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(54) Title: NEW NON-ABUSABLE PHARMACEUTICAL COMPOSITION COMPRISING OPIOIDS

(57) Abstract: There is provided pharmaceutical compositions for the treatment of pain comprising a pharmacologically-effective amount of an opioid analgesic, or a pharmaceutically-acceptable salt thereof, presented in particulate form upon the surfaces of carrier particles comprising a pharmacologically-effective amount of an opioid antagonist, or a pharmaceutically-acceptable salt thereof, which carrier particles are larger in size than the particles of the opioid analgesic. The compositions are also useful in prevention of opioid abuse by addicts.



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## NEW NON-ABUSABLE PHARMACEUTICAL COMPOSITION COMPRISING OPIOIDS

5 This invention relates to new, fast acting, non-abusable pharmaceutical compositions that are useful in the treatment of pain, which compositions may be administered transmucosally and in particular sublingually.

10 Opioids are widely used in medicine as analgesics. Indeed, it is presently accepted that, in the palliation of more severe pain, no more effective therapeutic agents exist.

The term "opioid" is typically used to describe a drug that activates opioid receptors, which are found in the brain, the spinal cord and the gut. Three classes of opioids exist:

- 15 (a) naturally-occurring opium alkaloids. These include morphine and codeine;
- (b) compounds that are similar in their chemical structure to the naturally-occurring opium alkaloids. These so-called semi-synthetics are produced by chemical modification of the latter and include the likes of
- 20 diamorphine (heroin), oxycodone and hydrocodone; and
- (c) truly synthetic compounds such as fentanyl and methadone. Such compounds may be completely different in terms of their chemical structures to the naturally-occurring compounds.

25 Of the three major classes of opioid receptors ( $\mu$ ,  $\kappa$  and  $\delta$ ), opioids' analgesic and sedative properties mainly derives from agonism at the  $\mu$  receptor.

Opioid analgesics are used to treat the severe, chronic pain of terminal cancer, often in combination with non-steroid anti-inflammatory drugs (NSAIDs), as well

30 as acute pain (e.g. during recovery from surgery). Further, their use is increasing in the management of chronic, non-malignant pain.

Opioid-requiring cancer patients are usually given slow-release opiates (slow-release morphine or ketobemidone, or transdermal fentanyl). A characteristic feature of such treatments is periods of inadequate analgesia (so-called "breakthrough" pain). Such periods are thought to be due to increased physical activity of the patient. However, treatment of breakthrough pain by administration of increased time-contingent doses of long-acting analgesic formulations is known to cause adverse side effects, including excess sedation, nausea, and constipation.

Presently-available oral, rectal and sublingual opioid analgesic formulations have relatively lengthy onset times and/or erratic absorption characteristics, which makes them not entirely suitable for the control of acute and/or breakthrough pain.

In order to obtain rapid onset of analgesia in the treatment of other types of acute pain, including operative pain, post-operative pain, traumatic pain, post-traumatic pain, and pain caused by severe diseases, such as myocardial infarction, nephrolithiasis, etc., opioid analgesics are often administered parenterally (e.g. by intravenous or intramuscular injection). However, injections are an unpopular mode of administration, often being regarded as inconvenient and painful.

In view of the above, there is a real and growing clinical need for fast-acting orally-delivered drug compositions comprising opioid analgesics. In particular, a need exists for further or better fast-acting formulations comprising opioid analgesics, which may be administered by a convenient route, for example transmucosally, particularly, as is usually the case, when such active ingredients are incapable of being delivered perorally due to poor and/or variable bioavailability.

However, a perennial problem with potent opioid analgesics such as fentanyl is one of abuse by drug addicts. Addicts normally abuse pharmaceutical formulations by extracting a large quantity of active ingredient from that formulation into solution, which is then injected intravenously. With most commercially-available pharmaceutical formulations, this can be done relatively

easily, which renders them unsafe or "abusable". Thus, there also is a need for a fast acting, non-abusable pharmaceutical formulation comprising opioid analgesics.

5 Naloxone is a selective opioid antagonist that is used to reverse the pharmacological effects of opioids. Naloxone may therefore be used to treat narcotic drug overdose or to diagnose suspected opioid addiction. Naloxone has poor bioavailability when administered transmucosally but has good bioavailability when administered by injection.

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A simple mixture combination of the opioid partial agonist buprenorphine and naloxone for sublingual administration is available under the trademark Suboxone®. This and other abuse-resistant opioid-containing formulations are reviewed by Fudula and Johnson in *Drug and Alcohol Dependence*, **83S**, S40  
15 (2006). See also US patent applications US 2003/0124061 and US 2003/0191147.

International patent applications WO 00/16750, WO 2004/067004 and WO 2006/103418, all disclose drug delivery systems for the treatment of e.g. acute  
20 pain by sublingual administration in which the active ingredient in microparticulate form and is adhered to the surface of larger carrier particles in the presence of a bioadhesive and/or mucoadhesive promoting agent. Specific combinations of opioid analgesics and opioid antagonists are not mentioned or suggested anywhere in these documents.

25

In endeavouring to solve the above-mentioned problems, and to provide an improved, effective, fast-acting, non-abusable bioadhesive formulation comprising a potent opioid analgesic, such as fentanyl, in combination with a sufficient dose of an opioid antagonist, such as naloxone, we have found that it is not possible to  
30 provide both active ingredients upon the surfaces of inert carrier particles as disclosed in the aforementioned patent documents. We have therefore devised an elegant solution to this problem by providing particles of opioid analgesic drug

upon the surfaces of carrier particles comprising an opioid antagonist, such as naloxone.

According to a first aspect of the invention there are provided particulate pharmaceutical compositions for the treatment of pain comprising a pharmacologically-effective amount of an opioid analgesic, or a pharmaceutically-acceptable salt thereof, presented in particulate form upon the surfaces of carrier particles comprising a pharmacologically-effective amount of an opioid antagonist, or a pharmaceutically-acceptable salt thereof, which carrier particles are larger in size than the particles of the opioid analgesic, which compositions are referred to hereinafter as "the compositions of the invention".

Compositions of the invention may further comprise a bioadhesion and/or a mucoadhesion promoting agent, which agent is, at least in part, presented on the surfaces of the carrier particles.

The compositions of the invention are interactive mixtures. The term "interactive" mixture will be understood by those skilled in the art to denote a mixture in which particles do not appear as single units, as in random mixtures, but rather where smaller particles (of, for example, opioid analgesic and/or bioadhesion and/or mucoadhesion promoting agent) are attached to (i.e. adhered to or associated with) the surfaces of larger opioid antagonist-containing, or opioid antagonist-based, carrier particles. Such mixtures are characterised by interactive forces (for example van der Waals forces, electrostatic or Coulombic forces, and/or hydrogen bonding) between carrier and surface-associated particles (see, for example, Staniforth, *Powder Technol.*, **45**, 73 (1985)). In the final mixture, the interactive forces need to be strong enough to keep the adherent particles at the carrier surface, in order to create a homogeneous mixture.

The term "opioid analgesic" will be understood by the skilled person to include any substance, whether naturally-occurring or synthetic, with opioid or morphine-like properties and/or which binds to opioid receptors, particularly the  $\mu$ -opioid

receptor, having at least partial agonist activity, thereby capable of producing an analgesic effect.

Opioid analgesics that may be mentioned include opium derivatives and the opiates, including the naturally-occurring phenanthrenes in opium (such as morphine, codeine, thebaine and Diels-Alder adducts thereof) and semisynthetic derivatives of the opium compounds (such as diamorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, etorphine, nicomorphine, hydrocodeine, dihydrocodeine, metopon, normorphine and N-(2-phenylethyl)normorphine).

Other opioid analgesics that may be mentioned include fully synthetic compounds with opioid or morphine-like properties, including morphinan derivatives (such as racemorphan, levorphanol, dextromethorphan, levallorphan, cyclorphan, butorphanol and nalbuphine); benzomorphan derivatives (such as cyclazocine, pentazocine and phenazocine); phenylpiperidines (such as pethidine (meperidine), fentanyl, alfentanil, sufentanil, remifentanil, ketobemidone, carfentanyl, anileridine, piminodine, ethoheptazine, alphaprodine, betaprodine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), diphenoxylate and loperamide), phenylheptamines or "open chain" compounds (such as methadone, isomethadone, propoxyphene and levomethadyl acetate hydrochloride (LAAM)); diphenylpropylamine derivatives (such as dextromoramide, piritramide, bezitramide and dextropropoxyphene); mixed agonists/antagonists (such as buprenorphine, nalorphine and oxilorphan) and other opioids (such as tilidine, tramadol and dezocine). More preferred opioid analgesics include buprenorphine, alfentanil, sufentanil, remifentanil and, particularly, fentanyl.

The term "opioid antagonist" will be understood by the skilled person to include any substance, whether naturally-occurring or synthetic, which binds to opioid receptors, particularly the  $\mu$ -opioid receptor, having at least partial antagonist activity, thereby for example at least partially reversing one or more of the pharmacological effects of an opioid analgesic mentioned hereinbefore. Opioid antagonists that may be mentioned include naloxone, cyclazocine, nalmefene, opioid antagonist compounds having the same pentacyclic nucleus as nalmefene,

naltrexone, methylnaltrexone, nalorphine, nalbuphine, thebaine, levallorphan, pentazocine, oxymorphone, butorphanol, bupremorphine, levorphanol, meptazinol, dezocine, or pentazocine or their pharmacologically effective salts or esters such as, but not limited to, their hydrochlorides, maleates, tartrates and lactates.

5 Preferred opioid antagonists include nalmefene, preferably methylnaltrexone, more preferably naltrexone and, particularly, naloxone.

Any of the active ingredients mentioned in the above groupings may also be used in combination as required. Moreover, the above active ingredients may be used

10 in free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. If the drugs have a carboxyl group, their esters may be employed. Active ingredients can be used as racemic mixtures or as single enantiomers.

The term "pharmacologically effective amount" refers to an amount of an active

15 ingredients, which is capable of conferring a desired therapeutic effect on a treated patient, whether administered alone or in combination with another active ingredient. Such an effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, an effect).

20 Appropriate pharmacologically effective amounts of opioid analgesic compounds include those that are capable of producing (preferably rapid) relief of pain when administered transmucosally, whereas appropriate pharmacologically effective amounts of opioid antagonist compounds in the carrier particles must be sufficient so as not to compete with the pain-relieving effect of the opioid analgesic present

25 in the composition of the invention upon transmucosal administration, but to block the effect of the opioid analgesic if an attempt is made by an opioid-addicted individual to inject a composition of the invention. As stated above, we have found that this can be achieved elegantly by presenting smaller microparticles of opioid analgesic on the surfaces of larger carrier particles comprising opioid

30 antagonist, and the skilled person will appreciate that the relative sizes of the two active ingredients can be utilised to achieve the necessary relevant doses in this respect.

The amounts of active ingredients that may be employed in compositions of the invention may thus be determined by the physician, or the skilled person, in relation to what will be most suitable for an individual patient. This is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the age, weight, sex, renal function, hepatic function and response of the particular patient to be treated.

The total amount of opioid analgesic active ingredient that may be employed in a composition of the invention will depend upon the nature of the relevant active ingredient that is employed, but may be in the range of about 0.0005%, such as about 0.1% (e.g. about 1%, such as about 2%) to about 20%, such as about 10%, for example about 7%, by weight based upon the total weight of the composition. The amount of this active ingredient may also be expressed as the amount in a unit dosage form (e.g. a tablet). In such a case, the amount of opioid analgesic active ingredient that may be present may be sufficient to provide a dose per unit dosage form that is in the range of between about 1  $\mu$ g (e.g. about 5  $\mu$ g) and about 20 mg (e.g. about 15 mg, such as about 10 mg).

The total amount of opioid antagonist that may be employed in a composition of the invention may be in the range about 1%, such as about 2% (e.g. about 5%, such as about 10%) to about 98%, such as about 99%, for example about 99.9% (e.g. 99.9995%). The amount of this active ingredient may also be expressed as the amount in a unit dosage form (e.g. a tablet). In such a case, the amount of opioid antagonist active ingredient that may be present may be sufficient to provide a dose per unit dosage form that is in the range of between about 0.1 mg and about 10 mg, such as about 1 to about 5 mg (e.g. about 4 mg).

The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.



Opioid analgesic active ingredients in the compositions of the invention are preferably in the form of microparticles, preferably with a weight based mean diameter of between about 0.5  $\mu\text{m}$  and about 15  $\mu\text{m}$ , such as about 1  $\mu\text{m}$  and about 10  $\mu\text{m}$ . The term "weight based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by weight, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the weight fraction, as obtained e.g. by sieving.

Microparticles of active ingredients may be prepared by standard micronisation techniques, such as grinding, dry milling, wet milling, precipitation, etc.

Preferably, opioid antagonist-containing carrier particles for use in compositions of the invention are of a size that is between about 50 and about 1000  $\mu\text{m}$  (e.g. about 800  $\mu\text{m}$ , such as about 750  $\mu\text{m}$ ), and preferably between about 100 and about 600  $\mu\text{m}$ .

It is possible for certain active ingredients that the relative sizes and amounts of the particles of opioid analgesic active ingredient and the opioid antagonist-containing carrier particles that are employed are sufficient to ensure that the carrier particles may be at least about 90% covered by the opioid analgesic, for example at least about 100% and up to about 200% (e.g. between about 130% and about 180%) covered. The skilled person will appreciate in this context that "100% coverage" of the carrier particles by the opioid analgesic means that the relative particle sizes and amounts of the relevant particles that are employed are sufficient to ensure that the entire surface area of each carrier particle could be covered by particles of the opioid analgesic notwithstanding that other ingredients (e.g. mucoadhesion promoting agent) may also be present in a composition. Obviously, if other such ingredients are employed, then the actual degree of coverage of carrier particles by active ingredient may be less than the amounts specified above. 200% coverage means that there is sufficient particles of opioid

analgesic to cover the surfaces of the carrier particles twice over, notwithstanding the presence of other ingredients.

It is surprising that compositions with greater than 90% theoretical coverage are effective. Based on current knowledge, the skilled person would understand that, in order to ensure rapid dissolution, it would be important to ensure that the relative sizes/amounts of opioid analgesic/carrier particles are sufficient to ensure that 70% or less of the surfaces of the latter could be covered by the former.

As mentioned hereinbefore, compositions of the invention may comprise one or more bioadhesion and/or mucoadhesion promoting agent at least in part presented on, and/or adhered to, the surface of an opioid antagonist-containing carrier particle, and may thus facilitate the partial or complete adhesion of active ingredients to a biological surface, such as a mucosal membrane.

The terms "mucoadhesive" and "mucoadhesion" refer to adhesion or adherence of a substance to a mucous membrane within the body, wherein mucous is present on the surface of that membrane (e.g. the membrane is substantially (e.g. >95%) covered by mucous). The terms "bioadhesive" and "bioadhesion" refer to adhesion or adherence of a substance to a biological surface in a more general sense. Biological surfaces as such may include mucous membranes wherein mucous is not present on that surface, and/or surfaces that are not substantially (e.g. <95%) covered by mucous. The skilled person will appreciate that, for example, the expressions "mucoadhesion" and "bioadhesion" may often be used interchangeably. In the context of the present invention, the relevant terms are intended to convey a material that is capable of adhering to a biological surface when placed in contact with that surface (in the presence of mucous or otherwise) in order to enable compositions of the invention to adhere to that surface. Such materials are hereinafter referred to together as "bio/mucoadhesives" or "bio/mucoadhesion promoting agents", and such properties together as "bio/mucoadhesion" or "bio/mucoadhesive".

A variety of polymers known in the art can be used as bio/mucoadhesion promoting agents, for example polymeric substances, preferably with an average (weight average) molecular weight above 5,000. It is preferred that such materials are capable of rapid swelling when placed in contact with water and/or, more preferably, mucous, and/or are substantially insoluble in water at room temperature and atmospheric pressure.

Bio/mucoadhesive properties may be routinely determined in a general sense *in vitro*, for example as described by G. Sala *et al* in *Proceed. Int. Symp. Contr. Release. Bioact. Mat.*, **16**, 420, 1989. Examples of suitable bio/mucoadhesion promoting agents include cellulose derivatives such as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, modified cellulose gum and sodium carboxymethyl cellulose (NaCMC); starch derivatives such as moderately cross-linked starch, modified starch and sodium starch glycolate; acrylic polymers such as carbomer and its derivatives (Polycarbophyl, Carbopol®, etc.); polyvinylpyrrolidone; polyethylene oxide (PEO); chitosan (poly-(D-glucosamine)); natural polymers such as gelatin, sodium alginate, pectin; scleroglucan; xanthan gum; guar gum; poly co-(methylvinyl ether/maleic anhydride); and crosscarmellose (e.g. crosscarmellose sodium). Such polymers may be crosslinked. Combinations of two or more bio/mucoadhesive polymers can also be used.

Suitable commercial sources for representative bio/mucoadhesive polymers include: Carbopol® acrylic copolymer (BF Goodrich Chemical Co, Cleveland, OH, USA); HPMC (Dow Chemical Co., Midland, MI, USA); NEC (Natrosol; Hercules Inc., Wilmington, DE. USA); HPC (Klucel®; Dow Chemical Co., Midland, MI, USA); NaCMC (Hercules Inc. Wilmington, DE. USA); PEO (Aldrich Chemicals, USA); sodium alginate (Edward Mandell Co., Inc., Carmel, NY, USA); pectin (BF Goodrich Chemical Co., Cleveland, OH, USA); crosslinked polyvinylpyrrolidone (Kollidon CL®, BASF, Germany, Polyplasdone XL®, Polyplasdone XL-10® and Polyplasdone INF-10®, ISP Corp., US); Ac-Di-Sol®

(modified cellulose gum with a high swellability; FMC Corp., USA); Actigum (Mero-Rousselot-Satia, Baupre, France); Satiexana (Sanofi BioIndustries, Paris, France); Gantrez® (ISP, Milan, Italy); chitosan (Sigma, St Louis, MS, USA); and sodium starch glycolate (Primojel®, DMV International BV, Netherlands, Vivastar®, J. Rettenmaier & Söhne GmbH & Co., Germany, Explotab®, Roquette America, US).

Preferred bio/mucoadhesion promoting agents that may be employed in compositions of the invention include internally crosslinked sodium carboxymethylcellulose, such as croscarmellose sodium NF (e.g. Ac-Di-Sol® (FMC Corp., USA)) and crosslinked polyvinylpyrrolidone (e.g. Kollidon CL®, BASF, Germany).

Depending on the type of the bio/mucoadhesion promoting agent used, the rate and intensity of bio/mucoadhesion may be varied.

Suitably, the amount of bio/mucoadhesion promoting agent that is present in a composition of the invention may be in the range of about 0.1 to about 25% by weight based upon the total weight of the composition. A preferred range is from about 0.5 to about 15% by weight, such as about 1 to about 10% (e.g. about 2 to about 8%) by weight.

The carrier particles that are employed in compositions of the invention comprise opioid antagonist as defined herein. Carrier particles may or may not consist essentially of opioid antagonist. By "consisting essentially" of opioid antagonist, we mean that the carrier particles comprise at least about 95%, such as at least about 98%, more preferably greater than about 99%, and particularly at least about 99.5% by weight (based on the total weight of the carrier particle) of such an antagonist. These percentages exclude the presence of trace amounts of water and/or any impurities that may be present in such materials, which impurities may arise following the production of such materials, either by a commercial or non-commercial third party supplier, or by a skilled person making a composition of

the invention. In any event, the possibility of particles of opioid antagonist also being presented, at least in part, upon the surfaces of, and/or between, such carrier particles is not excluded.

- 5 When the carrier particles do not consist essentially of opioid antagonist, additional materials that may also form part of the carrier particles include pharmaceutically-acceptable substances, such as carbohydrates, e.g. sugar, mannitol and lactose; pharmaceutically-acceptable inorganic salts, such as sodium chloride, calcium phosphate, dicalcium phosphate hydrate, dicalcium phosphate  
10 dehydrate, tricalcium phosphate, calcium carbonate, and barium sulfate; polymers, such as microcrystalline cellulose, cellulose and crosslinked polyvinylpyrrolidone; or mixtures thereof.

When carrier particles do not consist essentially of opioid antagonist, additional  
15 materials may be admixed together with opioid antagonist by a variety of techniques, such as dry mixing, extrusion and/or spheronisation, or a process of granulation, which may comprise wet and/or dry granulation.

Wet granulation techniques are well known to those skilled in the art and include  
20 any technique involving the massing of a mix of dry primary powder particles using a granulating fluid, which fluid comprises a volatile, inert solvent, such as water, ethanol or isopropanol, either alone or in combination, and optionally in the presence of a binder or binding agent. The technique may involve forcing a wet mass through a sieve to produce pellets by spheronisation or wet granules which  
25 are then dried. Dry granulation techniques are also well known to those skilled in the art and include any technique in which primary powder particles are aggregated under high pressure, including slugging and roller compaction, for example as described hereinafter.

30 Primary particles of ingredients (e.g. opioid antagonist and other carrier particle materials) may be processed by techniques, such as grinding, dry milling, wet milling, precipitation, etc, prior to granulation.

Granulates comprising opioid antagonist may be further processed following their formation and prior to admixing with other ingredients to produce a composition of the invention. For example, a dry granulate may be ground or milled using a suitable milling technique to produce particulate material of a smaller size, which  
5 may also be sieved to separate the desired size fraction. Wet granulate may be screened to break up agglomerates of granules and remove fine material. In either case, the unused fine material may be reworked to avoid waste. Suitable granulate particle sizes are in the range of about 0.05 mm to about 1.2 mm (e.g.  
10 about 1 mm), such as about 0.1 mm to about 1.0 mm (e.g. about 0.8 mm), for example about 0.2 to about 0.6 mm.

Compositions of the invention, once prepared, are preferably directly compressed/compacted into unit dosage forms (e.g. tablets) for administration to  
15 mammalian (e.g. human) patients, for example as described hereinafter.

A disintegrating agent, or "disintegrant" may also be included in the composition the invention, particularly those that are in the form of tablets for e.g. sublingual administration. Such an agent may be defined as any material that is capable of  
20 accelerating to a measurable degree the disintegration/dispersion of a composition of the invention, and in particular carrier particles, as defined herein. This may be achieved, for example, by the material being capable of swelling and/or expanding when placed in contact with water and/or mucous (e.g. saliva), thus causing tablet formulations/carrier particles to disintegrate when so wetted. Suitable  
25 disintegrants include cross-linked polyvinylpyrrolidone, carboxymethyl starch and natural starch and mixtures thereof.

If present, disintegrating agent is preferably employed in an amount of between 0.5 and 10% by weight based upon the total weight of the composition. A  
30 preferred range is from 1 to 8%, such as from about 2 to about 7% (e.g. about 5%, such as about 4%) by weight.

It will be evident from the list of possible disintegrants provided above that certain materials may function in compositions of the invention in the form of tablets both as bio/mucoadhesion promoting agents and as disintegrating agents. Thus, these functions may both be provided by different substances or may be provided by the same substance.

When the "same" material is employed as a bio/mucoadhesive and as a disintegrant, the material can be said to be in two separate fractions (a bio/mucoadhesive fraction and a disintegrant fraction). In such instances, it is preferred that the particles within the disintegrant fraction are coarser (i.e. are, relatively speaking, of a larger particle size) than those in the bioadhesive fraction (*vide infra*).

In any event, the skilled person will appreciate that, in compositions of the invention in the form of tablets, any disintegrant (or disintegrant fraction) will be largely not presented on (i.e. attached to, adhered to and/or associated with) the surfaces of the carrier particles, but rather will be largely presented (i.e. at least about 60%, such as about 70%, e.g. about 80% and, more particularly, about 90% by weight presented) between such particles. Conversely, bio/mucoadhesive (or bio/mucoadhesive fraction) is always largely associated (i.e. is at least about 60%, such as about 70%, e.g. about 80% and, more particularly, about 90% by weight associated) with the carrier particles, that is to say presented on (i.e. attached to, adhered to and/or associated with) the surfaces of the carrier particles, or presented within such particles (*vide infra*), or both.

Compositions of the invention in the form of tablets for e.g. sublingual administration may also comprise a binder. A binder may be defined as a material that is capable of acting as a bond formation enhancer, facilitating the compression of the powder mass into coherent compacts. Suitable binders include cellulose gum and microcrystalline cellulose. If present, binder is preferably employed in an amount of between 0.5 and 20% by weight based upon the total

weight of the tablet formulation. A preferred range is from 1 to 15%, such as from about 2.0 to about 12% (e.g. about 10%) by weight.

Compositions of the invention may comprise a pharmaceutically acceptable  
5 surfactant or wetting agent, which may enhance the hydration of active ingredients and carrier particles, resulting in faster initiation of both bio/mucoadhesion and dissolution. If present, the surfactant should be provided in finely dispersed form and mixed intimately with the active ingredients. Examples of suitable surfactants include sodium lauryl sulphate, lecithin, polysorbates, bile acid salts and mixtures  
10 thereof. If present, the surfactant may comprise between about 0.1% (e.g. about 0.3%) and about 5% by weight based upon the total weight of the composition, and preferably between about 0.5 and about 3% by weight.

Suitable further additives and/or excipients that may be employed in compositions  
15 of the invention, in particular those in the form of tablets for e.g. sublingual administration may comprise:

- (a) lubricants (such as sodium stearyl fumarate or, preferably, magnesium stearate). When a lubricant is employed it should be used in very small amounts (e.g. up to about 3%, and preferably up to 2%, by weight based  
20 upon the total weight of the tablet formulation);
- (b) flavourings (e.g. lemon, menthol or, preferably, peppermint powder), sweeteners (e.g. neohesperidin) and dyestuffs;
- (c) antioxidants, which may be naturally occurring or otherwise (e.g. vitamin C, vitamin E,  $\beta$ -carotene, uric acid, ubiquinol, SOD, glutathione peroxidase  
25 or peroxidase catalase); and/or
- (d) other ingredients, such as carrier agents, preservatives and gliding agents.

Compositions of the invention may be prepared by standard techniques, and using standard equipment, known to the skilled person.

30 In one embodiment, particles of opioid analgesic may be dry mixed with opioid antagonist-containing carrier particles over a period of time that is sufficiently



long to enable appropriate amounts of active ingredients to adhere to the surface of the carrier particles (with or without the presence of bio/mucoadhesion promoting agent).

- 5 The skilled person will appreciate that, in order to obtain a dry powder formulation in the form of an interactive mixture, larger carrier particles must be able to exert enough force to break up agglomerates of smaller particles. This ability will primarily be determined by particle density, surface roughness, shape, flowability and, particularly, relative particle sizes.

10

Standard mixing equipment may be used in this regard. The mixing time period is likely to vary according to the equipment used, and the skilled person will have no difficulty in determining by routine experimentation a suitable mixing time for a given combination of opioid analgesic active ingredient and carrier particle

15 material(s).

20

Similarly, bio/mucoadhesion promoting agent (if present) may be admixed with opioid antagonist-containing carrier particles may be mixed together with opioid antagonist-containing carrier particles for a sufficient time in order to produce an ordered or interactive mixture. This results in discrete particles of bio/mucoadhesion promoting agent being presented on and/or adhered to the surfaces of the carrier particles.

25

The bio/mucoadhesion promoting agent suitably has a particle size with a weight based mean diameter of between about 0.1 and about 100  $\mu\text{m}$  (e.g. about 1 and about 50  $\mu\text{m}$ ).

Ordered, or interactive, mixtures may also be provided using techniques other than dry mixing, which techniques will be well known to those skilled in the art.

30

Other ingredients (e.g. disintegrants and surfactants) may be incorporated by standard mixing as described above for the inclusion of active ingredients.

The compositions of the invention may be administered transmucosally, such as buccally, rectally, nasally or preferably sublingually by way of appropriate dosing means known to the skilled person. A sublingual tablet may be placed under  
5 tongue, and the active ingredients absorbed through the surrounding mucous membranes.

In this respect, the compositions of the invention may be incorporated into various kinds of pharmaceutical preparations intended for transmucosal (e.g. sublingual)  
10 administration using standard techniques (see, for example, Lachman *et al*, "*The Theory and Practice of Industrial Pharmacy*", Lea & Febiger, 3<sup>rd</sup> edition (1986) and "*Remington: The Science and Practice of Pharmacy*", Gennaro (ed.), Philadelphia College of Pharmacy & Sciences, 19<sup>th</sup> edition (1995)).

15 Pharmaceutical preparations for sublingual administration may be obtained by combining compositions of the invention with conventional pharmaceutical additives and/or excipients used in the art for such preparations, and thereafter preferably directly compressed/compacted into unit dosage forms (e.g. tablets). (See, for example, *Pharmaceutical Dosage Forms: Tablets. Volume 1*, 2<sup>nd</sup>  
20 Edition, Lieberman *et al* (eds.), Marcel Dekker, New York and Basel (1989) p. 354-356 and the documents cited therein.) Suitable compacting equipment includes standard tableting machines, such as the Kilian SP300 or the Korsch EK0.

25 Suitable final sublingual tablet weights are in the range of about 30 to about 400 mg, such as about 40 (e.g. about 50) to about 200 mg, for example about 50 (e.g. about 60) to 180 mg, more preferably between about 60 (e.g. about 70) and about 160 mg. Suitable final tablet diameters are in the range 4 to 10 mm, for example 5 to 9 mm, and more preferably about 6 to about 8 mm.

30

Irrespective of the foregoing, compositions of the invention should be essentially free (e.g. less than about 20% by weight based on the total weight of the

formulation) of water. It will be evident to the skilled person that "premature" hydration will dramatically decrease the mucoadhesion promoting properties of a tablet formulation and may result in premature dissolution of active ingredients.

5    Wherever the word "about" is employed herein in the context of dimensions (e.g. tablet sizes and weights, particle sizes etc.), surface coverage (e.g. of opioid antagonist-containing carrier particles by particles of opioid analgesic), amounts (e.g. relative amounts of individual constituents in a composition or a component of a composition and absolute doses of active ingredients), it will be appreciated  
10    that such variables are approximate and as such may vary by  $\pm 10\%$ , for example  $\pm 5\%$  and preferably  $\pm 2\%$  (e.g.  $\pm 1\%$ ) from the numbers specified herein.

Compositions of the invention may be administered by way of appropriate dosing means known to the skilled person. For example, a sublingual tablet may be  
15    placed under the tongue, and the active ingredients absorbed through the surrounding mucous membrane.

The compositions of the invention are useful in the treatment of pain for example the symptomatic treatment of pain, particularly severe, acute and/or breakthrough  
20    pain. According to a further aspect of the invention there is provided a method of treatment of pain which method comprises administration of a composition of the invention to a person suffering from, or susceptible to, such a condition.

For the avoidance of doubt, by "treatment" we include the therapeutic treatment,  
25    as well as the symptomatic treatment, the prophylaxis, or the diagnosis, of the condition.

The compositions of the invention enable the production of unit dosage forms that are easy and inexpensive to manufacture, and which enable the rapid release  
30    and/or a rapid uptake of the active ingredients employed through the mucosa, such as the oral mucosa, thus enabling rapid relief of pain symptoms, such as those described hereinbefore.

The compositions of the invention also have the advantage that, if injected by an opioid addict, they do not produce the euphoric effects that such an addict seeks and indeed induce opioid withdrawal syndrome.

5 The compositions of the invention may also have the advantage that they substantially reduce the degree of absorption of active ingredients *via* swallowed saliva, as well as enabling the administration of “reduced” amounts of the opioid analgesic active ingredient that is employed, so substantially reducing the risk of side effects, as well as intra- and interpatient variability of therapeutic response.

10 Compositions of the invention may also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials that are approved for use in foods or pharmaceuticals or of like regulatory status.

15 Compositions of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile than, and/or have other useful pharmacological, physical,  
20 or chemical properties over, pharmaceutical compositions known in the prior art, whether for use in the treatment of pain or otherwise.

The invention is illustrated by way of the following examples.

#### 25 **Example 1**

##### **Naloxone/fentanyl – Sublingual tablets**

An ordered mixture of micronised fentanyl citrate and a mucoadhesive component adhered to the surface of water-soluble carrier particles, consisting of a dry  
30 granulate of a water-soluble excipient and naloxone hydrochloride is prepared as follows.

Active ingredients are accurately weighed out, along with the other excipients (see below), in appropriate proportions that enable the production of tablets with the absolute amounts of various ingredients mentioned below.

- 5 Naloxone hydrochloride (Mallinckrodt, USA) and mannitol (Roquette, France) are mixed in a tumbling mixer (2 L Turbula W. A. Bachofen AG, Basel, Switzerland) for 60 minutes at 32 rpm.

10 The resultant mixture is then processed in a roller compaction into compacts which are reduced in size by a rotor sieving mill. The particle size of the resultant particles, which are used as carrier particles in the formulation, is larger than 90  $\mu\text{m}$ .

15 The carrier particles are then mixed with fentanyl citrate (Diosynth, Netherlands) in a tumbling mixer for 72 hours (laboratory scale) at 32 rpm.

Croscarmellose sodium (Ac-Di-Sol®; FMC, USA) and silicified microcrystalline cellulose (ProSolv; Penwest pharmaceuticals Co, USA) are added to the resultant mixture and the mixing is continued for another 30 minutes.

20

Finally, magnesium stearate (Peter Greven, Netherlands) is added to the mixture and the mixing is continued for another 2 minutes.

25 The powder mixture is then compacted in a single punch press with 6 mm flat bevel edged punches, to give a tablet weight of 70 mg.

In-process controls, such as tablet weight, crushing strength and disintegration time, are employed, with test samples being withdrawn throughout the tableting process. Tablets are packaged and labelled.

30

One tablet contains – Ingredient	Amount (mg)
Fentanyl citrate (corresponding to fentanyl base 200 µg)	0.314
Naloxone hydrochloride (corresponding to naloxone base 8 mg)	9.77
Mannitol	49.49
Silicified microcrystalline cellulose	9.35
croscarmellose sodium	0.73
magnesium stearate	0.35
Total tablet weight	70.00

**Example 2****Naloxone/fentanyl – Sublingual tablets (incorporating a dry granulation process step)**

5

Sublingual tablets were made using the same materials, in the same proportions, as those specified in Example 1 above.

Carrier particles were manufactured by mixing mannitol and naloxone HCl in the tumbling mixer at 32 rpm for 60 minutes. Dry granulation was performed by compaction of the mixture in a single punch press (Korsch EK0, Germany) using 20 mm flat-faced punches. The compacts were then crushed by sieving (1.4, 1.0 and 0.8 mm) and a final fraction of 90-800 µm particles was obtained by sieving.

Fentanyl citrate was added to the carrier material in amounts corresponding to a batch size of 300 tablets. Mixing was carried out under the same conditions as those described in Example 1. Croscarmellose sodium and silicified microcrystalline cellulose, and then magnesium stearate, were added and admixed under the same conditions as those described in Example 1.

20

The mixture was compressed into tablets in the single punch press using 6 mm flat faced bevel edged punches.

### Example 3

#### 5 Naloxone/fentanyl – Sublingual tablets (incorporating a wet granulation process step)

Sublingual tablets were made using the same materials, in the same proportions, as those specified in Example 1 above.

10

To make carrier particles, mannitol and naloxone HCl were firstly mixed as described in Example 2 above. 18.5 mL of ethanol was then added to the mixture, the wet mass was sieved (1.0 mm) and the granulate was dried at room temperature for 18 hours. The granulate was then sieved to obtain particles with a  
15 fraction of 90-800  $\mu\text{m}$  particles.

15

Fentanyl citrate, croscarmellose sodium and silicified microcrystalline cellulose, and then magnesium stearate, were all added and admixed under the same conditions as those described in Examples 1 and 2 above. The mixture was  
20 compressed as described in Example 2.

20

## Claims

1. A particulate pharmaceutical composition for the treatment of pain comprising a pharmacologically-effective amount of an opioid analgesic, or a pharmaceutically-acceptable salt thereof, presented in particulate form upon the surfaces of carrier particles comprising a pharmacologically-effective amount of an opioid antagonist, or a pharmaceutically-acceptable salt thereof, which carrier particles are larger in size than the particles of the opioid analgesic.
2. A composition as claimed in Claim 1, wherein the opioid analgesic is a naturally-occurring opium-derived compound, a semisynthetic derivative of an opium compound, or a synthetic compound with opioid or morphine-like properties.
3. A composition as claimed in Claim 2, wherein the synthetic compound is a morphinan derivative, a benzomorphan derivative, a phenylpiperidine, a phenylheptamine, an open chain compound, a diphenylpropylamine derivative, a mixed agonist/antagonist or another synthetic opioid.
4. A composition as claimed in Claim 2 or Claim 3, wherein the opioid analgesic is selected from morphine, codeine, thebaine or a Diels-Alder adduct thereof, diamorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, etorphine, nicomorphine, hydrocodeine, dihydrocodeine, metopon, normorphine, N-(2-phenylethyl)normorphine, racemorphan, levorphanol, dextromethorphan, levallorphan, cyclorphan, butorphanol, nalbuphine, cyclazocine, pentazocine, phenazocine, pethidine (meperidine), fentanyl, alfentanil, sufentanil, remifentanil, ketobemidone, carfentanyl, anileridine, piminodine, ethoheptazine, alphaprodine, betaprodine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, diphenoxylate, loperamide, methadone, isomethadone, propoxyphene, levomethadyl acetate hydrochloride, dextromoramide, piritramide, bezitramide, dextropropoxyphene, buprenorphine, nalorphine, oxilorphan, tilidine, tramadol and dezocine.



5. A composition as claimed in Claim 4, wherein the opioid analgesic is selected from buprenorphine, alfentanil, sufentanil, remifentanil and fentanyl.

6. A composition as claimed in Claim 5, wherein the opioid analgesic is fentanyl.

5

7. A composition as claimed in any one of the preceding claims, wherein the opioid analgesic is in the form of microparticles.

8. A composition as claimed in Claim 7, wherein the microparticles have a weight  
10 based mean diameter of less than about 15  $\mu\text{m}$ .

9. A composition as claimed in any one of the preceding claims wherein the total amount of opioid analgesic that is employed is in the range of about 0.0005% to about 20% by weight based upon the total weight of the composition.

15

10. A composition as claimed in Claim 9 wherein the range is about 2% to about 7%.

11. A composition as claimed in any one of the preceding claims wherein the  
20 amount of opioid analgesic that is present is sufficient to provide a dose per unit dosage form of between about 1  $\mu\text{g}$  and about 20 mg.

12. A composition as claimed in Claim 11 wherein the amount is between about 5  $\mu\text{g}$  and about 10 mg.

25

13. A composition as claimed in any one of the preceding claims wherein the opioid antagonist is selected from nalmeferene, methylnaltrexone, naltrexone and naloxone.

30 14. A composition as claimed in Claim 13, wherein the opioid antagonist is naloxone.

15. A composition as claimed in any one of the preceding claims wherein the total amount of opioid antagonist that is employed is in the range of about 1% to about 99.9995% by weight based upon the total weight of the composition.

5 16. A composition as claimed in Claim 15, wherein the range is about 10% to about 98%.

17. A composition as claimed in any one of the preceding claims wherein the amount of opioid antagonist that is present is sufficient to provide a dose per unit  
10 dosage form of between about 0.1 mg and about 10 mg.

18. A compositions as claimed in Claim 17, wherein the amount is between about 1 and about 5 mg.

15 19. A composition as claimed in any one of the preceding claims, wherein the carrier particles are of a size that is between about 50 and about 1,000  $\mu\text{m}$ .

20. A composition as claimed in Claim 19, wherein the size range is between about 100 and about 800  $\mu\text{m}$ .

20

21. A composition as claimed in any one of the preceding claims, which further comprises a bioadhesion and/or a mucoadhesion promoting agent, which agent is, at least in part, presented on the surfaces of the carrier particles.

25 22. A composition as claimed in Claim 21, wherein the bioadhesion and/or mucoadhesion promoting agent is a polymeric substance with a weight average molecular weight above 5,000.

30 23. A composition as claimed in Claim 22, wherein the bioadhesion and/or mucoadhesion promoting agent is selected from a cellulose derivative, a starch derivative, an acrylic polymer, polyvinylpyrrolidone, polyethylene oxide,

chitosan, a natural polymer, scleroglucan, xanthan gum, guar gum, poly co-(methylvinyl ether/maleic anhydride) and crosscarmellose, or a mixture thereof.

24. A composition as claimed in Claim 23, wherein the bioadhesion and/or  
5 mucoadhesion promoting agent is selected from hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, modified cellulose gum, sodium carboxymethyl cellulose, moderately cross-linked starch, modified starch, sodium starch glycolate, carbomer or a derivative thereof, crosslinked  
10 polyvinylpyrrolidone, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, poly co-(methylvinyl ether/maleic anhydride) and crosscarmellose sodium, or a mixture thereof.

25. A composition as claimed in Claim 24, wherein the bioadhesion and/or  
15 mucoadhesion promoting agent is crosscarmellose sodium or crosslinked polyvinylpyrrolidone.

26. A composition as claimed in any one of Claims 21 to 25 wherein the amount  
of bioadhesion and/or mucoadhesion promoting agent present is in the range of  
20 about 0.1 to about 25% by weight based upon the total weight of the composition.

27. A composition as claimed in Claim 26, wherein the range is about 1 to about  
15% by weight.

25 28. A composition as claimed in any one of Claims 21 to 27, wherein the bioadhesion and/or mucoadhesion promoting agent has a particle size in the range of about 1 to about 100  $\mu\text{m}$ .

29 A composition as claimed in any one of the preceding claims, wherein the  
30 carrier particles further comprise a carbohydrate, a pharmaceutically-acceptable inorganic salt or a polymer.

30. A composition as claimed in Claim 29, wherein the particles comprise sugar, mannitol, lactose, sodium chloride, calcium phosphate, dicalcium phosphate hydrate, dicalcium phosphate dehydrate, tricalcium phosphate, calcium carbonate, barium sulfate, microcrystalline cellulose, cellulose, crosslinked  
5 polyvinylpyrrolidone or a mixture thereof.

31. A composition as claimed in Claim 30, wherein the particles comprise mannitol and/or lactose.

10 32. A composition as claimed in any one of the preceding claims, wherein the relative sizes and amounts of the particles of opioid analgesic and the carrier particles that are employed are sufficient to ensure that the carrier particles may be at least about 90% covered by the opioid analgesic particles.

15 33. A composition as claimed in any one of the preceding claims which is in the form of a tablet suitable for sublingual administration.

34. A composition as claimed in Claim 33, wherein the composition further comprises a disintegrating agent.

20

35. A composition as claimed in Claim 34, wherein the disintegrating agent is selected from crosslinked polyvinylpyrrolidone, carboxymethyl starch, natural starch and mixtures thereof.

25 36. A composition as claimed in Claim 34 or Claim 35, wherein the amount of disintegrating agent is between about 2 and about 7% by weight based upon the total weight of the composition.

30 37. A process for the preparation of a composition as defined in any one of Claims 1 to 36, which comprises dry mixing the carrier particles with the opioid analgesic.

38. A process for the preparation of a sublingual tablet as defined in any one of Claims 33 to 36, which comprises directly compressing or compacting a composition as defined in any one of Claims 1 to 32.

5 39. A process as claimed in Claim 38 or Claim 39 which further comprises a process step in which the carrier particles are prepared by a process of dry or wet granulation.

40. The use of a composition as defined in any one of Claims 1 to 36 for the  
10 manufacture of a medicament for the treatment of pain.

41. A method of treatment of pain which method comprises administration of a composition as defined in any one of Claims 1 to 36 to a patient suffering from, or susceptible to, such a condition.

15

42. A use as claimed in Claim 40, or a method as claimed in Claim 41, wherein the pain is severe, acute and/or breakthrough pain.

43. A use or method as claimed in Claim 42, wherein the medicament and/or  
20 composition is resistant to abuse by an opioid addict.

# INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/004627

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/16 A61K9/26 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/16751 A (DIABACT AB [SE]; PETTERSSON ANDERS [SE]; NYSTROEM CHRISTER [SE]; LENNE) 30 March 2000 (2000-03-30) example 1	1-43
Y	US 2003/124061 A1 (RICHARD H. ROBERTS) 3 July 2003 (2003-07-03) figure 1b paragraph [0024] paragraph [0037] claims 1,9,10	1-43
X	WO 2004/093801 A (EURO CELTIQUE SA [LU]; OSHLACK BENJAMIN [US]; VAN BUSKIRK GLEN [US]; C) 4 November 2004 (2004-11-04) claim 12	1-4, 9-32, 34-43

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

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

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

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

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

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

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

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

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

\*G\* document member of the same patent family

Date of the actual completion of the international search

11 March 2008

Date of mailing of the international search report

18/03/2008

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2007/004627

### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 41-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/004627

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