

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> : <b>A61K 9/00, 31/485, A61M 15/08, A61P 25/36</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 00/62757</b> (43) International Publication Date: 26 October 2000 (26.10.00)</p>
<p>(21) International Application Number: PCT/GB00/01509 (22) International Filing Date: 18 April 2000 (18.04.00) (30) Priority Data: 9908921.1 19 April 1999 (19.04.99) GB (71) Applicant (for all designated States except US): BRITANNIA PHARMACEUTICALS LIMITED [GB/GB]; 41-51 Brighton Road, Redhill, Surrey RH1 6YS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DAVIES, David, Keith [GB/GB]; 36 Harvest Bank Road, West Wickham, Kent BR4 9DJ (GB). HASLAM, David [GB/GB]; Greystones, 9 Linton Avenue, Wetherby, West Yorkshire LS22 6SQ (GB). (74) Agent: WOODCRAFT, David, Charles; Brookes &amp; Martin, High Holborn House, 52/54 High Holborn, London WC1V 6SE (GB).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: COMPOSITION CONTAINING OPIOID ANTAGONISTS AND SPRAY DISPENSER</p>		
<p>(57) Abstract</p> <p>A spray applicator is disclosed for administering an opioid antagonist selected from naloxone and/or naltrexone. The applicator is capable of delivering single or multiple doses of the antagonist through a projecting delivery portion which is shaped or dimensioned for introduction into the nose or mouth. A pharmaceutical composition for nasal or oral administration is also disclosed which comprises an opioid antagonist, such as naloxone and/or naltrexone, and which comprises a water-susceptible solid carrier admixed with the opioid antagonist.</p>		

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## COMPOSITION CONTAINING OPIOID ANTAGONISTS AND SPRAY DISPENSER

This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage.

Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a  
5 result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation.

10 The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage.

According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or  
15 naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient.

According to another aspect of the invention there is provided a  
20 pharmaceutical composition for oral or nasal administration comprising an opioid antagonist, the composition being in finely-divided solid form and comprising a water-susceptible solid carrier and the opioid antagonist.

The spray applicator may be designed for dispensing the solution into the mouth, e.g. sub-lingually, and be provided with a projecting delivery portion for this  
25 purpose. However, in a preferred embodiment, the applicator has a delivery portion which is shaped and dimensioned for introduction into a nostril so that the dose is sprayed directly into the nasal passages. The latter mention of administration may be more convenient and enables resuscitation to be continuously and simultaneously applied. Also, a device which has such a projecting delivery portion can also, if  
30 appropriate, be applied directly into the mouth.

SUBSTITUTE SHEET (RULE 26)

Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle.

According to the aspect of the invention in which the pharmaceutical composition is in powder form, it is preferably administered nasally. In this embodiment, the composition is packaged via a dispenser having a projecting portion for introduction into a nostril. Normally, a propellant is employed for generating an aerosol of the powdered pharmaceutical in a stream of gas. The dispenser will generally include means for metering doses of the composition dispensed into the patient's nasal passages.

A preferred opioid antagonist for use in the compositions of this invention is naloxone, which is:-

17-allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine.

Another example of an opioid antagonist is naltrexone, which is:-

17-(cyclopropylmethyl)-4,5 $\alpha$ -epoxy-3,14-dihydroxymorphinan-6-one.

A mixture of two or more opioid antagonists may be employed. Preferably, naloxone is used as a sprayable liquid composition and naltrexone is preferably used in the form of a powdered, solid composition, usually for nasal administration.

Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution. A concentration of about 0.9 weight/volume NaCl in purified water is suitable. The composition may include a buffering agent to maintain the opioid in solution in the salt form, e.g. a phosphate buffer, such as sodium hydrogen phosphate to maintain the solution at a slightly acid pH. A solution of the antagonist, usually in the form of the hydrochloride, at a concentration of from about 0.5 to 5% by weight, preferably about 1 to 2%, may be employed for nasal or buccal administration. The



liquid composition may be packaged in a metered dosage spray dispenser, using a pump or propellant. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20 $\mu$ l and 100 $\mu$ l, with the dose per shot preferably varying between 200 and 5 1200 $\mu$ g.

In the case of a solid, powdered composition for nasal administration, the antagonist is mixed with one or more solid, powdered carriers. Suitable carriers include saccharides such as sorbitol, mannitol, lactose, fructose, glucose and sucrose. Other carriers include water-soluble or swellable polymers such as cellulose 10 derivatives, for example, hydroxypropyl methyl cellulose and carboxymethyl cellulose. A solid salt of the antagonist, e.g. the hydrochloride, maybe mixed with a carrier, or coated with the carrier or with a third material such as a hydrophilic polymer.

Solid, powdered formulations generally are dispensed at a total shot weight of about 20mg, giving a naloxone dose of 400 $\mu$ g per shot. Typical total shot weights 15 may vary between about 10 mg and 30mg and the naloxone dose per shot may be between about 200 and 1200 $\mu$ g.

The solid, powdered composition containing the opioid antagonist may be packaged in a dispenser with a suitable propellant, such as HFC-134a or HFC-227. Again, a valve may be provided, which is adapted to dispense a dosage unit of the 20 antagonist of about 0.2 to 5 mg, e.g. 0.4 to 2mg preferably 0.4 to 1.2mg.

It may be desirable to include an anti-oxidant, such as ascorbic acid or citric acid in the powdered formulation.

The invention is illustrated by the following Examples of pharmaceutical compositions suitable for use in dispensing the opioid antagonist and by the 25 accompanying drawing and description of one form of spray applicator suitable for dispensing the liquid composition.

#### Example 1

Sprayable aqueous liquid composition for a nasal applicator.

Naloxone hydrochloride was dissolved in a solution of purified water to form a 30 solution containing 0.8% weight/volume of the naloxone. Benzalkonium chloride was

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.