwirkungen von Licht und Luftsauerstoff zu berücksichtigen. Trockene Zubereitungen und auch Lösungen verfärben sich unter Licht- und Lufteinwirkung langsam rosa oder bräunlich. Die Lösungen in Alkoholen und Polyolen, die in gut verschlossenen Ampullen unter Lichtausschluß aufbewahrt werden, zeigen keine Verfärbungserscheinungen. Es ist jedoch zu empfehlen, die Herstellung, Abfüllung und Aufbewahrung der Lösungen unter einem Inertgas, wie Argon oder Stickstoff vorzunehmen.

Ausführungsbeispiele

Beispiel 1:

Bendamustinhydrochlorid wird in einer Inertgasatmosphäre in 1,2-Propylenglykol in einer Konzentration von 2,5 g/100 ml unter Rühren gelöst. Die Lösung wird über eine geeignete Filtereinrichtung, ggf. nach Erwärmen auf 50 °C, schwebstofffrei und keimfrei filtriert. In 10-ml-Ampullen wird jeweils 1,0 ml der Lösung abgefüllt, die Ampullen mit Inertgas gefüllt und verschmolzen. Unmittelbar vor der Injektion sind in die geöffnete Ampulle 9,0 ml des vorgesehenen Verdünnungsmittels zu geben. Nach dem Umschütteln ist die Lösung injektionsfertig.

Beispiel 2:

5,0 g Bendamustinhydrochlorid werden in 100 ml Ethanol unter den bei Beispiel 1 genannten Bedingungen gelöst, filtriert

und in Ampullen abgefüllt. Die Aufbewahrung der Ampullen erfolgt bei Temperaturen von +15 °C bis +25 °C.

Erfindungsanspruch

1. Verfahren zur Herstellung stabiler Injektionslösungen von N-Lostverbindungen gekennzeichnet dadurch, daß N-Lostderivate in Konzentrationen von 25 mg/ml bis zu 100 mg/ml in einem wasserfreien ein- oder mehrwertigen Alkohol (Polyol) gelöst werden, wobei das Lösen, Abfüllen und Aufbewahren der Lösung unter Inertgas erfolgt, und die Lösung vor der medizinischen Anwendung im Verhältnis von 1:5 bis 1:20 mit einem wäßrigen Injektionsträger verdünnt wird.

2. Verfahren nach Punkt 1 gekennzeichnet dadurch, daß als Wirkstoff Benzimidazol-Loste, insbesondere Bendamustinhydrochlorid angewendet werden.

3. Verfahren nach Punkt 1 gekennzeichnet dadurch, daß als Polyol insbesondere 1,2-Propylenglykol verwendet wird.

Field of the Invention

The invention relates to a method for producing injection solutions which may be used for medical treatment.

Characteristic of the Background Art

N-mustard compounds have been used for some years as highly effective cytostatics. It is estimated that mustards can be used in the therapy of 70 % of all treated malign tumors. More recent synthesis research was aimed at, for example, synthesizing a multivalent antagonist type out of said compound group. In said experiments and in vast pharmacological and clinical trials, bendamustine hydrochloride (trial ID IMET 3393), the compound synthesized by OZEGOWSKI and KREBS in 1963, was for example selected (BRUNS, KNÖLL) from a larger number of compounds. Bendamustine hydrochloride is γ-[1-methyl-5-bis-(β-chloroethyl)-aminobenzimidazo-lyl-(2)]-butyric acid hydrochloride. In 1971, the compound was introduced as pharmaceutical preparation under the trade name of CYTOSTASAN® (0.025 g bendamustine hydrochloride per dry ampoule) for the therapy of hemoblastoses, particularly such as chronic lymphadenosis, lymphoreticulosis, lymphogranulomatosis and of reticuloses.

Bendamustine hydrochloride is a relatively instable compound. Its mustard-halogen groups are almost completely hydrolyzed in aqueous solutions after a short period of time. Therefore, the injection solutions can only be produced shortly before injection. The kinetic experiments regarding the chloride hydrolysis of the N-mustard group of the bendamustine hydrochloride showed a reaction course in acid and neutral solutions which could be calculated according to the pseudo first order of the reaction for a consecutive reaction of the symmetric di-halogen compound (U. OLTHOFF, Abstr. Congr. Pharm. Hung. VI; Budapest 1974, p. 72). Independently of the pH value and of the buffer system used, the separation of the chloride and protons from the β-chloroethyl groups is complete and occurs at very high velocity. As far as this aspect is concerned, bendamustine hydrochloride is even more reactive than the particularly reactive mustards N-methyl mustard, chlorambucil and uracil mustard.

These data explain particular difficulties encountered in the production of stable medical preparations out of bendamustine hydrochloride.

According to the patent from the former German Democratic Republic WP 80 967, the N-mustard derivative bendamustine hydrochloride has to be produced in a sterile crystal form which is free of aerosols and suited for quick dissolution. The preparation form is a dry ampoule containing a mixture of 25 mg of bendamustine hydrochloride and 175 mg of ascorbic acid. Before the application, the content of the ampoule has to be dissolved in water for the injection. The ascorbic acid is included for the objective to produce a powder mixture which can be filled and to ensure the durability and the pH value of the injection solution. Moreover, the shelf life of the dry mixture should be guaranteed. According to the present results of the experiments, the hydrolysis rate is not influenced by the addition of the ascorbic acid.

The pH value of a bendamustine hydrochloride solution, which is within the range of 2.4 to 3.0, is not significantly altered by the addition of the ascorbic acid. Thus, the addition of the ascorbic acid does not match the characteristics which are to be required from a stabilizer. After a certain storage period, solid bendamustine hydrochloride shows a pink to brown-red discoloration, which starts at the surface of the substance and which, after a longer period of time, renders the whole substance unsuitable for the production of pharmaceutical preparations. The mixture with ascorbic acid shows the same discoloration.

Furthermore, it was proposed to lyophilize the aqueous solution of the substance bendamustine hydrochloride and to dissolve it in water or sodium chloride solution before the application (production method of the ZIMET (= former Central Institute for microbiology and experimental therapy in the GDR), pharmaceutical expertise IfAr/ Nr. 180/ 80). The lyophilisate obtained (25 mg/ ampoule) has significant disadvantages for a technological production process. In particular, the technological realization is complicated even more by the extreme hygroscopicity and the fact that the process takes place under inert gas. Moreover, during the production of the preparation, clear signs for decomposition of 5 to 10 % of the active substance were observed. It is furthermore unsatisfying that high amounts of micro particles were

found after the dissolution of the lyophilisate, which indicate a further instability of the system.

The disadvantage of the extreme hygroscopicity of the lyophilisate can be eliminated by the addition of polyols which are solid at room temperature, such as in particular mannitol. In addition to the large technological efforts, also the disadvantages of significant decomposition and of the manifestation of undissolved micro particles have to be considered.

Objective of the Invention

It is the objective of the invention to produce a stable and ready-to-use injection solution out of N-mustard compounds, avoiding the technical solution of a dry ampoule.

Description of the Character of the Invention

In the technical solutions known so far, the injection preparation was realized either as a filled powder under addition of a stabilizer and other auxiliary substances respectively, or in form of a lyophilisate, if necessary, with auxiliary substances. By these measures, a suitable injection preparation can only be realized with significant disadvantages or can't be realized at all. The dry fillings thus obtained are characterized by insufficient chemical and physical stability. Besides, lyophilization means that significantly increased technical efforts have to be made, a fact which might be limiting as far as the capacities are concerned.

Surprisingly it has been found that the substance bendamustine hydrochloride has a sufficient solubility and particularly a extraordinarily high chemical stability for the production of injection solutions in monovalent alcohols, glycols and other polyvalent alcohols. The stability of the solutions produced according to the invention is unexpected, since compounds with extreme sensitivity to hydrolysis are generally also sensitive to other solvents which contain OH-groups. In the case of alcohols or polyols, such reactions are known as alcoholysis.

It has now been found that N-mustard compounds of the bendamustine hydrochloride type do not undergo an alcoholysis reaction. The use of anhydrous solvents is required in order to avoid decomposition caused by the mentioned sensitivity to hydrolysis. Under these conditions, bendamustine hydrochloride, for example, is chemically stable for long periods of time in the mentioned group of solvents and does not form the monohydroxy and dihydroxy or monoalkoxy or dialkoxy derivatives known from aqueous solutions.

In order to examine the stability, bendamustine hydrochloride in a concentration of 25 mg/ ml was dissolved in ethanol and 1,2-propylene glycol and the solution was stored at room temperature, as well as at increased temperatures (50° C, 75° C, 130° C)

[missing sentence]

examined for the formation of cleavage products by means of a specific, thin film chromatography procedure (quantity applied 0.025 mg bendamustine hydrochloride, silica gel G, mobile phase: butanol/ acetic acid/ water 4:1:5; detection UV 360 nm or respectively Dragendorff reagent); results:

Formation of decomposition products in:

time	ethanol solution		propylene glycol solution		
	25° C	50° C	25° C	75° C	130° C
0.5 h	-	-	-	-	(traces)
1 h	-	-	-	none	-
1.5 h	-	-	-	-	(traces)
2 h	-	-	-	none	minor decomposition
5 h	none	none	-	none	-
7 h	none	none	-	-	-
24 h	none	-	-	-	-
8 weeks	none	-	none	-	-

For pharmacological reasons and for reasons concerning the production, monovalent alcohols are of limited use for the production of injection solutions. 1,2-propylene glycol is used more frequently. The solubilites of bendamustine hydrochloride which can be achieved at 25° C in some of the solvents used are of about

ethanol abs.	ca.	50 mg/ ml
propylene glycol	ca.	125 mg/ ml and
glycerol	ca.	50 mg/ ml

In the injection forms of bendamustine hydrochloride known so far, 25 mg active substance are used in 10 ml solvent. It is now proposed to dissolve the active substance in polyols, particularly in 1,2-propylene glycol in order to ensure a more simple production technology, an improved stability of the active substance during the production and storing of the solutions as well as a simplified handling during the production of the ready to inject solution when the active substance is solved in polyols, particularly in 1,2-propylene glycol and filled into ampoules. Immediately before the injection, the polyol solution is diluted by means of the addition of an aqueous diluent (sodium chloride solution in water for injection) such that the solution which is to be applied contains only about 10% polyol, sometimes even less. The polyol solutions can be diluted as desired with the diluents described before, without causing any disadvantages for the active substance. Due to the numerous possible variations of the contents of polyol and the diluent, there are several other advantages for the choice of an optimized, particularly acceptable injection preparation. In addition to the sensitivity to hydrolysis, other stability factors which have to be considered are the influence of light and atmospheric oxygen. Dry preparations and solutions change color under the influence of light and air until they have a pink or brownish color. As far as the solutions in alcohols and polyols which are stored in closed ampoules and under exclusion of light are concerned, no discoloration was observed. It is, however, recommended that the solutions are produced, filled and stored under an inert gas, such as argon or nitrogen.

Exemplary embodiments:

Example 1:

Bendamustine hydrochloride is dissolved under stirring in an inert gas atmosphere in 1,2-propylene glycol in an concentration of 2.5 g/ 100 ml. The solution is filtered by means of a suitable filter device, if necessary after heating to 50° C, such that it is free of aerosols and germs. 1.0 ml of the solution is filled in 10 ml ampoules, the ampoules are filled with inert gas and sealed by heating. Immediately before the injection, 9.0 ml of the chosen diluent is to be added into the opened ampoule. After reshuffling, the solution is ready to inject.

Example 2:

5.0 g bendamustine hydrochloride are dissolved in 100 ml ethanol under the conditions described in example 1, filtered and filled into ampoules. The ampoules are stored at temperatures of +15° C to +25° C.

CLAIMS

1. Method for producing stable injection solutions of N-mustard compounds, characterized in that N-mustard derivatives in concentrations of 25 mg/ ml to 100 mg/ ml are dissolved in an anhydrous monovalent or polyvalent alcohol (polyol), wherein the solution is dissolved, filled and stored under inert gas and the solution is diluted before medical application in a ratio of 1:5 to 1:20 with an aqueous injection medium.

2. Method according to claim 1, characterized in that benzimidazole mustards are used as active substance, in particular bendamustine hydrochloride.

3. Method according to claim 1, characterized in that particularly 1,2-propylene glycol is used as polyol.

Electronic Patent Application Fee Transmittal

Application Number:	13719379
Filing Date:	19-Dec-2012
Title of Invention:	Bendamustine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Jason Edward Brittain
Filer:	Stephanie A. Barbosa/D. McCarty
Attorney Docket Number:	CEPH-4457/CP391B US

Filed as Large Entity

Utility under 35 USC 111(a) 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($)
Miscellaneous:				
Statutory or Terminal Disclaimer	1814	2	160	320
		Total in USD ($)		**320**

Electronic Acknowledgement Receipt

EFS ID:	15927563
Application Number:	13719379
International Application Number:	
Confirmation Number:	6187
Title of Invention:	Bendamustine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Barbosa/D. McCarty
Filer Authorized By:	Stephanie A. Barbosa
Attorney Docket Number:	CEPH-4457/CP391B US
Receipt Date:	03-JUN-2013
Filing Date:	19-DEC-2012
Time Stamp:	11:08:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$320
RAM confirmation Number	10158
Deposit Account	233050
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	Transmittal Letter	CEPH-4457-Transmittal-reply-to-3-01-13.PDF	262743 976a9d83229b497ab40b95c99f3ac8ba3d776121	no	2
Warnings:					
Information:					
2		CEPH-4457-Reply-to-03-01-13.PDF	142764 141ae0c09fff1d6c9b9cdbf422898ff4a9dcd042	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	6

Warnings:					
Information:					
3	Terminal Disclaimer Filed	CEPH-4457-Terminal-Disclaimer-8436190.PDF	374491 d59ad7cdaa68ce84ae1422eb88af205c0302ce09	no	2
Warnings:					
Information:					
4	Terminal Disclaimer Filed	CEPH-4457-Terminal-Disclaimer-13719409.PDF	342777 54c8d0e8d5608aee2c5ef2fd7990dda91e13974e	no	2
Warnings:					
Information:					
5	Oath or Declaration filed	CEPH-4457-CP391B-Brittain-Declaration-with-exhibit-A.PDF	2530735 585ffe52aea620dff3c072863c5f6558fc8641b0	no	25
Warnings:					
Information:					
6	Notice of Appeal Filed	DD_159289_wEngTrans.PDF	613806 ccdde81e72bdc5a788dd6697a4e62ae03ccfda5e	no	16
Warnings:					

Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	30133 2bc97d67d45de0508f36fd1c16c750bf436eb716	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4297449	

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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.

Doc Code: TRAN.LET

Document Description: Transmittal Letter

PTO/SB/21 (07-09)
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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.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	13/719,379
Filing Date	December 19, 2012
First Named Inventor	Jason Edward Brittain
Art Unit	1617
Examiner Name	Ali Soroush
Attorney Docket Number	CEPH-4457/CP391B US

ENCLOSURES (*Check all that apply*)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☑ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation
- ☐ Change of Correspondence Address
- ☑ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

Declaration of Jason E. Brittain; DD 159289 with English Translation.

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Woodcock Washburn, LLP		
Signature	/Stephanie A. Barbosa/		
Printed name	Stephanie A. Barbosa		
Date	June 3, 2013	Reg. No.	51,430

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

This collection of information is required by 37 CFR 1.5. 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 and1.14. This collection is estimated to 2 hours 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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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.
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PTO/SB/26 (08-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT

Docket Number (Optional)
CEPH-4457/CP391B US

In re Application of: Jason Edward Brittain

Application No.: 13/719.379

Filed: December 19, 2012

For: Bendamustine Pharmaceutical Compositions

The owner*, Cephalon, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8436190 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 51,430

/Stephanie A. Barbosa/ — Signature
June 3, 2013 — Date

Stephanie A. Barbosa — Typed or printed name

25-568-3100 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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PTO/SB/25 (08-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION

Docket Number (Optional)
CEPH-4457/CP391B US

In re Application of: Jason Edward Brittain

Application No.: 13/719.379

Filed: December 19, 2012

For: Bendamustine Pharmaceutical Compositions

The owner*, Cephalon, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 13/719,409, filed December 19, 2012, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

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/Stephanie A. Barbosa/ — Signature
June 3, 2013 — Date

Stephanie A. Barbosa — Typed or printed name

215-568-3100 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
(use as many sheets as necessary)				**Examiner Name**	Soroush, Ali
Sheet	1	of	1	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PATENT APPLICATION DOCUMENTS				
Examiner Initials	Cite No.	Application Number	Fling Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	116	13/719,409	12-19-2012	Cephalon, Inc.

U. S. PUBLICATION AND PATENT DOCUMENTS				
Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	117	2013/0041003 A1	02-14-2013	Cephalon, Inc.
	118	8,436,190	05-07-2013	Brittain, J.E. et al.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
	119	Teagarden et al., "Practical aspects of lyophilization using non-aqueous co-solvent systems," European Journal of Pharmaceutical Sciences, March 2002, 15(2), 115-133	
	120	Wittaya-Areekul et al., "Freeze-drying of tert-butyl alcohol/water cosolvent systems: Effects of formulation and process variables on residual solvents," Journal of Pharmaceutical Sciences, April 1998, 87(4), 491-495	

Examiner Signature		**Date Considered**	

Electronic Patent Application Fee Transmittal

Application Number:	13719379
Filing Date:	19-Dec-2012
Title of Invention:	Bendamustine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Jason Edward Brittain
Filer:	Stephanie A. Barbosa/D. McCarty
Attorney Docket Number:	CEPH-4457/CP391B US

Filed as Large Entity

Utility under 35 USC 111(a) 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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	15930903
Application Number:	13719379
International Application Number:	
Confirmation Number:	6187
Title of Invention:	Bendamustine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Barbosa/D. McCarty
Filer Authorized By:	Stephanie A. Barbosa
Attorney Docket Number:	CEPH-4457/CP391B US
Receipt Date:	03-JUN-2013
Filing Date:	19-DEC-2012
Time Stamp:	14:31:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	893
Deposit Account	233050
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 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	Transmittal Letter	CEPH-4457-SIDS-Transmittal.PDF	104015 ed6a190276ffe1f43df322a1c6bd787996b29843	no	3
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	CEPH-4457-SIDS-1449.PDF	122563 e9b138528e4afbf0b937f44d1b64a72511eaaaa37	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Teagarden_EuropeanJPharmaceuticalSciences_2002_115-133.PDF	1709072 23de2c7ba37ec82152732d8ed7a333f065d48aa8	no	19
Warnings:					
Information:					
4	Non Patent Literature	Wittaya-Areekul_JPharmaceuticalSciences_1998_491-495.PDF	983709 d1b1cf94489591175201dd458526e0879f620ad9	no	5
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30255 dd4f3deda8d025f9837de90f27fdfde323eeb8ce	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2949614		

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.

DOCKET NO.: CEPH-4457 / CP391B US **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Jason Edward Brittain **Confirmation No.: 6187**

Application No.: 13/719,379 **Group Art Unit: 1617**

Filing Date: December 19, 2012 **Examiner: Soroush, Ali**

For: Bendamustine Pharmaceutical Compositions

Filed Via EFS

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

☐ **IDS Filed Under 37 CFR 1.97(b)**

In accordance with § 1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in § 1.491, before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of request for continued examination under § 1.114, no additional fee is required.

☒ **IDS filed Under 37 CFR 1.97(c)**

In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:

☐ Certification in Accordance with § 1.97(e) is attached; or

☒ The fee of **$180.00** as set forth in § 1.17(p) is attached.

☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of **$180.00** as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

☒ Copies of reference numbers 116-118 listed on the attached Form 1449/PTO or Substitute for Form 1449/PTO are not required to be submitted pursuant to 37 CFR § 1.98(a)(2)(iii).

☒ Copies of reference numbers 119-120 listed on the attached Form 1449/PTO or Substitute for Form 1449/PTO are enclosed herewith.

☐ Copies of reference numbers are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number , filed for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☐ The month of publication for reference numbers is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

☐ The following documents are not in the English language. Accordingly, a concise explanation of the relevance of the document was incorporated in the specification passages identified below, the document was identified in a foreign communication as identified below or an English language counterpart application has been provided as indicated below.

Foreign Language Document	Cite No.	Pages of Reference in Specification or Relevance of Document

Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

☐ Each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

☐ No item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: June 3, 2013

/Stephanie A. Barbosa/
Stephanie A. Barbosa
Registration No. 51,430

WOODCOCK WASHBURN LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. 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 13/719,379	Filing Date 12/19/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT **06/03/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 4	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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.

LIE
/BRENDA TURNER/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US

CONFIRMATION NO. 6187

46347
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

PUBLICATION NOTICE

Title: Bendamustine Pharmaceutical Compositions

Publication No.US-2013-0123316-A1
Publication Date:05/16/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

DOCKET NO.: CEPH-4449/CP391A US

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	**BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS**

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ the attached application; or

☒ United States application or PCT international application number 13/654,898 filed on October 18, 2012.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above-identified application, and I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF INVENTOR:

Inventor: Jason Edward Brittain	Date: 10 February 2013
Signature	

Electronic Acknowledgement Receipt

EFS ID:	15697680
Application Number:	13719379
International Application Number:	
Confirmation Number:	6187
Title of Invention:	Bendamustine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Barbosa/Ann Trevisani
Filer Authorized By:	Stephanie A. Barbosa
Attorney Docket Number:	CEPH-4457/CP391B US
Receipt Date:	06-MAY-2013
Filing Date:	19-DEC-2012
Time Stamp:	14:03:47
Application Type:	Utility under 35 USC 111(a)

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	Transmittal Letter	Transmittal_Letter_CEPH4457.PDF	262825 b49fb82414cba243fe2424b469d3f54d30a382ed	no	2

Warnings:	
Information:	

2	Miscellaneous Incoming Letter	Request_to_Change_Applilcant_Name.PDF	76684 11eb264af70cc532e2da9cd71af93063642af226	no	1
Warnings:					
Information:					
3	Application Data Sheet	Updated_Application_Data_Sheet_CEPH-4457.PDF	1038076 ba27c287c9b7ac3f42980074e046b4ac9f6411d6	no	6
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
4	Miscellaneous Incoming Letter	Substitute_Statement_CEPH-4457.PDF	221862 f60a322bc1a100a95452868c70d715df057e7bfe	no	3
Warnings:					
Information:					
5	Assignee showing of ownership per 37 CFR 3.73.	Assignee_Statement_CEPH-4457.PDF	119259 80f2bfd63058bef6492990d4314d11b7f71d102a	no	3
Warnings:					
Information:					
6	Oath or Declaration filed	Declaration_Brittain_CEPH-4457.PDF	438473 e3572740b353bd73e11d9e656567de05bc3ad8fc	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	2157179		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

Doc Code: TRAN.LET

Document Description: Transmittal Letter

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	13/719,379
Filing Date	December 19, 2012
First Named Inventor	Jason Edward Brittain
Art Unit	1617
Examiner Name	Ali Soroush
Attorney Docket Number	CEPH-4457/CP391B US

ENCLOSURES (*Check all that apply*)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation
- ☐ Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  - Request/Communication
  - Updated ADS
  - Substitute Statement in Lieu of Declaration
  - Statement Under 37 CFR 3.73(c)
  - Copy of Brittain Declaration from parent

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Woodcock Washburn LLP		
Signature	/Stephanie A. Barbosa/		
Printed name	Stephanie A. Barbosa		
Date	May 6, 2013	Reg. No.	51,430

CERTIFICATE OF TRANSMISSION/MAILING

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Signature			
Typed or printed name		Date	

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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.

DOCKET NO.: CEPH-4457 (CP391B US) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Jason Edward Brittain, Joe Craig Franklin**	**Confirmation No.: 6187**
Application No.: 13/719,379	**Group Art Unit: 1617**
Filing Date: December 19, 2012	**Examiner: Ali Soroush**

For: Bendamustine Pharmaceutical Compositions

Mail Stop Issue Fee
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P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

REQUEST UNDER 37 CFR 1.46(c) TO CHANGE NAME OF APPLICANT

Please change the name of the Applicant of the above-referenced U.S. application to:

CEPHALON, INC.
41 Moores Road
Frazer, PA 19355

An updated Application Data Sheet accompanies this request.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050

Date: May 6, 2013

/Stephanie A. Barbosa/
Stephanie A. Barbosa
Registration No. 51,430

Woodcock Washburn LLP
Cira Centre, 12th Floor
2929 Arch Street
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

PTO/AIA/14 (08-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CEPH-4457/CP391B US
	Application Number	13/719,379
Title of Invention	Bendamustine Pharmaceutical Compositions	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City		State/Province		Country of Residence	

Mailing Address of Inventor:

Address 1	
Address 2	

City		State/Province	
Postal Code		Country	

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City		State/Province		Country of Residence	

Mailing Address of Inventor:

Address 1	
Address 2	

City		State/Province	
Postal Code		Country	

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (08-12)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CEPH-4457/CP391B US
	Application Number	
Title of Invention	Bendamustine Pharmaceutical Compositions	

☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	46347		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	Bendamustine Pharmaceutical Compositions		
Attorney Docket Number	CEPH-4457/CP391B US	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	6	**Suggested Figure for Publication (if any)**	1

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	46347		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CEPH-4457/CP391B US
	Application Number	
Title of Invention	Bendamustine Pharmaceutical Compositions	

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of		
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of		

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ◉ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CEPH-4457/CP391B US
	Application Number	
Title of Invention	Bendamustine Pharmaceutical Compositions	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Cephalon, Inc.		
Mailing Address Information:			
Address 1	41 Moores Road		
Address 2			
City	Frazer	**State/Province**	PA
Country	US	Postal Code	19355
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CEPH-4457/CP391B US
	Application Number	
Title of Invention	Bendamustine Pharmaceutical Compositions	

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information:

Address 1	
Address 2	

City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Stephanie A. Barbosa/			Date (YYYY-MM-DD)	May 6, 2013
First Name	Stephanie	Last Name	Barbosa	Registration Number	51430

Additional Signature may be generated within this form by selecting the Add button.

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 the Freedom of Information Act requires disclosure of these records.

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 inspections 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.

Doc code: Oath
Document Description: Oath or declaration filed

PTO/AIA/02 (06-12)
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SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

This statement is directed to:

☐ The attached application,

OR

☒ United States application or PCT international application number 13/719,379 filed on 12/19/2012.

LEGAL NAME of inventor to whom this substitute statement applies:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Joe Craig Franklin

Residence (except for a deceased or legally incapacitated inventor):

City	State	Country

Mailing Address (except for a deceased or legally incapacitated inventor):

City	State	Zip	Country

I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.

The above-identified application was made or authorized to be made by me.

I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Relationship to the inventor to whom this substitute statement applies:

☐ Legal Representative (for deceased or legally incapacitated inventor only),

☒ Assignee,

☐ Person to whom the inventor is under an obligation to assign,

☐ Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or

☐ Joint Inventor.

PTO/SB/AIA02 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- [x] Inventor is deceased,
- [ ] Inventor is under legal incapacity,
- [ ] Inventor cannot be found or reached after diligent effort, or
- [ ] Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- [x] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: Rona A. Nardone, Senior Counsel Cephalon, Inc. (Reg. No. 55,481)	Date (Optional): 05/01/2013

Signature: /Rona A. Nardone/

Residence (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City Frazer	State PA	Country US

Mailing Address (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

41 Moores Road

City Frazer	State PA	Zip 19355	Country US

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

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.

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Jason Edward Brittain, et al.

Application No./Patent No.: 13/719,379 Filed/Issue Date: December 19 2012

Titled: Bendamustine Pharmaceutical Compositons

Cephalon, Inc., 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 017302, Frame 0847, 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: _____ 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.

PTO/AIA/96 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.

/Rona A. Nardone/	05/01/2013
Signature	Date
Rona Nardone (Reg. No. 55,481)	55,481
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).
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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

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US	6187

46347 7590 03/01/2013

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EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
03/01/2013	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):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	13/719,379	BRITTAIN ET AL.	
	Examiner	Art Unit	
	ALI SOROUSH	1617	

-- 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 *19 December 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1-4* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-4* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ 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).

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) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01282013*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-4 are pending.

Claims 1-4 have been examined.

Claims 1-4 are rejected.

Priority

Priority to CON of 13/654,898 filed on 10/18/2012 which is a CON of 11/330,868 filed on 01/12/2006 which claims benefit of 60/644,354 filed on 01/14/2005 is acknowledged.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 01/28/2013 w is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 4 is rejected under 35 U.S.C. 102(a) as being anticipated by Kanekal et al. (SDX-105(TREANDA) Enhances the Tumor Growth Inhibitory Effect of Rituximab in

Daudi Lymphoma Xenografts, Published 2004) as evidenced by RxList (Treanda, Published 2013).

The claim is directed to a stabilized lyophilized bendamustine hydrochloride and mannitol in a ratio is 15:25.5.

Kanekal et al. teach Treanda (abstract). RxList teach that Treanda is a lyophilized powder comprising either 25mg bendamustine and 42.5 mg mannitol or 100mg bendamustine hydrochloride and 170mg mannitol to be reconstituted in sterile water for injection (page 1, lines 11-17). With regard to the method of preparing the lyophilized preparation is a product-by-process limitation which is not given patentable where the product is structurally indistinguishable. Therefore the instant claims are anticipated by the prior art.

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.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oltoff et al. (DE 159289, Published 06/01/1981) in view of Ni et al. (Use of pure t-butanol as a solvent for freeze-drying: a case study, Published 2001).

The claims are directed to a stable lyophilized preparation of 25 or 100mg bendamustine hydrochloride, mannitol, and trace amount of t-butyl alcohol.

Oltoff et al. teach 25mg lyophilisate of bendamustine hydrochloride (page 3, lines 21-28). Mannitol can be added to the lyophilisate to eliminate the hygroscopicity of the lyophilisate (page 4, lines 3-5).

Oltoff et al. lacks a teaching wherein the composition comprises a trace amount of t-butanol.

T-butanol can be added as a solvent for freeze-drying (lyophilizing) (title). After freeze-drying less than 0.01% of the solvent remains (page 45, column 2, lines 37-38). T-butanol improves the solubility and stability of hydrophobic and/or water sensitive drugs that must be freeze-dried (page 45, column 2, lines 33-35).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the instant invention to use t-butanol as the solvent in the lyophilisate of Oltoff et al. and have a reasonable expectation of success. One would have been motivated to do so improve the solubility and stability of bendamustine hydrochloride. Therefore, the instant claims are rendered obvious by the teachings of the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached on M-F (9am-6pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on (571)272-3311. 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.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

February 25, 2013

Notice of References Cited	Application/Control No. 13/719,379	Applicant(s)/Patent Under Reexamination BRITTAIN ET AL.	
	Examiner ALI SOROUSH	Art Unit 1617	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	DE-159289	06-1981	DE	Oltoff et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Kanekal et al., Kanekal et al. (SDX-105(TREANDA) Enhances the Tumor Growth Inhibitory Effect of Rituximab in Daudi Lymphoma Xenografts, 2004, Blood (ASH Annual Meeting Abstracts), vol. 104
	V	RxList, Treanda, 2013, pp. 1-2.
	W	Ni et al, Use of pure t-butanol as a solvent for freeze-drying: a case study, 2001, International Journal of Pharmaceitcs, vol. 2001, pp. 39-46.
	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.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1337	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:38
S2	173689	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:39
S3	175501	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol mannite (manna adj sugar)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:39
S4	19	S1 near5 S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:40
S5	23	S1 with S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 14:40
S6	1337	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:28
S7	1337	S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:28
S8	175501	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol mannite (manna adj sugar)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:29
S9	47	S7 same S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:29
S10	24	S7 same lyophilized	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	OFF	2013/02/14 16:29

			JPO; DERWENT; IBM_TDB			
S11	445	S7 and lyophilized	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:29
S12	97	S6.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:30
S13	97	cyclophosphamide with mannitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:40
S14	5	S13 same lyophilization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:40
S15	0	cyclophosphamide with (butyl$1alcohol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:42
S16	0	cyclophosphamide with ($9butyl adj alcohol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:42
S17	1337	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:56
S18	8	S17 and Astellas.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:56
S19	173689	mannitol "(2R,3R,4R,5R)-Hexan-1,2,3,4,5,6-hexol" osmitrol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:57
S20	40	S17 same S19	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 16:57
S21	163	ribomustin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:00
S22	40	S21 and @PD<="20051301"	US-PGPUB; USPAT; USOCR;	OR	OFF	2013/02/14 17:01

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S23	19	bendamustine near5 mannitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:05
S24	40	S19 same S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:05
S25	0	S24 and @PD<="20051301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:05
S26	1287	lundbeck.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:30
S27	0	S26 and S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/14 17:30
S28	2	"8349613".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 11:42
S29	2270	bendamustine sarcnu	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:26
S30	5	bendamustine with sarcnu	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:26
S31	37	bendamustine with nitrosurea	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:26
S32	37	bendamustine and @pd<="20051301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:27
S33	11	S32 and (lyophilize lyophilization lyophilized "freeze-dry" "feeze-dried" "freeze-drying")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:28
S34	0	bendamustine with (ascrobic adj acid)	US-PGPUB; USPAT; USOCR;	OR	OFF	2013/02/19 15:37

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S35	19	bendamustine with (ascorbic adj acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:37
S36	0	(alkylating adj agent) with lyophilize	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:47
S37	0	(alkylating adj agent) same lyophilize	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:47
S38	40337	(alkylating adj agent)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:47
S39	8	S38 same (lyophilize lyophilization)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:48
S40	1398	(lyophilize lyophilization) with mannitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 15:50
S41	1339	bendamustine "4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid" Treakisym Ribomustin Treanda "SDX-105" "SDX105" "SDX 105"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:28
S42	1339	S41	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:28
S43	27	S42 with (lyophilize lyophilized lyophilization lyophilisate "freeze-dry" "freeze-dried" "freeze-drying")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:28
S44	32	S42 same (lyophilize lyophilized lyophilization lyophilisate "freeze-dry" "freeze-dried" "freeze-drying")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/19 18:29
S45	5	"09323915"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:28
S46	12	"3223206"	US-PGPUB;	OR	OFF	2013/02/20

			USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			10:30
S47	0	3-223206	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:30
S48	36	"386812"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/02/20 10:31

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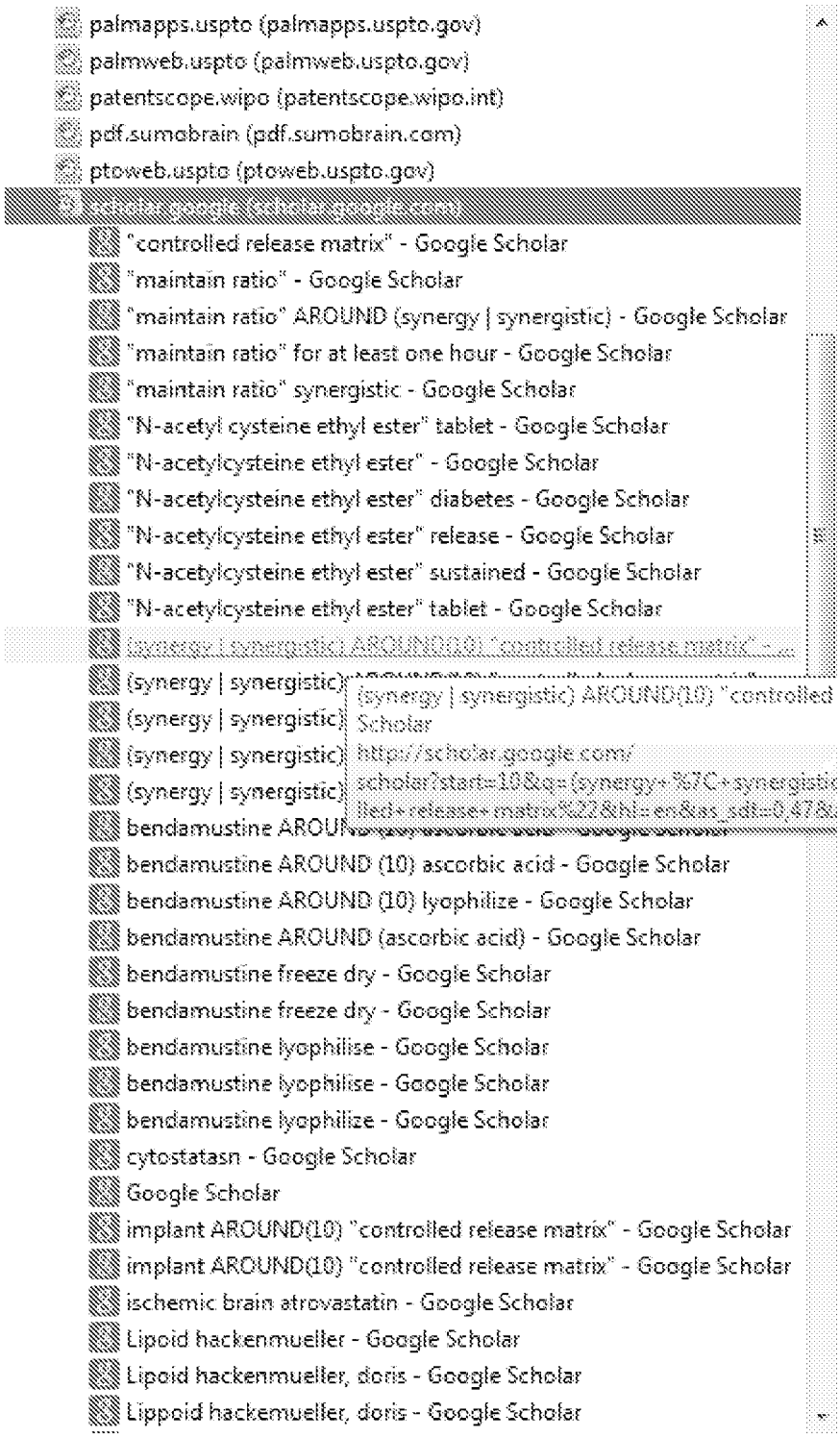
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Lipoid hackenmueller - Google Scholar
Lipoid hackenmueller, doris - Google Scholar
Lippoid hackemueller, doris - Google Scholar

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13719409	BRITTAIN ET AL.
	Examiner	Art Unit
	ALI SOROUSH	1617

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
See search history printouts	02/25/2013	AS
Inventor/Assignee search EAST/PALM (Jason Edward Brittain, Joe Craig Franklin)	02/25/2013	AS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/ALI SOROUSH/ Primary Examiner.Art Unit 1617	

Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1629
(use as many sheets as necessary)				**Examiner Name**	Not Yet Assigned
Sheet	1	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**1**	2002/0102215	08-01-2002	Klaveness et al.
	2	2003/0232874	12-18-2003	Nardella
	3	2004/0053972	03-18-2004	Nara
	4	2004/0058956	03-25-2004	Akiyama et al.
	5	2004/0072889	04-15-2004	Masferrer
	6	2004/0096436	05-20-2004	Carson et al.
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Examiner Signature	/Ali Soroush/	**Date Considered**	02/25/2013

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	2	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
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Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
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Sheet	3	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

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Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number -Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T
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	65	WO 2006/076620	07-20-2006	Cephalon, Inc.	
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Examiner Signature	/Ali Soroush/	**Date Considered**	02/25/2013

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
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				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	4	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
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				Examiner Name	Not Yet Assigned
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Examiner Signature	/Ali Soroush/	**Date Considered**	02/25/2013

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				Art Unit	1629
				Examiner Name	Not Yet Assigned
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Sheet	7	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

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Examiner Signature	/Ali Soroush/	**Date Considered**	02/25/2013

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2929 ARCH STRET
PHILADELPHIA PA 19104-2891

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/719,379

1. THE REQUEST FILED 12/19/12 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Cheryl Gibson-Baylor at (571)272-3213, Office of Petitions. In his/her absence, calls may be directed to Brian W. Brown, (571)272-5338.

Cheryl Gibson-Baylor
/Cheryl Gibson-Baylor/
[*Signature*]

Petitions Examiner
(Title)

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/719,379

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	390
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	4 minus 20 =	*			OR	x 62 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 250 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1260

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(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))	*	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	

AMENDMENT B

	(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 found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/719,379	12/19/2012	1629	1560	CEPH-4457/CP391B US	4	2

CONFIRMATION NO. 6187

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FILING RECEIPT

Date Mailed: 02/06/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Jason Edward Brittain, El Cajon, CA;
Joe Craig Franklin, Tulsa, OK;

Applicant(s)

Jason Edward Brittain, El Cajon, CA;
Joe Craig Franklin, Tulsa, OK;

Power of Attorney: The patent practitioners associated with Customer Number 46347

Domestic Priority data as claimed by applicant

This application is a CON of 13/654,898 10/18/2012
which is a CON of 11/330,868 01/12/2006
which claims benefit of 60/644,354 01/14/2005

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 02/01/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/719,379**

Projected Publication Date: 05/16/2013

Non-Publication Request: No

Early Publication Request: No

Title

Bendamustine Pharmaceutical Compositions

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/719,379	12/19/2012	Jason Edward Brittain	CEPH-4457/CP391B US

CONFIRMATION NO. 6187

46347
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

NOTICE

OC000000059021989

Date Mailed: 02/06/2013

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

A new inventor's oath or declaration that identifies this application (e.g., by Application Number and filing date) is required. The inventor's oath or declaration does not comply with 37 CFR 1.63 in that it:

- does not state that the above-identified application was made or authorized to be made by the person executing the oath or declaration.

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2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

POA ACCEPTANCE LETTER

OC00000059021551

Date Mailed: 02/06/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/19/2012.

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.

/sgorems/

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

Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/719,379
				Filing Date	December 19, 2012
				First Named Inventor	Jason Edward Brittain
				Art Unit	1629
(use as many sheets as necessary)				**Examiner Name**	Not Yet Assigned
Sheet	1	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
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	2	2003/0232874	12-18-2003	Nardella
	3	2004/0053972	03-18-2004	Nara
	4	2004/0058956	03-25-2004	Akiyama et al.
	5	2004/0072889	04-15-2004	Masferrer
	6	2004/0096436	05-20-2004	Carson et al.
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	10	2005/0060028	03-17-2005	Horres et al.
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Examiner Signature		**Date Considered**	

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(use as many sheets as necessary)				**Examiner Name**	Not Yet Assigned
Sheet	2	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
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Sheet	4	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
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				Art Unit	1629
(use as many sheets as necessary)				**Examiner Name**	Not Yet Assigned
Sheet	5	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

NON PATENT LITERATURE DOCUMENTS			
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Examiner Signature		**Date Considered**	

Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/719,379
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				Art Unit	1629
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Sheet	6	of	7	**Attorney Docket Number**	CEPH-4457 / CP391B US

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Examiner Signature		**Date Considered**	

Electronic Acknowledgement Receipt

EFS ID:	14802679
Application Number:	13719379
International Application Number:	
Confirmation Number:	6187
Title of Invention:	Bendamustine Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Barbosa/Viantinna Campana Bordas
Filer Authorized By:	Stephanie A. Barbosa
Attorney Docket Number:	CEPH-4457/CP391B US
Receipt Date:	28-JAN-2013
Filing Date:	
Time Stamp:	11:05:57
Application Type:	Utility under 35 USC 111(a)

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	Transmittal Letter	CEPH-4457_IDS_Trans_01-28-13.PDF	104481 3eb9bd58f332904c87a4fe451cfb313e303da881	no	3

Warnings:	
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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.

DOCKET NO.: CEPH-4457 / CP391B US **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Jason Edward Brittain **Confirmation No.: 6187**

Application No.: 13/719,379 **Group Art Unit: 1629**

Filing Date: December 19, 2012 **Examiner: Not Yet Assigned**

For: Bendamustine Pharmaceutical Compositions

Filed Via EFS

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

☒ **IDS Filed Under 37 CFR 1.97(b)**

In accordance with § 1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in § 1.491, before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of request for continued examination under § 1.114, no additional fee is required.

☐ **IDS filed Under 37 CFR 1.97(c)**

In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:

- ☐ Certification in Accordance with § 1.97(e) is attached; or
- ☐ The fee of **$180.00** as set forth in § 1.17(p) is attached.

☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of **$180.00** as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

☒ Copies of reference numbers 1-46 listed on the attached Form 1449/PTO or Substitute for Form 1449/PTO are not required to be submitted pursuant to 37 CFR § 1.98(a)(2)(iii).

☐ Copies of reference numbers listed on the attached Form 1449/PTO or Substitute for Form 1449/PTO are enclosed herewith.

☒ Copies of reference numbers 47-115 are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number 13/654,898, filed October 18, 2012 for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☒ The month of publication for reference numbers 68, 70, 73, 81-90, 94, 96, 99, 104, 106-108, 110-112 and 114-115 is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

☐ The following documents are not in the English language. Accordingly, a concise explanation of the relevance of the document was incorporated in the specification passages identified below, the document was identified in a foreign communication as identified below or an English language counterpart application has been provided as indicated below.

Foreign Language Document	Cite No.	Pages of Reference in Specification or Relevance of Document

Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

☐ Each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

☐ No item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: January 28, 2013

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PTO/AIA/15 (07-12)
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U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	CEPH-4457/CP391B US
First Inventor	Jason Edward Brittain
Title	Bendamustine Pharmaceutical Compositions
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form.** (PTO/SB/17 or equivalent)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **Specification.** [*Total Pages* 53] Both the claims and abstract must start on a new page *(For information on the preferred arrangement, see MPEP § 608.01(a))*
4. ☑ **Drawing(s).** (*35 U.S.C. 113*) [*Total Sheets* 6]
5. **Inventor's Oath or Declaration.** [*Total Sheets* ____] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☑ A copy from a prior application (37 CFR 1.63(d))
6. ☑ **Application Data Sheet.** **See Note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
7. ☐ **CD-ROM or CD-R.** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission.** *(if applicable, items a. – c. are required)*
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

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P.O. Box 1450
Alexandria VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers.** (cover sheet & document(s))
   Name of Assignee ____
10. ☑ **37 CFR 3.73(c) Statement.** ☑ **Power of Attorney.** *(when there is an assignee)*
11. ☐ **English Translation Document.** *(if applicable)*
12. ☐ **Information Disclosure Statement.** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☐ **Preliminary Amendment.**
14. ☐ **Return Receipt Postcard.** *(MPEP § 503) (Should be specifically itemized)*
15. ☐ **Certified Copy of Priority Document(s).** *(if foreign priority is claimed)*
16. ☐ **Nonpublication Request.** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☑ **Other:** Request for Prioritized Examination; Authorization for Extension of Time

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

18. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 46347 ***OR*** ☐ Correspondence address below

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Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Stephanie A. Barbosa/	Date	December 19, 2012
Name (Print/Type)	Stephanie A. Barbosa	Registration No. (Attorney/Agent)	51430

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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.
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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.

BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 13/654,898, filed October 18, 2012, which is a continuation of U.S. Application No. 11/330,868, filed January 12, 2006, which claims the benefit of U.S. Provisional Application No. 60/644,354, filed January 14, 2005, the entireties of which are incorporated herein for all purposes.

FIELD OF THE INVENTION

The present invention pertains to the field of pharmaceutical compositions for the treatment of various disease states, especially neoplastic diseases and autoimmune diseases. Particularly, it relates to pharmaceutical formulations comprising nitrogen mustards, particularly the nitrogen mustard bendamustine, e.g., bendamustine HCl.

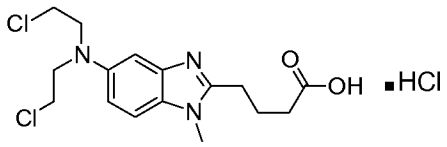
BACKGROUND OF THE INVENTION

The present invention claims the benefit of and priority to US Serial No. 60/644,354, filed January 14, 2005, entitled, "Bendamustine Pharmaceutical Compositions," which is incorporated herein by reference in its entirety, including figures and claims.

The following description includes information that may be useful in understanding the present invention. It is not an admission that any such information is prior art, or relevant, to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

Because of their high reactivity in aqueous solutions, nitrogen mustards are difficult to formulate as pharmaceuticals and are often supplied for administration in a lyophilized form that requires reconstitution, usually in water, by skilled hospital personal prior to administration. Once in aqueous solution, nitrogen mustards are subject to degradation by hydrolysis, thus, the reconstituted product should be administered to a patient as soon as possible after its reconstitution.

Bendamustine, (4-{5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolyl} butyric acid, is an atypical structure with a benzimidazole ring, whose structure includes an active nitrogen mustard (see Formula I, which shows bendamustine hydrochloride).



Formula I

Bendamustine was initially synthesized in 1963 in the German Democratic Republic (GDR) and was available from 1971 to 1992 in that location under the name Cytostasan®. Since that time, it has been marketed in Germany under the tradename Ribomustin®. It has been widely used in Germany to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer.

Due to its degradation in aqueous solutions (like other nitrogen mustards), bendamustine is supplied as a lyophilized product. The current lyophilized formulation of bendamustine (Ribomustin®) contains bendamustine hydrochloride and mannitol in a sterile lyophilized form as a white powder for intravenous use following reconstitution. The finished lyophilisate is unstable when exposed to light. Therefore, the product is stored in brown or amber-colored glass bottles. The current lyophilized formulation of bendamustine contains degradation products that may occur during manufacturing of the drug substance and/or during the lyophilization process to make the finished drug product.

Currently bendamustine is formulated as a lyophilized powder for injection with 100 mg of drug per 50 mL vial or 25 mg of drug per 20 mL vial. The vials are opened and reconstituted as close to the time of patient administration as possible. The product is reconstituted with 40 mL (for the 100 mg presentation) or 10 mL (for the 25 mg presentation) of Sterile Water for Injection. The reconstituted product is further diluted into 500 mL, q.s., 0.9% Sodium Chloride for Injection. The route of administration is by intravenous infusion over 30 to 60 minutes.

Following reconstitution with 40 mL Sterile Water for Injection, vials of bendamustine are stable for a period of 7 hours under room temperature storage or for 6 days upon storage at 2-8°C. The 500 mL admixture solution must be administered to the patient within 7 hours of vial reconstitution (assuming room temperature storage of the admixture).

The reconstitution of the present bendamustine lyophilized powder is difficult. Reports from the clinic indicate that reconstitution can require at least fifteen minutes and may require as long as thirty minutes. Besides being burdensome and time-consuming for the healthcare professional responsible for reconstituting the product, the lengthy exposure of bendamustine to water during the reconstitution process increases the potential for loss of potency and impurity formation due to the hydrolysis of the product by water.

Thus, a need exists for lyophilized formulations of bendamustine that are easier to reconstitute and which have a better impurity profile than the current lyophilate (lyophilized powder) formulations of bendamustine.

German (GDR) Patent No. 34727 discloses a method of preparing ω-[5-bis-(β-chloroethyl)-amino-benzimidazolyl-(2)]-alkane carboxylic acids substituted in the 1-position.

German (GDR) Patent No. 80967 discloses an injectable preparation of γ-[1-methyl-5-bis-(β-chloroethyl)-amino-benzimaidazolyl-(2)]-butric acid hydrochloride.

German (GDR) Patent No. 159877 discloses a method for preparing 4-[1-methyl-5-bis (2-chloroethyl) amino-benzimidazolyl-2)-butyric acid.

German (GDR) Patent No. 159289 discloses an injectable solution of bendamustine.

Ribomustin® bendamustine Product monograph (updated 1/2002) http://www.ribosepharm.de/pdf/ribomustin_bendamustin/productmonograph.pdf provides information about Ribomustin® including product description.

Ni et al. report that the nitrosourea SarCNU was more stable in pure tertiary butanol than in pure acetic acid, dimethyl sulfoxide, methylhydroxy, water or in TBA/water mixtures (Ni et al. (2001) *Intl. J. Phamaceutics* 226:39-46).

Lyophilized cyclophoshamide is known in the art see e.g., US Patent Nos. 5,418,223; 5,413,995; 5,268,368; 5,227,374; 5,130,305; 4,659,699; 4,537,883; and 5,066,647.

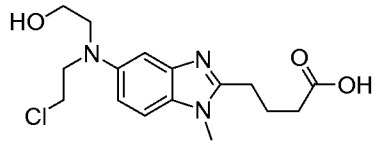
The lyophilized nitrogen mustard Ifosfamide is disclosed in International Publication No. WO 2003/066027; US Pat. Nos. 6,613,927; 5,750,131; 5,972,912; 5,227,373; and 5,204,335.

Teagarden et al. disclose lyophilized formulations of prostaglandin E-1 made by dissolving PGE-1 in a solution of lactose and tertiary butyl alcohol (US Pat. No. 5,770,230).

SUMMARY OF THE INVENTION

The present invention is directed to stable pharmaceutical compositions of nitrogen mustards, in particular lyophilized bendamustine and its use in treatment of various disease states, especially neoplastic diseases and autoimmune diseases.

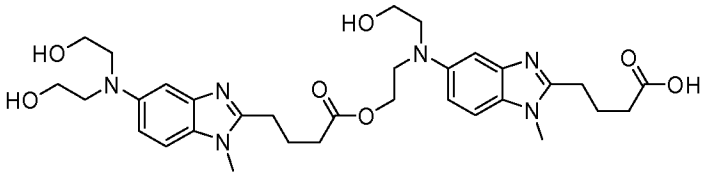
An embodiment of the invention is a pharmaceutical composition of bendamustine containing not more than about 0.5% to about 0.9% (area percent of bendamustine) HP1, as shown in Formula II,



Formula II

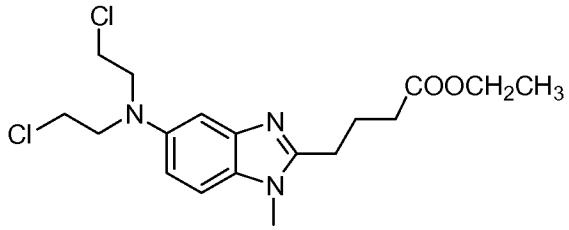
at the time of release or where the HP1 is the amount of HP1 present at time zero after reconstitution of a lyophilized pharmaceutical composition of bendamustine as described herein. In a preferred embodiment is a pharmaceutical composition of bendamustine containing not more than about 0.5% (area percent of bendamustine) HP1, preferably not more than about 0.45%, more preferably not more than about 0.40%, more preferably not more than about 0.35%, even more preferably not more than 0.30%.

Another embodiment of the invention is a lyophilized preparation of bendamustine containing not more than about 0.1 % to about 0.3 % bendamustine dimer as shown in Formula III at release or at time zero after reconstitution



Formula III.

Yet another embodiment of the invention is a lyophilized preparation of bendamustine containing not more than about 0.5%, preferably 0.15% to about 0.5%, bendamustine ethylester, as shown in Formula IV at release or at time zero after reconstitution



Formula IV.

Yet another embodiment of the invention is a lyophilized preparation of bendamustine wherein the concentration of bendamustine ethylester (Formula IV) is no more than 0.2%, preferably 0.1%, greater than the concentration of bendamustine ethylester as found in the drug substance used to make the lyophilized preparation.

In another embodiment of the invention is a lyophilized preparation of bendamustine containing not more than about 0.5% to about 0.9% (area percent of bendamustine) HP1 at the time of drug product release. In a preferred embodiment is a lyophilized preparation of bendamustine containing not more than about 0.50% (area percent of bendamustine) HP1, preferably not more than about 0.45%, more preferably not more than about 0.40%, more preferably not more than about 0.35%, even more preferably not more than 0.30%. An aspect of this embodiment is lyophilized preparations of bendamustine containing not more than about 0.5% to about 0.9%, preferably 0.5%, (area percent of bendamustine) HP1 at the time of release of drug product where the lyophilized preparation is packaged in a vial or other pharmaceutically acceptable container.

In yet another aspect of the invention, the lyophilized preparations of bendamustine are stable with respect to the amount of HP1 for at least about 6 months, preferably 12 months, preferably 24 months, to about 36 months or greater when stored at about 2° to about 30°. Preferred temperatures for storage are about 5° C and about room temperature.

Another embodiment of the invention is a pharmaceutical dosage form that includes a pharmaceutical composition of bendamustine containing not more than about 0.5% to about 0.9% HP1, preferably not more than about 0.50%, preferably not more than about 0.45%, more preferably not more than about 0.40%, more preferably not more than about 0.35%, even more preferably not more than 0.30%, where the HP1 is the amount of HP1 present at release or at time zero after reconstitution of a lyophilized preparation of bendamustine of the present invention. In preferred aspects of the invention, the dosage form can be about 5 to about 500 mg of bendamustine, about 10 to about 300 mg of bendamustine, about 25 mg of bendamustine, about 100 mg of bendamustine, and about 200 mg of bendamustine.

Yet another embodiment of the invention is a pharmaceutical dosage form that includes a lyophilized preparation of bendamustine containing not more than about 0.5% to about 0.9%, preferably 0.5%, HP1. Preferred dosage forms can be about 5 to about 500 mg of bendamustine, about 10 to about 300 mg of bendamustine, about 25 mg of bendamustine, about 100 mg of bendamustine, and about 200 mg of bendamustine.

In still another embodiment, the invention includes a pharmaceutical composition of bendamustine including bendamustine containing not more than about 0.5% to about 0.9% (area percent of bendamustine), preferably not more than about 0.50%, preferably not more than about 0.45%, more preferably not more than about 0.40%, more preferably not more than about 0.35%, even more preferably not more than 0.30%, and a trace amount of one or more organic solvents, wherein said HP1 is the amount of HP1 present at release or time zero after reconstitution of a lyophilized pharmaceutical composition of bendamustine as disclosed herein. In different aspects of this embodiment, the organic solvent is selected from one or more of tertiary butanol, n-propanol, n-butanol, isopropanol, ethanol, methanol, acetone, ethyl acetate, dimethyl carbonate, acetonitrile, dichloromethane, methyl ethyl ketone, methyl isobutyl ketone, 1-pentanol, methyl acetate,

carbon tetrachloride, dimethyl sulfoxide, hexafluoroacetone, chlorobutanol, dimethyl sulfone, acetic acid, and cyclohexane. Preferred organic solvents include one or more of ethanol, methanol, propanol, butanol, isopropanol, and tertiary butanol. A more preferred organic solvent is tertiary butanol, also known as TBA, t-butanol, tert-butyl alcohol or tertiary butyl alcohol.

The present invention involves a method for obtaining agency approval for a bendamustine product, the improvement which includes setting a release specification for bendamustine degradants at less than about 4.0%, preferably about 2.0 % to about 4.0 %, (area percent bendamustine) or otherwise to achieve the pharmaceutical compositions described herein. An aspect of this embodiment is a method for obtaining agency approval for a bendamustine product which includes setting a release specification for HP1 to be less than or equal to 1.5% (area percent Bendamustine). The bendamustine product herein contains not more than about 0.5% (area percent of bendamustine) HP1 at release.

Another embodiment is a method for obtaining agency approval for a bendamustine product, the improvement which includes setting a shelf-life specification for bendamustine degradants at less than about 7.0%, preferably about 5.0% to about 7.0%, (area percent bendamustine) where the product is stored at about 2°C to about 30°C. Preferred temperatures for storage are about 5°C and about room temperature. The bendamustine product herein contains not more than about 0.5% (area percent of bendamustine) HP1 at release.

Another embodiment of the invention is a process for manufacturing a lyophilized preparation of bendamustine which includes controlling for the concentration of bendamustine degradants in the final product, such that the concentration of bendamustine degradants is less than about 4.0%, preferably no more than about 2.0 % to about 4.0 %, (area percent of bendamustine) at release or otherwise to achieve the pharmaceutical compositions described herein. The bendamustine product herein contains not more than about 0.5% to about 0.9%, preferably about 0.5%, (area percent of bendamustine) HP1 at release.

The present invention discloses a process for manufacturing a lyophilized preparation of bendamustine which comprises controlling for the concentration of

bendamustine degradants in the final product, such that, at release, the concentration of HP1 is less than 0.9%, preferably 0.5%, (area percent of bendamustine) and, at the time of product expiration, the concentration of bendamustine degradants is less than about 7.0%, preferably no more than about 5.0% to about 7.0%; wherein said product is stored at about 2°C to about 30°C.

Another embodiment of the invention is a bendamustine pre-lyophilization solution or dispersion comprising one or more organic solvents where the solution or dispersions include at least one stabilizing concentration of an organic solvent which reduces the level of degradation of bendamustine so that the amount of HP1 produced during lyophilization from about 0 to 24 hours does not exceed about 0.5% to about 0.9% (area percent of bendamustine) preferably 0.50%, preferably 0.45%, more preferably 0.40%, more preferably 0.35%, even more preferably 0.30%. An aspect of this embodiment is the lyophilized powder produced from the pre-lyophilization solution or dispersion.

Still another embodiment of the invention is a bendamustine pre-lyophilization solution or dispersion comprising one or more organic solvents where the solution or dispersions include at least one stabilizing concentration of an organic solvent which reduces the level of degradation of bendamustine so that the amount of bendamustine ethylester produced during lyophilization from about 0 to 24 hours does not exceed about 0.5% (area percent bendamustine). An aspect of this embodiment is the lyophilized powder produced from the pre-lyophilization solution or dispersion.

Still another embodiment of the invention is a bendamustine pre-lyophilization solution or dispersion comprising one or more organic solvents where the solution or dispersions include at least one stabilizing concentration of an organic solvent which reduces the level of degradation of bendamustine so that the amount of bendamustine ethylester (as shown in Formula IV) produced during lyophilization from about 0 to 24 hours is no more than 0.2%, preferably 0.1%, greater than the concentration of bendamustine ethylester as found in the drug substance used to make the pre-lyophilization solution. A preferred organic solvent is tertiary butanol.

The invention also discloses methods for preparing a bendamustine lyophilized preparation that includes dissolving bendamustine in a stabilizing concentration of an

alcohol solvent of between about 5% to about 100% (v/v alcohol to form a pre-lyophilization solution; and lyophilizing the pre-lyophilization solution; wherein the bendamustine lyophilized preparation made from such methods contains not more than about 0.5% to about 0.9%, preferably 0.5%, (area percent of bendamustine) HP1 as shown in Formula II, wherein said HP1 is the amount of HP1 present at release or at time zero after reconstitution of the lyophilized pharmaceutical composition of bendamustine. Other alcohol concentrations include about 5% to about 99.9%, about 5% to about 70%, about 5% to about 60%, about 5% to about 50%, about 5% to about 40%, about 20% to about 35%. Preferred concentrations of alcohol are from about 20% to about 30%. Preferred alcohols include one or more of methanol, ethanol, propanol, iso-propanol, butanol, and tertiary-butanol. A more preferred alcohol is tertiary-butanol. A preferred concentration of tertiary-butanol is about 20% to about 30%, preferably about 30%. An aspect of this embodiment is the addition of an excipient before lyophilization. A preferred excipient is mannitol. Preferred pre-lyophilized concentrations of bendamustine are from about 2 mg/mL to about 50 mg/mL.

In a preferred method for preparing a bendamustine lyophilized preparation, lyophilizing the pre-lyophilization solution comprises i) freezing the pre-lyophilization solution to a temperature below about -40˚C, preferably -50˚C, to form a frozen solution; ii) holding the frozen solution at or below -40˚C, preferably -50˚C, for at least 2 hours; iii) ramping the frozen solution to a primary drying temperature between about -40˚C and about -10˚C to form a dried solution; iv) holding for about 10 to about 70 hours; v) ramping the dried solution to a secondary drying temperature between about 25˚C and about 40˚C; and vii) holding for about 5 to about 40 hours to form a bendamustine lyophilized preparation. In a more preferred method lyophilizing the pre-lyophilization solution comprises i) freezing the pre-lyophilization solution to about -50°C to form a frozen solution; ii) holding the frozen solution at about -50°C for at least 2 hours to about 4 hours; iii) ramping to a primary drying temperature between about -20°C and about -12°C to form a dried solution; iv) holding at a primary drying temperature for about 10 to about 48 hours; v) ramping the dried solution to a secondary drying temperature between about 25°C and about 40°C; and vi) holding at a secondary drying temperature for at least 5 hours up to about 20 hours. A preferred alcohol is tertiary-butanol. A preferred

concentration of tertiary-butanol is about 20% to about 30%, preferably about 30%. An aspect of this embodiment is the addition of an excipient before lyophilization. A preferred excipient is mannitol. Preferred pre-lyophilized concentrations of bendamustine are from about 2 mg/mL to about 50 mg/mL.

Another embodiment of the invention is the lyophilized powder or preparation obtained from the methods of preparing a bendamustine lyophilized preparation disclosed herein.

The invention also involves bendamustine formulations for lyophilization that include an excipient and a stabilizing concentration of an organic solvent. A preferred formulation includes bendamustine at a concentration of about 15 mg/mL, mannitol at a concentration of about 25.5 mg/mL, tertiary-butyl alcohol at a concentration of about 30% (v/v) and water. Included in this embodiment of the invention are the lyophilized preparations made from such bendamustine formulations.

Included in the inventions are methods of treating a medical condition in a patient that involve administering a therapeutically effective amount of a pharmaceutical composition of the invention where the condition is amenable to treatment with said pharmaceutical composition. Some conditions amenable to treatment with the compositions of the invention include chronic lymphocytic leukemia (CLL), Hodgkin's disease, non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), breast cancer, small cell lung cancer, hyperproliferative disorders, and an autoimmune disease. Preferred conditions include NHL, CLL, breast cancer, and MM. Preferred autoimmune diseases include rheumatoid arthritis, multiple sclerosis or lupus.

Included in the inventions are the use of the pharmaceutical compositions or pharmaceutical preparations of the invention in the manufacture of a medicament for the treatment of a medical condition, as defined herein, in a patient that involve administering a therapeutically effective amount of a pharmaceutical composition of the invention where the condition is amenable to treatment with said pharmaceutical composition.

Also included in the invention are methods of treating in which the pharmaceutical compositions of the invention are in combination with one or more anti-neoplastic agents where the antineoplastic agent is given prior, concurrently, or subsequent to the

administration of the pharmaceutical composition of the invention. Preferred antineoplastic agents are antibodies specific for CD20.

Another embodiment of the invention is a lyophilization cycle for producing lyophilized bendamustine preparations of the invention. A preferred lyophilization cycle includes a) freezing to about -50˚C over about 8 hours; b) holding at -50˚C for about 4 hours; c) ramping to -25˚C over about 3 hours; d) holding at -10˚C for 30 hours; e) ramping to between about 25˚C and about 40˚C or higher for about 3 hours; f) holding between about 25˚C and about 40˚C for about 25 hours; g) ramping to about 20˚C in 1 hour; h) unloading at about 20˚C, at a pressure of 13.5 psi in a pharmaceutically acceptable container that is hermetically sealed; wherein the pressure is about 150 microns throughout primary drying and 50 microns throughout secondary drying. An aspect of this cycle involves step (e) which is ramped to about 30-35˚C for 3 hours and then ramped to 40˚C for 5 hours. Another aspect of this embodiment is the lyophilized powered prepared from such lyophilization cycles. A more preferred lyophilization cycle includes i) starting with a shelf temperature of about 5˚C for loading; ii) freezing to about -50˚C over about 8 hours; iii) holding at -50˚C for about 4 hours; iv) ramping to about -20˚C over about 3 hours; v) holding at about -20˚C for 6 hours; ramping to about -15°C over about 1 hour; vi) holding at -15°C for about 20 hours; vii) ramping to about -15˚C over about 1 hour; viii) holding at about -15˚C for about 20 hours; ix) ramping to about -12˚C over about 0.5 hours; x) holding at about -12˚C for about 15.5 hours; xi) ramping to between about 25˚C and about 40˚C or higher for about 15 hours; xii) holding between about 25˚C and about 40˚C for about 10 hours; xiii) ramping to about 40˚C over about 1 hour; and xiv) holding at about 40˚C for about 5 hours; unloading at about 5˚C, at a pressure of about 13.5 psi in a pharmaceutically acceptable container that is hermetically sealed; wherein the pressure is about 150 microns throughout primary drying and 50 microns throughout secondary drying. In a preferred embodiment step (xi) is ramped to about 30-35˚C for about 15 hours.

The invention also encompasses a pharmaceutical dosage form of bendamustine containing not more than about 0.5% to about 0.9%, preferably 0.5%, HP1 (area percent of bendamustine) wherein said dosage form comprises a vial or other pharmaceutically acceptable container, wherein said HP1 is the amount of HP1 present pre-reconstitution or

at time zero after reconstitution of said dosage form. Preferred concentrations of bendamustine include about 10 to about 500 mg/container, about 100 mg/container, about 5 mg to about 2 g/container and about 170 mg/container.

The present invention also includes pre-lyophilized pharmaceutical compositions of bendamustine. A preferred pre-lyophilized composition includes bendamustine HCl about 15 mg/mL, mannitol about 25.5 mg/mL, about 30% (v/v) tertiary-butyl alcohol, and water.

These and other embodiments of the invention are described hereinbelow or are evident to persons of ordinary skill in the art based on the following disclosures.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the solubility of bendamustine at various temperatures for two different solutions of bendamustine in tertiary butanol.

Fig. 2 shows the purity results of an HPLC analysis after incubating bendamustine in various alcohols for 24 hours at 5°C. Results are presented as the area percent of the bendamustine peak.

Fig. 3 shows HP1 (Formula II) formation after 24 hours in various alcohol/water co-solvents at 5°C

Fig 4 shows dimer (Formula III) formation after 24 hours in various alcohol/water co-solvents at 5°C

Fig. 5- shows a lyophilization cycle for bendamustine using a TBA/water co-solvent.

Fig. 6 shows a chromatogram for Ribomustin® using HPLC method No. 1.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms “formulate” refers to the preparation of a drug, e.g., bendamustine, in a form suitable for administration to a mammalian patient, preferably a human. Thus, "formulation" can include the addition of pharmaceutically acceptable excipients, diluents, or carriers.

As used herein, the term “lyophilized powder” or “lyophilized preparation” refers to any solid material obtained by lyophilization, i.e., freeze-drying of an aqueous solution.

The aqueous solution may contain a non-aqueous solvent, i.e. a solution composed of aqueous and one or more non-aqueous solvent(s). Preferably, a lyophilized preparation is one in which the solid material is obtained by freeze-drying a solution composed of aqueous and one or more non-aqueous solvents, more preferably the non-aqueous solvent is an alcohol.

By "stable pharmaceutical composition" is meant any pharmaceutical composition having sufficient stability to have utility as a pharmaceutical product. Preferably, a stable pharmaceutical composition has sufficient stability to allow storage at a convenient temperature, preferably between -20°C and 40°C, more preferably about 2°C to about 30°C, for a reasonable period of time, e.g., the shelf-life of the product which can be as short as one month but is typically six months or longer, more preferably one year or longer even more preferably twenty-four months or longer, and even more preferably thirty-six months or longer. The shelf-life or expiration can be that amount of time where the active ingredient degrades to a point below 90% purity. For purposes of the present invention stable pharmaceutical composition includes reference to pharmaceutical compositions with specific ranges of impurities as described herein. Preferably, a stable pharmaceutical composition is one which has minimal degradation of the active ingredient, e.g., it retains at least about 85 % of un-degraded active, preferably at least about 90 %, and more preferably at least about 95%, after storage at 2-30°C for a 2-3 year period of time.

By "stable lyophilized preparation" is meant any lyophilized preparation having sufficient stability, such characteristics as similarly defined herein for a stable pharmaceutical composition, to have utility as a pharmaceutical product

By "degraded" is meant that the active has undergone a change in chemical structure.

The term "therapeutically effective amount" as used herein refers to that amount of the compound being administered that will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of neoplasms, a therapeutically effective amount refers to that amount which has the effect of (1) reducing the size of the tumor, (2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis, (3) inhibiting to some extent (that is, slowing to some extent, preferably

stopping) tumor growth, and/or, (4) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the cancer. Therapeutically effective amount can also mean preventing the disease from occurring in an animal that may be predisposed to the disease but does not yet experience or exhibit symptoms of the disease (prophylactic treatment). Further, therapeutically effective amount can be that amount that increases the life expectancy of a patient afflicted with a terminal disorder. Typical therapeutically effective doses for bendamustine for the treatment of non-Hodgkin's lymphoma can be from about 60-120 mg/m^2 given as a single dose on two consecutive days. The cycle can be repeated about every three to four weeks. For the treatment of chronic lymphocytic leukemia (CLL) bendamustine can be given at about 80-100 mg/m^2 on days 1 and 2. The cycle can be repeated after about 4 weeks. For the treatment of Hodgkin's disease (stages II-IV), bendamustine can be given in the "DBVBe regimen" with daunorubicin 25 mg/m^2 on days 1 and 15, bleomycin 10 mg/m^2 on days 1 and 15, vincristine 1.4 mg/m^2 on days 1 and 15, and bendamustine 50 mg/m^2 on days 1-5 with repetition of the cycle about every 4 weeks. For breast cancer, bendamustine (120 mg/m^2) on days 1 and 8 can be given in combination with methotrexate 40 mg/m^2 on days 1 and 8, and 5-fluorouracil 600 mg/m^2 on days 1 and 8 with repetition of the cycle about every 4 weeks. As a second-line of therapy for breast cancer, bendamustine can be given at about 100-150 mg/m^2 on days 1 and 2 with repetition of the cycle about every 4 weeks.

As used herein "neoplastic" refers to a neoplasm, which is an abnormal growth, such growth occurring because of a proliferation of cells not subject to the usual limitations of growth. As used herein, "anti-neoplastic agent" is any compound, composition, admixture, co-mixture, or blend which inhibits, eliminates, retards, or reverses the neoplastic phenotype of a cell.

As used herein "hyperproliferation" is the overproduction of cells in response to a particular growth factor. "Hyperproliferative disorders" are diseases in which the cells overproduce in response to a particular growth factor. Examples of such "hyperproliferative disorders" include diabetic retinopathy, psoriasis, endometriosis, cancer, macular degenerative disorders and benign growth disorders such as prostate enlargement.

As used herein, the term "vial" refers to any walled container, whether rigid or flexible.

"Controlling" as used herein means putting process controls in place to facilitate achievement of the thing being controlled. For example, in a given case, "controlling" can mean testing samples of each lot or a number of lots regularly or randomly; setting the concentration of degradants as a release specification; selecting process conditions, e.g., use of alcohols and/or other organic solvents in the pre-lyophilization solution or dispersion, so as to assure that the concentration of degradants of the active ingredient is not unacceptably high; etc. Controlling for degradants by setting release specifications for the amount of degradants can be used to facilitate regulatory approval of a pharmaceutical product by a regulatory agency, such as the U.S. Food and Drug Administration and similar agencies in other countries or regions ("agency").

The term "pharmaceutically acceptable" as used herein means that the thing that is pharmaceutically acceptable, e.g., components, including containers, of a pharmaceutical composition, does not cause unacceptable loss of pharmacological activity or unacceptable adverse side effects. Examples of pharmaceutically acceptable components are provided in The United States Pharmacopeia (USP), The National Formulary (NF), adopted at the United States Pharmacopeial Convention, held in Rockville, Md. in 1990 and FDA Inactive Ingredient Guide 1990, 1996 issued by the U.S. Food and Drug Administration (both are hereby incorporated by reference herein, including any drawings). Other grades of solutions or components that meet necessary limits and/or specifications that are outside of the USP/NF may also be used.

The term "pharmaceutical composition" as used herein shall mean a composition that is made under conditions such that it is suitable for administration to humans, e.g., it is made under GMP conditions and contains pharmaceutically acceptable excipients, e.g., without limitation, stabilizers, bulking agents, buffers, carriers, diluents, vehicles, solubilizers, and binders. As used herein pharmaceutical composition includes but is not limited to a pre-lyophilization solution or dispersion as well as a liquid form ready for injection or infusion after reconstitution of a lyophilized preparation.

A "pharmaceutical dosage form" as used herein means the pharmaceutical compositions disclosed herein being in a container and in an amount suitable for

reconstitution and administration of one or more doses, typically about 1-2, 1-3, 1-4, 1-5, 1-6, 1-10, or about 1-20 doses. Preferably, a "pharmaceutical dosage form" as used herein means a lyophilized pharmaceutical composition disclosed herein in a container and in an amount suitable for reconstitution and delivery of one or more doses, typically about 1-2, 1-3, 1-4, 1-5, 1-6, 1-10, or about 1-20 doses. The pharmaceutical dosage form can comprise a vial or syringe or other suitable pharmaceutically acceptable container. The pharmaceutical dosage form suitable for injection or infusion use can include sterile aqueous solutions or dispersions or sterile powders comprising an active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol such as glycerol, propylene glycol, or liquid polyethylene glycols and the like, vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The prevention of the growth of microorganisms can be accomplished by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

As used herein, the term "excipient" means the substances used to formulate active pharmaceutical ingredients (API) into pharmaceutical formulations; in a preferred embodiment, an excipient does not lower or interfere with the primary therapeutic effect of the API. Preferably, an excipient is therapeutically inert. The term "excipient" encompasses carriers, diluents, vehicles, solubilizers, stabilizers, bulking agents, and binders. Excipients can also be those substances present in a pharmaceutical formulation as an indirect or unintended result of the manufacturing process. Preferably, excipients are approved for or considered to be safe for human and animal administration, i.e., GRAS substances (generally regarded as safe). GRAS substances are listed by the Food and Drug administration in the Code of Federal Regulations (CFR) at 21 CFR § 182 and 21 CFR § 184, incorporated herein by reference. Preferred excipients include, but are not limited to, hexitols, including mannitol and the like.

As used herein "a stabilizing concentration of an organic solvent" or "a stabilizing concentration of an alcohol" means that amount of an organic solvent or alcohol that reduces the level of degradation of bendamustine to achieve a specified level of

degradants in the final drug product. For example, with respect to the degradant HP1, a stabilizing concentration of an organic solvent is that amount which results in an HP1 concentration (area percent of bendamustine) of less than about 0.5%, preferably less than 0.45 %, preferably less than 0.40 %, more preferably less than 0.35%, more preferably less than 0.30%, and even more preferably less than 0.25%. With respect to the overall or total degradant concentration of the final drug product, a stabilizing concentration of an organic solvent is that amount that results in a total degradant concentration (at the time of drug product release) of less than about 7% (area percent bendamustine), preferably less than about 6%, more preferably less than about 5%, and even more preferably less than about 4.0%. By "area percent of bendamustine" is meant the amount of a specified degradant, e.g., HP1, relative to the amount of bendamustine as determined, e.g., by HPLC.

The term “organic solvent” means an organic material, usually a liquid, capable of dissolving other substances.

As used herein, “trace amount of an organic solvent” means an amount of solvent that is equal to or below recommended levels for pharmaceutical products, for example, as recommended by ICH guidelines (International Conferences on Harmonization, Impurities-- Guidelines for Residual Solvents. Q3C. Federal Register. 1997;62(247):67377). The lower limit is the lowest amount that can be detected.

The term “release” or “at release” means the drug product has met the release specifications and can be used for its intended pharmaceutical purpose.

A. General

The invention provides stable, pharmaceutically acceptable compositions prepared from bendamustine. In particular, the invention provides formulations for the lyophilization of bendamustine HCl. The lyophilized powder obtained from such formulations is more easily reconstituted than the presently available lyophilized powder of bendamustine. Further, the lyophilized products of the present invention have a better impurity profile than Ribomustin® with respect to certain impurities, in particular HP1, bendamustine dimer, and bendamustine ethylester, prior to reconstitution, upon storage of the lyophilate, or following reconstitution and admixture.

The present invention further provides formulations of bendamustine useful for treating neoplastic diseases. The formulations described herein can be administered alone or in combination with at least one additional anti-neoplastic agent and/or radioactive therapy.

An aspect of the invention is conditions and means for enhancing the stability of bendamustine prior to and during the lyophilization process, upon shelf storage or upon reconstitution.

Anti-neoplastic agents which may be utilized in combination with the formulations of the invention include those provided in the Merck Index 11, pp 16-17, Merck & Co., Inc. (1989) and The Chemotherapy Source Book (1997). Both books are widely recognized and readily available to the skilled artisan.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, covalent DNA-binding drugs, antimetabolite agents, hormonal agents, including glucocorticoids such as prednisone and dexamethasone, immunological agents, interferon-type agents, differentiating agents such as the retinoids, pro-apoptotic agents, and a category of miscellaneous agents, including compounds such as antisense, small interfering RNA, and the like. Alternatively, other anti-neoplastic agents, such as metallomatrix proteases (MMP) inhibitors, SOD mimics or $alpha_v$ $beta_3$ inhibitors may be used.

One family of antineoplastic agents which may be used in combination with the compounds of the inventions consists of antimetabolite-type antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from the group consisting of alanosine, AG2037 (Pfizer), 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim,

methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents which may be used in combination with the compounds of the invention consists of covalent DNA-binding agents . Suitable alkylating-type antineoplastic agents may be selected from the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, melphalan, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

Another family of antineoplastic agents which may be used in combination with the compounds disclosed herein consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, alanosine, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-Al, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen,

elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-Al, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with the compounds of the invention include a miscellaneous family of antineoplastic agents selected from the group consisting of alpha-carotene, alpha-difluoromethyl-arginine, acitretin, arsenic trioxide, Avastin® (bevacizumab), Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-ll, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin- B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, elliprabin, elliptinium acetate, epothionesTsumura EPMTC, erbitux, ergotamine, erlotnib, etoposide,

etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Gleevec® (imatnib), Chugai GLA-43, Glaxo GR-63178, gefitinib, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, indanocine, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, mefloquine, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N- acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, Rituxan® (and other anti CD20 antibodies, e.g. Bexxar®, Zevalin®), SmithKline SK&F-104864, statins (Lipitor® etc.), Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Thalidomide, Thalidomide analogs, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534, Zometa®.

Examples of radioprotective agents which may be used in the combination chemotherapy of this invention are AD-5, adchnon, amifostine analogues, detox, dimesna, 1-102, MM-159, N-acylated-dehydroalanines, TGF-Genentech, tiprotimod, amifostine,

WR-151327, FUT-187, ketoprofen transdermal, nabumetone, superoxide dismutase (Chiron and Enzon).

Methods for preparation of the antineoplastic agents described above may be found in the literature. Methods for preparation of doxorubicin, for example, are described in U.S. Pat. Nos. 3,590,028 and 4,012,448. Methods for preparing metallomatrix protease inhibitors are described in EP 780386. Methods for preparing .alpha$_v$ .beta$_3$ inhibitors are described in WO 97/08174.

Preferred anti-neoplastic agents include, without limitation, one or more of daunorubicin, bleomycin, vincristine, doxorubicin, dacarbazine, prednisolone, mitoxantrone, prednisone, methotrexate, 5-flurouracil, dexamethasone, thalidomide, thalidomide derivatives, 2ME2, Neovastat, R 11 5777, arsenic trioxide, bortezomib, tamoxifen, G3139 (antisense), and SU5416, mitomycin, anti-CD20 antibodies, such as Rituxan® and R-etodolac.

Preferred drug regimens for which the present formulation may be used in conjunction with or as a replacement for one or more of the components includes, without limitation, ABVD (doxorubicin, bleomycin, vincristine, dacarbazine), DBV (daunorubicin, belomycin, vincristine), CVPP (cyclophosphamide, vinblastine, procarbazine, prednisolone), COP (cyclophosphamide, vincristine, prednisolone), CHOP (cyclophosphamide, doxorubicin,

vincristine and prednisone) and CMF (cyclophosphamide, methotrexate, 5-fluorouracil). Additional regimens are given in Table A below.

Table A- Cancer Therapeutic Regimens

Abbreviation	Drugs Used	Disease
AC	Doxorubicin & Cyclophosphamide	Breast cancer
CFM (CF, FNC)	Cyclophosphamide, Fluorouracil, Mitaxantrone	Breast cancer
CMF	Cyclophosphamide, Methotrexate, Fluorouracil	Breast cancer

NFL	Mitoxantrone, Fluorouracil, Leucovorin	Breast cancer
Sequential Dox-CMF	Doxorubicin	Breast cancer
VATH	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast cancer
EMA-86	Etoposide, Mitoxantrone, Ctyarabine	AML (induction)
7 + 3	Cytarabine WITH Daunorubicin OR Idarobicin OR Mitoxantrone	AML (induction)
5 + 2	Cytarabine WITH Daunorubicin OR Mitoxantrone	AML (induction)
HiDAC	Cytarabine	AML (post-remission)
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Hodgkin's
ChlVPP	Chlorambucil, Vinblastine, Procarbazine, Prednisone	Hodgkin's
EVA	Etoposide, Vinblastine, Doxorubicin	Hodgkin's
MOPP	Mechlorethamine, Vincristine, Procarbazine, Prednisone	Hodgkin's
MOPP/ABV Hybrid	Mechlorethamine, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine	Hodgkin's
MOPP/ABVD	Mechlorethamine, Doxorubicin, Vinblastine, Bleomycin, Etoposide, Prednisone	Hodgkin's

CNOP	Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone	Non-Hodgkin's
COMLA	Cyclophosphamide, Vincristine, Methotrexate, Leucovorin, Cytarabine	Non-Hodgkin's
DHAP	Dexamethasone, Cisplatin, Cytarabine	Non-Hodgkin's
ESHAP	Etoposide, Methylprednisilone, Cisplatin, Cytarabine	Non-Hodgkin's
MACOP-B	Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, Bleomycin, Septra, Ketoconazole	Non-Hodgkin's
m-BACOD	Methotrexate, Leucovorin, Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, Dexamethasone	Non-Hodgkin's
MINE-ESHAP	Mesna, Ifosfamide, Mitoxantrone, Etoposide	Non-Hodgkin's
NOVP	Mitoxantrone, Vinblastine, Prednisone, Vincristine	Non-Hodgkin's
ProMACE/cytaBOM	Prednisone, Doxorubicin, Cyclophosphamide,	Non-Hodgkin's

	Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate, Leucovorin, Septra	
M2	Vincristine, Carmustine, Cyclophosphamide, Melphalan, Prednisone	Multiple Myeloma
MP	Melphalan, Prednisone	Multiple Myeloma
VAD	Vincristine, Doxorubicin, Dexamethasone	Multiple Myeloma
VBMCP	Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisone	Multiple Myeloma

As described herein, a lyophilized formulation of bendamustine is achieved following removal of an organic solvent in water. The most typical example of the solvent used to prepare this formulation is tertiary butanol (TBA). Other organic solvents can be used including ethanol, n-propanol, n-butanol, isoproponal, ethyl acetate, dimethyl carbonate, acetonitrile, dichloromethane, methyl ethyl ketone, methyl isobutyl ketone, acetone, 1-pentanol, methyl acetate, methanol, carbon tetrachloride, dimethyl sulfoxide, hexafluoroacetone, chlorobutanol, dimethyl sulfone, acetic acid, cyclohexane. These preceding solvents may be used individually or in combination. Useful solvents must form stable solutions with bendamustine and must not appreciably degrade or deactivate the API. The solubility of bendamustine in the selected solvent must be high enough to form commercially useful concentrations of the drug in solvent. Additionally, the solvent should be capable of being removed easily from an aqueous dispersion or solution of the

drug product, e.g., through lyophilization or vacuum drying. Preferably, a solution having a concentration of about 2-80 mg/mL, preferably about 5 to 40 mg/mL, more preferably 5-20 mg/mL and even more preferably 12 to 17 mg/mL bendamustine is used.

A pharmaceutically acceptable lyophilization excipient can be dissolved in the aqueous phase. Examples of excipients useful for the present invention include, without limitation, sodium or potassium phosphate, citric acid, tartaric acid, gelatin, glycine, and carbohydrates such as lactose, sucrose, maltose, glycerin, dextrose, dextran, trehalose and hetastarch. Mannitol is a preferred excipient. Other excipients that may be used if desired include antioxidants, such as, without limitation, ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butyl-hydroxyanisole, butyl-hydroxytoluene or alpha-tocopherol acetate, or chelators.

A typical formulation and lyophilization cycle useful in accordance with the present invention is provided below. Lyophilization can be carried out using standard equipment as used for lyophilization or vacuum drying. The cycle may be varied depending upon the equipment and facilities used for the fill/finish.

In accordance with a typical embodiment of the present invention, an aqueous pre-lyophilization solution or dispersion is first formulated in a pharmaceutically acceptable compounding vessel. The solution is aseptically filtered into a sterile container, filled into an appropriate sized vial, partially stoppered and loaded into the lyophilizer. Using lyophilization techniques described herein the solution is lyophilized until a moisture content in the range of about 0.1 to about 8.0 percent is achieved. The resulting lyophilization powder is stable as a lyophilized powder for about six months to greater than about 2 years, preferably greater than about 3 years at about 5°C to about 25° C and can be readily reconstituted with Sterile Water for Injection, or other suitable carrier, to provide liquid formulations of bendamustine, suitable for internal administration e.g., by parenteral injection. For intravenous administration, the reconstituted liquid formulation, i.e., the pharmaceutical composition, is preferably a solution.

The pre-lyophilization solution or dispersion normally is first formulated in a pharmaceutically acceptable container by: 1) adding an excipient, such as mannitol (about 0 to about 50 mg/mL) with mixing to water (about 65% of the total volume) at ambient temperature, 2) adding an organic solvent (0.5- 99.9% v/v), such as TBA to the aqueous

solution with mixing at about 20°-35°C, 4) adding bendamustine HCl to the desired concentration with mixing, 5) adding water to achieve the final volume, and 6) cooling the solution to about 1°C to about 30°C, preferably about 5°C. Although the preceding steps are shown in a certain order, it is understood that one skilled in the art can change the order of the steps and quantities as needed. Quantities can be prepared on a weight basis also.

The pre-lyophilization solution or dispersion can be sterilized prior to lyophilization, sterilization is generally performed by aseptic filtration, e.g., through a 0.22 micron or less filter. Multiple sterilization filters can be used. Sterilization of the solution or dispersion can be achieved by other methods known in the art, e.g., radiation.

In this case, after sterilization, the solution or dispersion is ready for lyophilization. Generally, the filtered solution will be introduced into a sterile receiving vessel, and then transferred to any suitable container or containers in which the formulation may be effectively lyophilized. Usually the formulation is effectively and efficiently lyophilized in the containers in which the product is to be marketed, such as, without limitation, a vial, as described herein and as known in the art.

A typical procedure for use in lyophilizing the pre-lyophilization solutions or dispersions is set forth below. However, a person skilled in the art would understand that modifications to the procedure or process may be made depending on such things as, but not limited to, the pre-lyophilization solution or dispersion and lyophilization equipment.

Initially, the product is placed in a lyophilization chamber under a range of temperatures and then subjected to temperatures well below the product's freezing point, generally for several hours. Preferably, the temperature will be at or below about -40°C for at least 2 hours. After freezing is complete, the chamber and the condenser are evacuated through vacuum pumps, the condenser surface having been previously chilled by circulating refrigerant. Preferably, the condenser will have been chilled below the freezing point of the solution preferably to about -40°, more preferably to about -50°C or lower, even more preferably to about -60°C or lower. Additionally, evacuation of the chamber should continue until a pressure of about 10 to about 600 microns, preferably about 50 to about 150 microns is obtained.

The product composition is then warmed under vacuum in the chamber and condenser. This usually will be carried out by warming the shelves within the lyophilizer on which the product rests during the lyophilization process at a pressure ranging from about 10 to about 600 microns. The warming process will optimally take place very gradually, over the course of several hours. For example, the product temperature should initially be increased from about -30°C to about -10°C and maintained for about 10-70 hours. Additionally, the product temperature can be increased from the freezing temperature to about 25°C-40°C over a period of 30-192 hours. To prevent powder ejection of the lyophilate from vials, complete removal of the organic solvent and water should be done during the initial drying phase. Complete drying can be confirmed by stabilization of vacuum, condenser temperature and product shelf temperature. After the initial drying, the product temperature should be increased to about 25°C-40°C and maintained for about 5-40 hours.

Once the drying cycle is completed, the pressure in the chamber can be slowly released to atmospheric pressure (or slightly below) with sterile, dry-nitrogen gas (or equivalent gas). If the product composition has been lyophilized in containers such as vials, the vials can be stoppered, removed and sealed. Several representative samples can be removed for purposes of performing various physical, chemical, and microbiological tests to analyze the quality of the product.

The lyophilized bendamustine formulation is typically marketed in pharmaceutical dosage form. The pharmaceutical dosage form of the present invention, although typically in the form of a vial, may be any suitable container, such as ampoules, syringes, co-vials, which are capable of maintaining a sterile environment. Such containers can be glass or plastic, provided that the material does not interact with the bendamustine formulation. The closure is typically a stopper, most typically a sterile rubber stopper, preferably a bromobutyl rubber stopper, which affords a hermetic seal.

After lyophilization, the bendamustine lyophilization powder may be filled into containers, such as vials, or alternatively the pre-lyophilization solution can be filled into such vials and lyophilized therein, resulting in vials which directly contain the lyophilized bendamustine formulation. Such vials are, after filling or lyophilization of the solution therein, sealed, as with a stopper, to provide a sealed, sterile, pharmaceutical dosage form.

Typically, a vial will contain a lyophilized powder including about 10-500 mg/vial, preferably about 100 mg/vial, bendamustine and about 5mg-2g/vial, preferably about 170 mg/vial, mannitol.

The lyophilized formulations of the present invention may be reconstituted with water, preferably Sterile Water for Injection, or other sterile fluid such as co-solvents, to provide an appropriate solution of bendamustine for administration, as through parenteral injection following further dilution into an appropriate intravenous admixture container, for example, normal saline.

B. Solubility

The solubility of bendamustine HCl (bendamustine) in water (alone) and with varying amounts of alcohols commonly used in lyophilization, e.g., methanol, ethanol, propanol, isopropanol, butanol and tertiary-butyl alcohol (TBA) was determined by visual inspection. Amounts of bendamustine at 15 mg/mL, combined with mannitol at 25.5 mg/mL were prepared in 10 mL of the indicated alcohol solutions at room temperature (see Table 1). Samples were then refrigerated at 5°C and inspected after 0, 3, 6 and 24 hours for particulates and/or precipitates.

The results shown in Table 1 indicate that bendamustine solubility is dependant on temperature and the amount of alcohol in aqueous solutions. For the alcohols tested, the solubility of bendamustine increased as the concentration of alcohol increased. The formation of a precipitant was also dependent on the temperature and time. Bendamustine did not precipitate immediately with any alcohol, but crystallized after storage at 5°C. Alcohols varied in their effect on solubility. Without wishing to be bound to any particular theory, smaller alcohols such as methanol and ethanol have less of an effect on solubility as compared with larger alcohols (tertiary-butanol and n-butanol). However, the shape of the alcohol is also important. For example n-propanol was found to be better than iso-propanol in preventing precipitation in this system. The two alcohols with the greatest effect on solubility were n-propanol and tertiary-butanol.

Table 1. Bendamustine solubility over a 24 hour period in various alcohols when stored at 5°C.

	Zero Time	3 Hours	6 Hours	24 Hours
Methanol (v/v)				
0% (Water Only)	CCS	CCS	Precipitate	Precipitate
5%	CCS	CCS	Precipitate	Precipitate