

USE OF OPIOID ANTAGONISTS FOR TREATING URINARY RETENTION

TECHNICAL FIELD OF THE INVENTION

- 5 The invention pertains to the use of opioid antagonists for the treatment of urinary retention.

BACKGROUND OF THE INVENTION

- 10 Urinary retention is a condition by which a substantial number of patients are affected and which results from different, often unrelated underlying causes.

It is defined by symptoms of decreased urinary stream with intermittence, straining, urgency and incomplete voiding. Acute and chronic retention has to be differentiated.

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- Urinary retention can cause urinary urge or overflow incontinence. It may cause abdominal distention and pain. Long-term urinary retention predisposes to urinary tract infections (UTI) and can increase bladder pressure, causing obstructive uropathy. Consequences of chronic urinary retention thus can include development of bladder stones, loss of detrusor muscle tone, hydronephrosis, hypertrophy of detrusor muscle and diverticula in the bladder wall. Particularly acute urinary retention can be very painful.
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- Several reasons, diseases, conditions can act as basis for development of urinary retention. This can be e.g. benign prostatic hypertrophy, prostatic cancer or other pelvic cancer, congenital abnormalities like urethral valve abnormalities, detrusor muscle dyssynergia, circumcision, damage to the bladder, obstruction in the urethra, paruresis, faecal impaction, acute or chronic prostatitis, blood clots in the bladder, retroverted gravid uterus, spinal anaesthesia or postoperative conditions, spinal cord injury, urethral rupture, anal pain, ureter stones. Drugs like anticholinergics, antidepressants, opioids can also cause urinary retention due to the effect of the neuronal system and smooth muscles.
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Urinary retention typically occurs although the kidney function may be normal, as urine will be produced but cannot be excreted. The therapeutic aim therefore usually is not to increase the production of urine but to ease excretion thereof.

- 5 Treatment for acute and chronic urinary retention may differ. In acute urinary retention, intravesicale catheterization via the urethra or suprapubic cystotomie may be the first therapeutic intervention. For chronic urinary retention being e.g. based on prostate hypertrophy, pharmaceutical treatments such as alpha reductase inhibitors or an operational ectomisation of the prostate gland via open prostatectomy or
- 10 transurethral resection (TURP) may be first choice.

- Although these principles are established as general treatment routes, therapy options may differ and have to be adapted dependent on the different pathophysiological causes for urinary retention. As mentioned, pharmaceuticals which are used in
- 15 urinary retention are e.g. alpha 1 receptor blockers (doxazosin, prazosin, phenoxybenzamine, phentolamine, tamsulosin, alfuzosin and terazosin) or 5 alpha reductase inhibitors (finasteride, dutasteride). There is no specific treatment for opioid induced urinary retention available.
- 20 There is nevertheless a continuing need for additional pharmaceutical dosage forms and treatment regimens.

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OBJECT AND SUMMARY OF THE INVENTION

It is one objective of the present invention to provide new pharmaceutical dosage
5 forms that allow treatment of urinary retention in human beings.

Further, it is an objective to provide novel uses of known pharmaceutical
preparations for treating urinary retention.

10 Yet another objective of the present invention is to provide methods for treating
urinary retention in human beings.

These and other objectives as they will become apparent from the ensuing
description are attained by the subject matter of the independent claims. Some of the
15 preferred embodiments of the inventions are the subject matter of the dependent
claims.

In one embodiment the present invention pertains to a pharmaceutical composition
comprising at least one opioid antagonist or a pharmaceutically acceptable salt
20 thereof for treating urinary retention.

In another embodiment the present invention relates to the use of at least one opioid
antagonist or a pharmaceutically acceptable salt thereof in the manufacture of a
pharmaceutical composition for treating urinary retention.

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In yet another embodiment the present invention relates to a method of treating a
human being suffering from urinary retention by administering a pharmaceutical
composition comprising at least one opioid antagonist or a pharmaceutically
acceptable salt thereof.

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The pharmaceutical compositions as they may be used and/or manufactured in accordance with the invention preferably comprise an opioid antagonist that is selected from the group comprising naloxone, methylnaltrexone, naltrexone, or nalbuphine.

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Preferably, the opioid antagonist is naloxone. A preferred pharmaceutically acceptable salt of naloxone is naloxone hydrochloride.

A particularly preferred embodiment relates to a pharmaceutical composition
10 comprising naloxone or a pharmaceutically acceptable salt thereof such as the hydrochloride salt as the sole opioid antagonist or even as the sole pharmaceutically active agent.

The pharmaceutical compositions in accordance with the invention may be used for
15 treating non-opioid induced urinary retention.

Pharmaceutical compositions in accordance with the invention may release the opioid antagonist or a pharmaceutically acceptable salt thereof immediately or in a controlled manner.

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A controlled release pharmaceutical composition comprising at least one opioid antagonist or a pharmaceutically acceptable salt thereof may comprise up to about 30% of the at least one opioid antagonist or a pharmaceutically acceptable salt thereof being formulated for immediate release and may nevertheless be classified as
25 a controlled release dosage form.

Controlled release pharmaceutical compositions comprising at least one opioid antagonist or a pharmaceutically acceptable salt thereof may comprise a matrix and/or a coating for providing controlled release properties.

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Pharmaceutical compositions in accordance with the invention may in addition to the at least one opioid antagonist or pharmaceutically acceptable salt thereof comprise additional pharmaceutically active agents. Such agents can preferably include opioid analgesics or pharmaceutically acceptable salts thereof, in particular if the urinary
5 retention from which the patient suffers causes moderate to severe pain. Opioid analgesics are preferably selected from the group comprising oxycodone, morphine, hydromorphone, oxymorphone, buprenorphine, noroxymorphone, tramadol or the like.

10 A preferred additional pharmaceutically active agent is oxycodone. A preferred pharmaceutically acceptable salt thereof is oxycodone hydrochloride.

The dosage forms in accordance with the present invention in a preferred embodiment comprise naloxone hydrochloride and oxycodone hydrochloride in a 1:2
15 ratio by weight. Preferably the dosage forms comprise the aforementioned active agents as the sole pharmaceutically active agents.

The pharmaceutical compositions in accordance with the invention may preferably be formulated for oral application. They may thus take the form of a liquid, a tablet,
20 a pill, a capsule, a granule, a spheroid etc. The pharmaceutical dosage forms may be multiparticulate dosage forms.

Another embodiment of the present invention relates to an oral pharmaceutical composition comprising at least oxycodone or a pharmaceutically acceptable salt
25 thereof and naloxone or a pharmaceutically acceptable salt thereof for treatment of pain in patients which have to discontinue opioid-based pain therapy for development of urinary retention wherein said composition is a controlled release dosage form.

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Preferably such pharmaceutical compositions comprise oxycodone hydrochloride and naloxone hydrochloride.

In one embodiment such pharmaceutical compositions comprise oxycodone
5 hydrochloride and naloxone hydrochloride in a 2:1 ratio by weight.

The compositions may comprise oxycodone or a pharmaceutically acceptable salt thereof such as the hydrochloride salt and naloxone or a pharmaceutically acceptable salt thereof such as the hydrochloride salt as the sole pharmaceutically active agents.
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DETAILED DESCRIPTION OF THE INVENTION

The inventors of the invention have found that the oral administration of naloxone in the form of a controlled release composition comprising the active agents oxycodone
15 hydrochloride and naloxone hydrochloride leads to a significant reduction of opioid induced urinary retention. Based on these findings, the present invention is directed at the use of an opioid antagonist or pharmaceutically acceptable salt thereof for treating urinary retention including non-opioid induced urinary retention in human patients.

20 Before specific aspects and some of the preferred embodiments as mentioned above are described in further detail, the following definitions are provided which shall have the indicated meaning throughout the description of the invention, unless explicitly indicated otherwise by the respective context.

25 The present invention as illustratively described hereinafter may suitably be practiced in the absence of any element or elements on the limitation or limitations not specifically disclosed herein.

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The present invention will be described with respect to particular embodiments but the invention is not limited thereto but only by the claims.

Where the term “comprising” is used in the present description and claims, it does
5 not exclude other elements. For the purposes of the present invention, the term
“consisting of” is to be a preferred embodiment of the term “comprising”. If
hereinafter a group is defined to comprise at least a certain number of embodiments,
this is also to be understood to disclose a group that preferably consists only of these
embodiments.

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Where an indefinite or definite article is used when referring to a singular noun, i.e.
“a”, “an”, or “the”, this includes a plural of that noun unless something else is
specifically stated. The terms “about” and “approximately” in the context of the
present invention denote an interval of accuracy that the person skilled in the art will
15 understand to still ensure the technical effect of the feature in question. The term
typically indicates the deviation from an indicated numerical value of $\pm 10\%$, and
preferably of $\pm 5\%$.

As already mentioned above the present invention relates to pharmaceutical
20 compositions comprising at least one opioid antagonist or a pharmaceutically
acceptable salt thereof for treating urinary retention.

According to the present invention “opioid antagonists” comprise such compounds
that counteract the effect of opioid agonists, the latter also being designated as opioid
25 analgesics. Such compounds can also be found in the ATC classification of the
WHO. Opioid antagonists in accordance with the present invention may be selected
from the group comprising naloxone, naltrexone, nalmefene, nalorphine,
nalbuphene, naloxoneazine, methyl naltrexone, ketylcyclazocene,
norbenaltorphan, naltrexone, 6- β -naloxone and 6- β -naltrexone. A preferred opioid
30 antagonist is naloxone.

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The opioid antagonist or any of the other pharmaceutically active agents mentioned hereinafter may be present in the pharmaceutical dosage forms of the present invention as free base. However, an opioid antagonist or any of the other

5 pharmaceutically active agents mentioned hereinafter may also be present in the form of its pharmaceutically acceptable salts. Such salts include e.g. the hydrochloride salt, the sulphate salt, the bisulphate salt, the tartrate salt, the nitrate salt, the citrate salt, the bitartrate salt, the phosphate salt, the malate salt, the maleate salt, the hydrobromide salt, the hydroiodide salt, the fumarate salt, the succinate salt and the

10 like. A pharmaceutically active agent as mentioned hereinafter may also be present as base addition salts such as metal salt of alkali metals including lithium, sodium and potassium. The pharmaceutically active agents may of course also be present in the form of derivatives of the free base. Such derivatives include e.g. esters.

15 In a preferred embodiment the present invention uses naloxone hydrochloride as the opioid antagonist. In a further preferred embodiment of the invention, the pharmaceutical dosage forms use an opioid antagonist and preferably naloxone and even more preferably naloxone hydrochloride as the sole pharmaceutically active agent.

20 The pharmaceutical dosage forms may comprise additional pharmaceutically acceptable excipients. These pharmaceutical excipients as well as the manufacturing methods may be chosen so as to convey certain release properties to the pharmaceutical dosage forms in accordance with the invention. Dependent on the

25 release characteristics, the pharmaceutical dosage forms in accordance with the invention may be classified as immediate release dosage forms or controlled release dosage forms.

The term "immediate release dosage form" is typically used to describe a

30 pharmaceutically dosage form that releases about 70% by weight of the

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pharmaceutically active agent, such as an opioid antagonist or pharmaceutically acceptable salt thereof within 30 minutes after administration. The release is typically measured using the European Pharmacopoeia Paddle Test at 50 rpm in 900 ml 0.1 N HCl pH 1.2 using UV detection at 270 nm.

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The term "controlled release dosage form" is typically used to highlight that a pharmaceutical dosage form is not an immediate release (IR) pharmaceutical dosage form, but releases the active agent(s) from the dosage form over longer periods of time than mentioned above such that a prolonged therapeutic activity is achieved. In
10 this case, controlled release dosage forms are also designated as "sustained release dosage forms".

The terms "controlled release" and "sustained release" refer thus to the release of a pharmaceutically active compound from a dosage form over an extended period of
15 time. In general, controlled release dosage forms in the context of the present invention means that the opioid antagonist or a pharmaceutically acceptable salt thereof and/or additional pharmaceutically active agents or their pharmaceutically acceptable salts as mentioned herein are released from the pharmaceutical dosage form over a time period of at least 4 hours. Preferably, the release of the
20 pharmaceutically active agents from the dosage form may take place over time periods of at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours or at least 14 hours.

The European Pharmacopoeia Paddle Test as mentioned above can be used to
25 determine the release of the active agent(s). Reference to the European Pharmacopoeia Paddle Test in the context of *in vitro* release data refers only to the method of measurement but not in any way to evaluating the measured data even if such evaluation approaches are mentioned in the Pharmacopoeia. Thus, the indicated release values do not relate to average values of such measurements unless indicated
30 otherwise.

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The controlled release pharmaceutical dosage forms in accordance with the invention may release the pharmaceutically active agent over prolonged periods of time such that the dosage forms can be administered at reduced frequency compared to

5 immediate release dosage forms. Depending on the frequency of administration, controlled release pharmaceutical preparations in accordance with the invention can be classified as three times a day, twice a day or once a day dosage forms. Twice a day or once a day dosage forms are preferred.

10 It is to be understood that the term "controlled release pharmaceutical dosage form" refers to a dosage form as such. Thus, the classification of a dosage form as providing controlled release is to be decided on the basis of the *in vitro* release data of the complete dosage form. Therefore, if a dosage form releases the active agent(s) over an extended period of time as mentioned above and described in further detail

15 hereinafter, it will be considered to be a controlled release dosage form even if it comprises in addition a portion of pharmaceutically active agent(s) that has been formulated to provide immediate release characteristics. Typically, the amount of pharmaceutically active agent within a dosage form that may be formulated for immediate release can be up to 30% with the overall dosage form still being

20 classified as a controlled release dosage form. Such immediate release phases may allow fast achievement of a therapeutic effect while the controlled release portion will ensure that the active agents are released over a prolonged period of time so that the therapeutic effect is maintained over a time longer than it would be for a purely immediate release dosage form.

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Controlled release characteristics can be achieved by different formulation approaches.

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For example, a pharmaceutical dosage form may comprise a controlled release matrix in which the pharmaceutically active agent is embedded in order to achieve the sustained release properties of the dosage form.

- 5 In another embodiment, a coating approach may be used to ensure the controlled release characteristics of a pharmaceutical dosage form.

These approaches for achieving controlled release of active agent, i.e. use of a matrix or use of a coating may of course also be combined. The person skilled in the art is
10 further aware of other technical approaches for achieving a sustained release of the dosage form that include e.g. osmotically driven controlled release dosage form.

In a preferred embodiment, the present invention contemplates pharmaceutical dosage forms that comprise a matrix for achieving controlled release of the e.g.
15 antagonist and/or the pharmaceutically acceptable salt thereof. To this end, the controlled release matrix may comprise a substantial amount of the opioid antagonist that is present within the dosage form. Typically, if a controlled release matrix system is used, the pharmaceutically active agents such as the opioid antagonist will be dispersed throughout a matrix-forming material.

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The matrix-forming materials may be chosen to achieve an erosive matrix, a diffusion matrix or a matrix system which combines the characteristic of an erosive and a diffusion matrix. Suitable materials for inclusion in a controlled release matrix include:

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- (a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1%

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and 80% (by weight) of one or more hydrophilic or hydrophobic polymers.

- 5 (b) Digestible, long chain (C_8 - C_{50} , especially C_{12} - C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glycerol esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25 and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one
- 10 digestible, long chain hydrocarbon.
- (c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

15 In a preferred embodiment, the pharmaceutical dosage forms as described in the present invention will use a diffusion matrix for achieving sustained release of the opioid antagonist or its pharmaceutically acceptable salt from the pharmaceutical dosage form.

To this end, the diffusion matrix may be made from a hydrophobic polymer and/or a

20 C_{12} - C_{36} fatty alcohol.

As regards the hydrophobic polymer, use of a hydrophobic cellulose ether and particularly ethyl cellulose may be preferred.

25 As regards the fatty alcohol, use of lauryl, myristyl, stearyl, cetylstearyl, ceryl and/or cetylalcohol will be preferably considered. The use of stearyl alcohol is particularly preferred.

A particularly preferred embodiment relates to pharmaceutical dosage forms in

30 which the controlled release properties of the opioid antagonist or the

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pharmaceutically acceptable salt thereof are provided by a diffusion matrix which is made from a hydrophobic polymer such as from ethyl cellulose and a fatty alcohol. The matrices of some of some of the preferred embodiments of the invention, which may e.g. be made from the aforementioned combination of ethyl cellulose and stearyl
5 alcohol, will be substantially non-swellable diffusion matrix.

The term "substantially non-swellable diffusion matrix" indicates that the matrix will be substantially non-erosive, i.e. that the size of the matrix will not significantly increase upon contact with fluids. Typically, the volume of a substantially non-
10 swellable diffusion matrix will increase at maximum up to 100 %, preferably at maximum up to 75 %, more preferably at maximum up to 50 %, even more preferably at maximum up to 25% and most preferably at maximum up to 10 % or at maximum up to 5 % in volume upon contacting an aqueous solution.

15 Pharmaceutical dosage forms which comprise a hydrophobic polymer with hydrophobic cellulose ethers such as ethyl cellulose being preferred as the sole or one of the components for providing a controlled release (non-swellable) diffusion matrix, will use an amount of such polymer of between 5 to 20%, preferably of between 6 and 15% by weight and more preferably of between 7 to 10% by weight.
20 The percentages indicate the amount of the matrix-forming material with respect to the total weight of the pharmaceutical dosage form.

Pharmaceutical dosage forms, which comprise a fatty alcohol as the sole or one of the components for providing a controlled release diffusion matrix, will use an
25 amount of fatty alcohol in the matrix of between 10 to 40%, preferably of between 15 to 35 % and more preferably of between 17 to 25% by weight. These percentages again indicate the amount of fatty alcohol based on the total weight of the dosage form.

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The person skilled in the art is further aware that such a controlled release matrix may also contain other pharmaceutically acceptable ingredients and excipients which are conventional in the pharmaceutical art such as diluents, lubricants, fillers, binders, flowing agents, colourants, flavourants, surfactants, pH-adjusters, anti-tacking agents. These excipients will typically have no substantial impact on the overall release behaviour of the pharmaceutical dosage form.

Typical examples of fillers comprise lactose, glucose, saccharose, starch and their hydrolyses, microcrystalline cellulose, calcium salts like calcium hydrogen phosphate etc. Granulating aids comprise *inter alia* povidone. Flowing agents and lubricants comprise *inter alia* highly dispersed silica, talcum, magnesium oxide and magnesium stearate. Matrix-based dosage form may e.g. comprise a cosmetic coating.

As mentioned above, controlled release characteristics of a pharmaceutical dosage form may also be achieved by a film coating that governs the release of the active agents from the dosage form. To this end, the pharmaceutical dosage form may comprise a carrier, which is associated with the opioid antagonist or the pharmaceutically acceptable salts thereof. For example, one may use nonpareil beads, sugar beads etc. on and/or into which the pharmaceutically active agents are disposed.

Such active-associated carriers may then be overcoated with a coating that provides controlled release characteristics. Suitable controlled release coating materials include hydrophobic polymers such as cellulose ethers and/or acrylic polymer resins. Ethylcellulose may be preferred.

The controlled release coatings may comprise other components such as hydrophilic substances including hydrophilic polymers such hydroxypropylmethylcellulose (HPMC), polyethylenglycols etc. These components may be used to adjust the

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controlled release characteristics of the coatings. In case of e.g. HPMC, the substances may act as pore formers. The coating may, of course, also comprise additional pharmaceutically acceptable excipients.

- 5 Controlled release dosage form that use a coating for providing prolonged release may comprise an immediate release phase of the active above the coating and typically still be classified as controlled release dosage form.

Further, the person skilled in the art will realize that not only controlled release
10 matrices and coatings as mentioned above, but also the pharmaceutical dosage forms as a whole may also comprise additionally the above mentioned pharmaceutically acceptable excipients

As mentioned above, the pharmaceutical dosage forms in accordance with the
15 invention can be used for treating urinary retention. Urinary retention may result from different, and in some cases unrelated underlying reasons. In one embodiment, the pharmaceutical dosage forms in accordance with the invention are used for the treatment of non-opioid induced urinary retention.

20 Urinary retention may result from bladder dysfunction and other underlying causes such as mentioned in the background section.

As mentioned above, a preferred opioid antagonist may be naloxone. A preferred pharmaceutically acceptable salt of an opioid antagonist to be used in preparations in
25 accordance with the invention may be naloxone hydrochloride.

Typically, naloxone or its pharmaceutically acceptable salt may be used in amounts in the dosage forms equivalent to about 1 to about 80 mg, about 1 to about 40 mg, preferably about 2 mg, about 4 mg, about 6 mg, about 8 mg, about 10 mg, about 15
30 mg, about 20 mg, about 25 mg or about 30 mg naloxone hydrochloride. These

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amounts refer to the amount of naloxone or a pharmaceutically acceptable salt thereof such as naloxone hydrochloride in the dosage form. As the dosage forms may administered in multiples, the administered amount of naloxone or its salts may be higher.

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Preferably the dosage forms in accordance with the invention will be a controlled release dosage form and will be formulated for oral administration.

A particularly preferred embodiment will relate to controlled release pharmaceutical
10 preparations for treating urinary retention which comprise 1 to 40 mg of naloxone hydrochloride per unit dose and which are formulated for oral administration.

The present invention in one of its most preferred embodiments relates to a controlled release oral pharmaceutical dosage form for treating urinary retention
15 wherein the pharmaceutical dosage form comprises naloxone or a pharmaceutically acceptable salt thereof in an amount equivalent to of 2.5 to 20 mg of naloxone hydrochloride per unit dose, and wherein the controlled release dosage form releases naloxone or a pharmaceutically acceptable salt thereof by the following *in vitro* dissolution rates when measured according to the European Pharmacopeia paddle
20 test at 50 rpm in 900 ml 0.1 N HCl pH 1.2 using UV detection at 270 nm:

- 10 - 30 % by weight of naloxone or said salt thereof at 15 min,
- 30 - 50 % by weight of naloxone or said salt thereof at 1 h,
- 45 - 65 % by weight of naloxone or said salt thereof at 2 h,
- 60 - 85 % by weight of naloxone or said salt thereof at 4 h,
- 25 70 - 95 % by weight of naloxone or said salt thereof at 7 h, and
- ≥ 80% by weight of naloxone or said salt thereof at 10 h.

In another embodiment the pharmaceutical dosage forms may display the following *in vitro* dissolution rates when measured according to the United States
30 Pharmacopoeia Basket Method at pH 1.2 using UV detection at 270 nm:

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15 to 30 % by weight of naloxone or said salt thereof at 15 min,
45 to 70% by weight of naloxone or said salt thereof at 2 h,
≥ 80% by weight of naloxone or said salt thereof at 7 h,
≥ 90% by weight of naloxone or said salt thereof at 12 h.

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Given that urinary retention is usually a painful condition for a patient suffering therefrom, it may be considered to include opioid analgesics as additional pharmaceutically active agents. Of course, one may also use pharmaceutically acceptable salts thereof as additional pharmaceutically active agents.

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The term "opioid agonist" is used as known in the art. For the purposes of the present invention it will be considered to be equivalent to the term "opioid analgesic". Typically, a pharmaceutically active agent will be considered to be an opioid analgesic or opioid agonist if it belongs to Class NO2A of opioid analgesics according to the Anatomical Therapeutic Chemical classification (ATC classification) of the World Health Organisation (WHO). Preferably, an opioid agonist may be selected from the group comprising morphine, oxycodone, hydromorphone, propoxyphene, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine, phenylpiperidine and derivatives thereof, methadone, dextropropoxyphene, buprenorphine, pentazocine, tilidine, tramadol, hydrocodone. Further examples for useable analgesics according to the invention are meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, metopone, levorphanol, phenazocine, etoheptazine, propiram, profadol, phenampromide, thiambuten, pholcodeine, codeine, dihydrocodeine, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexen, 3-dimethylamino-0-(4-methoxyphenyl-carbamoyl)-propiophenone oxime, (-) β -2'-hydroxy-2, 9-dimethyl-5-phenyl-6, 7-benzomorphone, (-)2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6, 7-benzomorphone, pirinitramide, (-) α -5,9-diethyl-2' hydroxy-2-methyl-6, 7-benzomorphone, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-

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6-phenyl-indol-2-carboxylate, 1-benzoylmethyl-2, 3-dimethyl-3- (m-hydroxy-phenyl) -piperidine, N-allyl-7 α (1-R-hydroxy-1-methylbutyl)-6,14-endo-ethanotetrahydronororipavine, (-)2'-hydroxy-2-methyl-6,7-benzomorphane, noracetylmethadol, phenoperidine, α -d1-methadol, α -1-methadol, β -d1-
5 acetylmethadol, α -1-acetylmethadol and β -1-acetylmethadol. Preferred opioid agonists according to the present invention are oxycodone, hydrocodone, hydromorphone, morphine, codeine, dihydrocodeine, oxymorphone and fentanyl. The opioid agonist oxycodone can be particularly preferred.

10 A particularly preferred pharmaceutically acceptable salt is oxycodone hydrochloride.

The person skilled in the art will be aware of selecting an amount of opioid agonist and to select the ratio of opioid agonist and antagonist such that the opioid agonist
15 will be capable of treating pain resulting from urinary retention while avoiding that urinary retention results as a side effect from the opioid treatment.

Typically, if oxycodone is used as an opioid analgesic as the additional pharmaceutically active agent, it will be included in an amount being equivalent to 5,
20 10, 20, 40, 60, 80, 100, 120 or 160 mg oxycodone hydrochloride per unit dose.

If the opioid antagonist is naloxone hydrochloride and the opioid agonist is oxycodone hydrochloride, these pharmaceutically active agents may be combined in a 1:2 ratio by weight of naloxone hydrochloride to oxycodone hydrochloride. In
25 such cases pharmaceutical dosage forms in accordance with the invention may comprise oxycodone in an amount up to and being equivalent to 5, 10, 20, 40, 80, 100, 120 or 160 mg of oxycodone hydrochloride per unit dose and naloxone in an amount up to and being equivalent to 2.5, 5, 10, 20, 40, 50 or 80 mg of naloxone

hydrochloride per unit dose. These dosage forms may preferably be controlled release dosage forms and be formulated for oral administration.

The present invention in one its most preferred embodiments relates to a controlled
5 release oral pharmaceutical dosage form for treating urinary retention and the pain
caused thereby wherein the pharmaceutical dosage form comprises oxycodone
hydrochloride and naloxone hydrochloride in a 2:1 weight ratio with oxycodone
hydrochloride being present in an amount of 10 to 40 mg per unit dose and naloxone
hydrochloride being present in an amount of 5 to 20 mg per unit dose.

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Preferably such controlled release dosage forms release oxycodone hydrochloride
and naloxone hydrochloride by the following *in vitro* dissolution rates when
measured according to the European Pharmacopeia paddle test at 50 rpm in 900 ml
0.1 N HCl pH 1.2 using UV detection at 270 nm:

- 15 10 - 30 % by weight of oxycodone hydrochloride at 15 min,
 30 - 50 % by weight of oxycodone hydrochloride at 1 h,
 40 - 65 % by weight of oxycodone hydrochloride at 2 h,
 60 - 85 % by weight of oxycodone hydrochloride at 4 h,
 70 - 95 % by weight of oxycodone hydrochloride at 7 h,
20 $\geq 80\%$ by weight of oxycodone hydrochloride at 10 h,
 10 - 30 % by weight of naloxone hydrochloride at 15 min,
 30 - 50 % by weight of naloxone hydrochloride at 1 h,
 45 - 65 % by weight of naloxone hydrochloride at 2 h,
 60 - 85 % by weight of naloxone hydrochloride at 4 h,
25 70 - 95 % by weight of naloxone hydrochloride at 7 h, and
 $\geq 80\%$ by weight of naloxone hydrochloride at 10 h.

In another embodiment the pharmaceutical dosage forms may display the following
in vitro dissolution rates when measured according to the United States

30 Pharmacopoeia Basket Method at pH 1.2 using UV detection at 270 nm:

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15 to 30 % by weight of oxycodone hydrochloride at 15 min,
45 to 70% by weight of oxycodone hydrochloride at 2 h,
≥ 80% by weight of oxycodone hydrochloride at 7 h,
5 ≥ 90% by weight of oxycodone hydrochloride at 12 h,
15 to 30 % by weight of naloxone hydrochloride at 15 min,
45 to 70% by weight of naloxone hydrochloride at 2 h,
≥ 80% by weight of naloxone hydrochloride at 7 h,
≥ 90% by weight of naloxone hydrochloride at 12 h.

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Another embodiment of the present invention relates to an oral pharmaceutical composition comprising at least oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for treatment of pain in patients which otherwise have to discontinue opioid-based pain therapy for development of urinary retention wherein said composition is an oral controlled release dosage form.

It has been observed that opioid-based treatment of moderate to severe pain can cause urinary retention as a side effect. In some patients, the impact of this side effect can reach a degree that opioid therapy has to be discontinued.

However, by combining the opioid agonist oxycodone and the opioid antagonist naloxone or their pharmaceutically acceptable salts, it is possible to treat patients suffering from pain which otherwise have to discontinue a pain treatment that is based on an opioid agonist as the sole pharmaceutically active agent. Therefore, such pharmaceutical dosage forms can particularly be used to treat patients such as the elderly which suffer from impaired activity of the urinary tract system.

Preferably such pharmaceutical compositions comprise oxycodone hydrochloride and naloxone hydrochloride.

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In one embodiment such pharmaceutical compositions comprise oxycodone hydrochloride and naloxone hydrochloride in a 2:1 ratio by weight.

5 Such preparations are preferably used for treatment of moderate to severe pain.

The compositions may comprise oxycodone or a pharmaceutically acceptable salt thereof such as the hydrochloride salt and naloxone or a pharmaceutically acceptable salt thereof such as the hydrochloride salt as the sole pharmaceutically active agents.

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The preparations are controlled release preparations and may be based on a controlled release matrix, a controlled release coating or other controlled release functionalities. As regards the structure, composition, excipients, *in vitro* release data, amount of active agents etc. of such controlled release preparations comprising
15 oxycodone and naloxone, reference is made to the passages mentioned before.

Typically, if oxycodone is used as an opioid analgesic as the additional pharmaceutically active agent, it will be included in an amount being equivalent to 5, 10, 20, 40, 60, 80, 100, 120 or 160 mg oxycodone hydrochloride per unit dose.

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If the opioid antagonist is naloxone hydrochloride and the opioid agonist is oxycodone hydrochloride, these pharmaceutically active agents may be combined in a 1:2 ratio by weight of naloxone hydrochloride to oxycodone hydrochloride. In such cases pharmaceutical dosage forms in accordance with the invention may
25 comprise oxycodone in an amount up to and being equivalent to 5, 10, 20, 40, 80, 100, 120 or 160 mg of oxycodone hydrochloride per unit dose and naloxone in an amount up to and being equivalent to 1, 2, 4, 6, 8, 10, 20, 40, 50, 60 or 80 mg of naloxone hydrochloride per unit dose. These dosage forms may preferably be controlled release dosage forms and be formulated for oral administration.

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- The present invention in one its most preferred embodiments relates to a controlled release oral pharmaceutical dosage form for treating urinary retention and the pain caused thereby wherein the pharmaceutical dosage form comprises oxycodone hydrochloride and naloxone hydrochloride in a 2:1 weight ratio with oxycodone hydrochloride being present in an amount of 10 to 40 mg per unit dose and naloxone hydrochloride being present in an amount of 5 to 20 mg per unit dose. Preferably the controlled release dosage forms release oxycodone hydrochloride and naloxone hydrochloride by the following *in vitro* dissolution rates when measured according to the European Pharmacopeia paddle test at 50 rpm in 900 ml 0.1 N HCl pH 1.2 using
- 10 UV detection at 270 nm:
- 10 - 30 % by weight of oxycodone hydrochloride at 15 min,
 - 30 - 50 % by weight of oxycodone hydrochloride at 1 h,
 - 40 - 65 % by weight of oxycodone hydrochloride at 2 h,
 - 60 - 85 % by weight of oxycodone hydrochloride at 4 h,
 - 15 70 - 95 % by weight of oxycodone hydrochloride at 7 h,
 - ≥ 80% by weight of oxycodone hydrochloride at 10 h,
 - 10 - 30 % by weight of naloxone hydrochloride at 15 min,
 - 30 - 50 % by weight of naloxone hydrochloride at 1 h,
 - 45 - 65 % by weight of naloxone hydrochloride at 2 h,
 - 20 60 - 85 % by weight of naloxone hydrochloride at 4 h,
 - 70 - 95 % by weight of naloxone hydrochloride at 7 h, and
 - ≥ 80% by weight of naloxone hydrochloride at 10 h.

- In another embodiment the pharmaceutical dosage forms may display the following
- 25 in vitro dissolution rates when measured according to the United States Pharmacopoeia Basket Method at pH 1.2 using UV detection at 270 nm:

- 15 to 30 % by weight of oxycodone hydrochloride at 15 min,
- 45 to 70% by weight of oxycodone hydrochloride at 2 h,
- 30 ≥ 80% by weight of oxycodone hydrochloride at 7 h,

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- 5 $\geq 90\%$ by weight of oxycodone hydrochloride at 12 h,
15 to 30 % by weight of naloxone hydrochloride at 15 min,
45 to 70% by weight of naloxone hydrochloride at 2 h,
 $\geq 80\%$ by weight of naloxone hydrochloride at 7 h,
 $\geq 90\%$ by weight of naloxone hydrochloride at 12 h.

10 In a particularly preferred embodiment, the dosage form may comprise 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and 5 mg of naloxone or a pharmaceutically acceptable salt thereof, 20 mg of oxycodone or a pharmaceutically acceptable salt thereof and 10 mg of naloxone or a pharmaceutically acceptable salt thereof or 40 mg of oxycodone or a pharmaceutically acceptable salt thereof and 20 mg of naloxone or a pharmaceutically acceptable salt thereof.

15 Such oral controlled release pharmaceutical dosage forms in accordance with the invention which comprise oxycodone and naloxone or their pharmaceutically acceptable salts in a 2:1 ratio by weight provide a mean $t_{\max}$ for oxycodone at about 1 to about 17 hours, at about 2 to about 15 hours, at about 3 to about 8 hours or at about 4 to about 5 hours after single dose administration to healthy human subjects.

20 Such dosage forms may also provide a mean AUC_t value for oxycodone of about 100 ng•h/mL to about 600 ng•h/mL, about 400 ng•h/mL to about 550 ng•h/mL, or about 450 to about 510 ng•h/mL after single dose administration to healthy human subjects.

25 In yet another embodiment, such dosage forms provide a mean $C_{\max}$ for oxycodone of about 5 ng/mL to about 50 ng/mL, about 30 ng/mL to about 40 ng/mL or about 35 ng/mL after single dose administration to healthy human subjects.

30 The $C_{\max}$ value indicates the maximum blood plasma concentration of the active agents, i.e. oxycodone and/or naloxone (or of their salts).

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The $t_{\max}$ value indicates the time point at which the $C_{\max}$ value is reached. In other words, $t_{\max}$ is the time point of the maximum observed plasma concentration.

- 5 The AUC (Area Under the Curve) value corresponds to the area of the concentration curve. The AUC value is proportional to the amount of active agents, i.e. oxycodone and naloxone absorbed into the blood circulation in total and is hence a measure for the bioavailability.
- 10 The AUCt value is the value for the area under the plasma concentration-time curve from the time of administration to the last measurable concentration. AUCt values are usually calculated using the linear trapezoidal method. Where possible, λ_z , which is the terminal phase rate constant, is estimated using those points determined to be in the terminal log-linear phase. $t_{1/2z}$, which is the apparent
- 15 terminal phase half-life, is commonly determined from the ratio of $\ln 2$ to λ_z . The areas under the plasma concentration-time curve between the last measured point and infinity may be calculated from the ratio of the final observed plasma concentration (C_{last}) to λ_z . This is then added to the AUCt to yield AUCinf, which is the area under the plasma concentration-time curve from the time of
- 20 administration to infinity.

The term "bioavailability" is defined for purposes of the present invention as the extent to which active agents such as oxycodone and naloxone or their pharmaceutically acceptable salts are absorbed from the unit dosage forms.

25

The term $T_{1/2}$ is defined for purposes of the present invention as the amount of time necessary for one half of the absorbable dose of opioid agonist, preferably oxycodone, and opioid antagonist, preferably naloxone, to be transferred to plasma. This value may be calculated as a "true" value (which would take into account the

30 effect of elimination processes), rather than an "apparent" absorption half-life.

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Parameters describing the blood plasma curve can be obtained in clinical trials, first by once-off administration of the active agent such as oxycodone and naloxone to a number of test persons. The blood plasma values of the individual test persons are then averaged, e.g. a mean AUC, $C_{\max}$ and $t_{\max}$ value is obtained. In the context of the present invention, pharmacokinetic parameters such as AUC, $C_{\max}$ and $t_{\max}$ refer to mean values. Further, in the context of the present invention, *in vivo* parameters such as values for AUC, $C_{\max}$, $t_{\max}$, or analgesic efficacy refer to parameters or values obtained after administration at steady state or of a single dose to human patients and/or healthy human subjects.

If pharmacokinetic parameters such as mean $t_{\max}$, $C_{\max}$ and AUC are measured for healthy human subjects, they are typically obtained by measuring the development of blood plasma values over time in a test population of approximately 16 to 24 healthy human subjects. Regulatory bodies such as the European Agency for the Evaluation of Medicinal Products (EMA) or the Food and Drug Administration (FDA) will usually accept data obtained from e.g. 20 or 24 test persons. However, initial trials involving fewer participants may also be acceptable.

The term “healthy” human subject in this context refers to a typical male or female of usually Caucasian origin with average values as regards height, weight and physiological parameters such as blood pressure etc. Healthy human subjects for the purposes of the present invention are selected according to inclusion and exclusion criteria which are based on and in accordance with recommendations of the International Conference for Harmonization of Clinical Trials (ICH). For the purposes of the present invention, healthy subjects may be identified according to the inclusion and exclusion criteria as outlaid in Example 7.

Thus, inclusion criteria comprise e.g. an age between ≥ 18 and ≤ 45 years; a BMI

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within the range 19 - 29 kg/m², and within the weight range 60 - 100 kg for males and 55 - 90 kg for females; that females must be non-nursing, non-pregnant, and provide a negative urine β -hCG pregnancy test within 24 hours before receiving the study medication; generally good health, evidenced by a lack of significantly
5 abnormal findings on medical history, physical examination, clinical laboratory tests, vital signs, and ECG etc.

Exclusion criteria comprise e.g. exposure to any investigational drug or placebo within 3 months of the first dose of study medication, any significant illness within
10 the 30 days before the first dose of study medication, any clinically significant abnormalities identified at prestudy screening for medical history, physical examination or laboratory analyses, use of any prescription medication (except HRT for postmenopausal females and contraceptive medication) in the 21 days, or over the counter medication including acid controllers, vitamins, herbal products and/or
15 mineral supplements in the 7 days, before first dose of study medication, concurrent medical condition known to interfere with gastrointestinal drug absorption (e.g. delayed gastric emptying, mal absorption syndromes), distribution (e.g. obesity), metabolism or excretion (e.g. hepatitis, glomerulonephritis), history of or concurrent medical condition, which in the opinion of the investigator would compromise the
20 ability of the subject to safely complete the study, history of seizure disorders for which subjects required pharmacologic treatment, current history of smoking more than 5 cigarettes a day, subjects with evidence of active or past history of substance or alcohol abuse according to DSM-IV criteria, subjects who reported regular consumption of 2 or more alcoholic drinks per day or have blood alcohol levels of
25 $\geq 0.5\%$ at screening, donation of more than 500 mL of blood or blood products or other major blood loss in the 3 months before first dose of study medication, any positive results in the prestudy screen for ethanol, opiates, barbiturates, amphetamines, cocaine metabolites, methadone, propoxyphene, phencyclidine, benzodiazepines, and cannabinoids in the specimen of urine collected at screening,
30 known sensitivity to oxycodone, naloxone, or related compounds etc.

If pharmacokinetic parameters such as mean t_{max} , c_{max} and AUC are obtained in patients, the patient group will comprise typically between 10 to 200 patients. A reasonable number of patients will e.g. be 10, 20, 30, 40, 50, 75, 100, 125 or 150
5 patients. Patients will be selected according to symptoms of the condition to be treated. For the purposes of the present invention, patients may be selected according to the inclusion and exclusion criteria of Example 7. Thus patients will be e.g. ≥ 18 years, suffer from severe chronic pain of tumor and non-tumor origin, will show insufficient efficacy and/or tolerability with a WHO step II or III analgesic etc. A
10 patient will not be considered for determination of pharmacokinetic parameters if there are indications of current alcohol or drug abuse, of current severe cardiovascular and respiratory diseases, of severe liver and renal insufficiency etc.

It is to be understood that values of pharmacokinetic parameters as indicated above
15 and below have been deduced on the basis of the data which were obtained in Example 7, all of which relate to single dose studies in healthy human subjects. However, it is assumed that comparable results will be obtained upon steady state administration in healthy human subject or single dose and steady state administration in human patients.

20

Pharmacokinetic parameter calculations may be performed with WinNonlin Enterprise Edition, Version 4.1.

The term "steady state" means that a plasma level for a given drug has been achieved
25 and which is maintained with subsequent doses of the drug at a level which is at or above the minimum effective therapeutic level and is below the minimum toxic plasma level for oxycodone. For opioid analgesics such as oxycodone, the minimum effective therapeutic level will be partially determined by the amount of pain relief achieved in a given patient. It will be well understood by those skilled in the medical

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art that pain measurement is highly subjective and great individual variations may occur among patients. It is clear that after the administration of each dose the concentration passes through a maximum and then again drops to a minimum.

- 5 The steady state may be described as follows: At the time $t = 0$, the time the first dose is administered, the concentration C is also 0. The concentration then passes through a first maximum and then drops to a first minimum. Before the concentration drops to 0, another dose is administered, so that the second increase in concentration doesn't start at 0. Building on this first concentration minimum, the
- 10 curve passes through a second maximum after the second dose has been administered, which is above the first maximum, and drops to a second minimum, which is above the first minimum. Thus, the blood plasma curve escalates due to the repeated doses and the associated step-by-step accumulation of active agent, until it levels off to a point where absorption and elimination are in balance. This state at
- 15 which absorption and elimination are in equilibrium and the concentration oscillates constantly between a defined minimum and a defined maximum, is called steady state.

The terms "maintenance therapy" and "chronic therapy" are defined for purposes of

20 the present invention as the drug therapy administered to a patient after a patient is titrated with an opioid analgesic to a steady state as define above.

The present invention has been described above with respect to some of its preferred cmbodiments. This however is not meant to limit the invention in any way.

25

EXAMPLES**Example 1: Production of tablets with different oxycodone/naloxone amounts
in a non-swellable diffusion matrix by spray granulation**

The following amounts of the listed components were used for the production of oxycodone/naloxone tablets according to the invention.

10 Table 1

Preparation (designation)	OXN_1	OXN_2	OXN-3
Oxycodone HCl	20.0 mg	20.0 mg	20.0 mg
Naloxone HCl	-	5.0 mg	10.0 mg
Lactose Flow Lac 100	59.25 mg	54.25 mg	49.25 mg
Povidone 30	5.0 mg	5.0 mg	5.0 mg
Surelease®	10.0 mg solid material	10.0 mg solid material	10.0 mg solid material
Stearyl alcohol	25.0 mg	25.0 mg	25.0 mg
Talcum	2.5 mg	2.5 mg	2.5 mg
Mg-Stearate	1.25 mg	1.25 mg	1.25 mg

The Surelease® E-7-7050 polymer mixture used had the following composition.

Table 2

Surelease®
Ethylcellulose 20 cps
Dibutylsebacate
Ammoniumhydroxide
Oleic acid
Siliciumdioxide
Water

15

For the production of tablets oxycodone HCl, naloxone HCl, Povidone 30 and Lactose Flow Lac 100 were mixed in a tumbling mixer (Bohle) and subsequently

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spray-granulated with Surelease® E-7-7050 in a fluidized bath granulating device (GPCG3). The material was sieved over a Comill 1.4 mm sieve. An additional granulation step was carried out with melted fatty alcohol in a high-shear mixer (Collette). All tablet cores produced by this approach had a weight of 123 mg, based on dry substance.

Example 2: Production of tablets with oxycodone and naloxone in a non-swelling diffusion matrix by extrusion

The following amounts of the listed components were used for the production of the oxycodone/naloxone tablets according to the invention.

Table 3

Preparation (designation)	OXN_4
Oxycodone HCl	20 mg
naloxone HCl	10 mg
Kollidon 30	6 mg
Lactose Flow Lac 100	49.25 mg
Ethylcellulose 45 cpi	10 mg
Stearyl alcohol	24 mg
Talcum	2.5 mg
Mg-Stearate	1,25 mg

The listed amounts of oxycodone HCl, naloxone HCl, ethylcellulose 45 cpi, Povidone 30, stearyl alcohol and Lactose Flow Lac 100 were mixed in a tumbling mixer (Bohle). This mixture was subsequently extruded with a counter-rotating twin screw extruder of the type Micro 18 GGL (Leistritz AG, Nürnberg, Germany). The temperature of heating zone 1 was 25°C, of heating zone 2, 50°C, of heating zones 3 to 5, 60°C, of heating zones 6 to 8, 55°C, of heating zone 9, 60°C and of heating zone 10, 65°C. The screw rotating speed was 150 revolutions per minute (rpm), the resulting melt temperature was 87°C, the feed rate was 1.5 kg/h and the diameter of the nozzle opening was 3 mm. The extruded material was sieved with a Frewitt 0.68

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x 1.00 mm sieve. The grinded extrudate was then mixed with talcum and magnesium stearate that had been added over a 1 mm hand sieve and was subsequently pressed into tablets.

- 5 In comparison to the oxycodone/naloxone tablets which also have the Surelease®-based non-swelling diffusion matrix produced by spray granulation (see Example 1), extruded preparations comprise less components.

Example 3: Release profile of the oxycodone/naloxone tablets from Example 1

10

The release of the active compounds was measured over a time period of 12 hours, applying the Basket Method according to USP at pH 1.2 using HPLC. Tablets OXN_1, OXN_2 and OXN_3 were tested.

- 15 The release rates of different oxycodone amounts, independent of the naloxone amount, remain equal (invariant). Correspondingly, invariant release profiles are observed for naloxone at different oxycodone amounts.

Table 4

Time (min)	OXN_1	OXN_2	OXN_2	OXN_3	OXN_3
	Oxyc.	Oxyc.	Nal.	Oxyc.	Nal.
0	0	0	0	0	0
15	26.1	24.9	23.5	22.8	24.1
120	62.1	63	61	57.5	60.2
420	91.7	94.5	91.9	89.4	93.5
720	98.1	99.6	96.6	95.7	100.6

20

The release values refer to oxycodone or naloxone (line 2) and are given as percentages. Oxyc. and Nal. stand for oxycodone and naloxone and indicate the compound measured.

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Example 4: Release profile of oxycodone/naloxone tablets from Example 2 at different pH-values

- 5 The release of active compounds from the tablets was measured over a time period of 12 hours at pH 1.2 or for 1 hour at 1.2 and subsequently for 11 hours at pH 6.5. Release rates were determined by the basket method according to USP using HPLC.

The following release rates were measured for 12 hours at pH 1.2:

10

Table 5

Time (min)	OXN_4	OXN_4
	Oxyc.	Nal.
0	0	0
15	24.1	24.0
120	62.9	63.5
420	92.9	93.9
720	96.9	98.1

The following release rates were measured for 1 hour at pH 1.2 and 11 hours at pH 6.5:

15

Table 6

Time (min)	OXN_4	OXN_4
	Oxyc.	Nal.
0	0	0
60	48.1	49.2
120	65.0	64.7
240	83.3	81.8
420	94.1	92.3

The release rates refer to oxycodone and naloxone (line 2) and are given as percentages. Oxyc. and Nal. stand for oxycodone and naloxone and indicate the compound measured.

20

Example 5: Production of tablets with different oxycodone/naloxone amounts in a non-swellaable diffusion matrix by extrusion

- 5 The following amounts of the listed components were used for the production of oxycodone/naloxone tablets according to the invention.

Table 7

Preparation (designation)	OXN_5	OXN_6	OXN_7	OXN_8
Oxycodone HCl	20 mg	20 mg	20 mg	20 mg
Naloxone HCl	1 mg	1 mg	1 mg	10 mg
Lactose Flow Lac 100	58.25 mg	58.25 mg	58.25 mg	49.25 mg
Kollidon® 30	6 mg	6 mg	6 mg	6 mg
Ethylcellulose	10 mg	10 mg	10 mg	10 mg
Stearly alcohol	24 mg	24 mg	24 mg	24 mg
Talcum	1.25 mg	1.25 mg	1.25 mg	1.25 mg
Mg-Stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg

- 10 Extrusion was performed as described above (Example 2) with the following parameters:

OXN_5: temperature: 55-63 °C
 rpm (screw): 150 rpm
 15 feeding rate: 1.5 kg/h

OXN_6: temperature: 55-63 °C
 rpm (screw): 155 rpm
 feeding rate: 1.5 kg/h

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OXN_7: temperature: 55-63 °C
 rpm (screw): 155 rpm
 feeding rate: 1.5 kg/h

5

OXN_8: temperature: 55-63 °C
 rpm (screw): 160 rpm
 feeding rate: 1.75 kg/h

10 Tablet production was performed with a common tableting device with the following parameters:

OXN_5: rpm: 40 rpm
 Pressure power: 9 kN

15

OXN_6: rpm: 42 rpm
 Pressure power: 8.9 kN

OXN_7: rpm: 36 rpm
20 Pressure power: 9 kN

OXN_8: rpm: 36 rpm
 Pressure power: 7.5 kN

25 The release of the active compounds was measured over a time period of 12 hours, applying the Basket Method according to USP at pH 1.2 using HPLC. Tablets OXN_5, OXN_6, OXN_7 and OXN_8 were tested.

Table 8

Time (min)	OXN_5		OXN_6		OXN_7		OXN_8	
	Oxyc.	Nal.	Oxyc.	Nal.	Oxyc.	Nal.	Oxyc.	Nal.
0	0	0	0	0	0	0	0	0
15	21.2	25.8	21.7	21.1	19.7	19.3	23.3	24.3
120	56.6	53.8	58.8	57.3	57.7	56.2	64.5	66.9
420	87.2	84.5	94.2	92.6	93.7	91.5	92.7	96.3
720	99.7	96.8	100.1	98	100.6	97.5	93.6	97.4

The release values refer to oxycodone or naloxone (line 2) and are given as
 5 percentages. Oxyc. and Nal. stand for oxycodone and naloxone and indicate the
 active compound which has been measured.

**Example 6: Production of tablets with oxycodone/naloxone in a non-swellable
 diffusion matrix by extrusion**

10

In the following example it is set out that using formulations according to the present
 invention, preparations comprising oxycodone and naloxone with particular release
 behaviours may be obtained.

15 The following amounts of the listed components were used for the production of
 oxycodone/naloxone tablets according to the invention.

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Table 9

Preparation (designation)	OXN_9	OXN_10	OXN_11	OXN_12	OXN_13	OXN_14
Oxycodone HCl	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
naloxone HCl	1 mg	1 mg	10 mg	10 mg	10 mg	10 mg
Lactose Flow Lac 100	56.25mg	56.25 mg	54.25 mg	65.25 mg	60.25 mg	55.25mg
Kollidon® 30	7 mg	6 mg	6 mg	7.25 mg	7.25 mg	7.25 mg
Ethylcellulose	11 mg	12 mg	10 mg	12 mg	12 mg	12 mg
Stearyl alcohol	24 mg	24 mg	24 mg	28.75 mg	28.75 mg	28.75 mg
Talcum	1.25 mg	1.25 mg	1.25 mg	1.25 mg	1.25 mg	1.25 mg
Mg-Stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg

Extrusion was performed as described above with the following parameters:

5	OXN_9:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h
10	OXN_10:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h
15	OXN_11:	temperature:	55-63 °C
		rpm (screw):	160 rpm
		feeding rate:	1.75 kg/h
20	OXN_12:	temperature:	55-63 °C
		rpm (screw):	160 rpm
		feeding rate:	1.75 kg/h

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	OXN_13:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h
5	OXN_14:	temperature:	55-63 °C
		rpm (screw):	150 rpm
		feeding rate:	1.5 kg/h

10 Tablet production was performed with a common tableting device with the following parameters:

	OXN_9:	rpm:	39 rpm
		Pressure power:	11 kN
15	OXN_10:	rpm:	39 rpm
		Pressure power:	10.5 kN
	OXN_11:	rpm:	36 rpm
		Pressure power:	9.5 kN
20	OXN_12:	rpm:	36 rpm
		Pressure power:	7.8 kN
	OXN_13:	rpm:	39 rpm
25		Pressure power:	9 kN
	OXN_14:	rpm:	39 rpm
		Pressure power:	7.5 kN

The release of the active compounds was measured over a time period of 12 hours, applying the Basket Method according to USP at pH 1.2 using HPLC. Tablets OXN_9, OXN_10, OXN_11, OXN_12, OXN_13 and OXN_14 were tested.

5 Table 10

Time (min)	OXN_9		OXN_10		OXN_11		OXN_12		OXN_13		OXN_14	
	Oxyc.	Nal	Oxyc.	Nal	Oxyc.	Nal	Oxyc.	Nal	Oxyc.	Nal	Oxyc.	Nal
0	0	0	0	0	0	0	0	0	0	0	0	0
15	16.6	16.2	17.4	17.2	26.1	26.8	21.8	21.9	18.5	18.2	18.4	18.2
120	47.6	46.9	49.6	49.7	71.1	73.0	61.2	61.8	52.8	52.8	53.3	53.3
420	82.7	84.5	84.6	85.7	94.3	96.6	93.2	94.7	86.3	86.3	87.2	88.2
720	95	97	95.2	95.8	94.9	97.9	96.4	97.9	94.8	94.8	95.7	96.5

The release values refer to oxycodone or naloxone (line 2) and are given as percentages. Oxyc. and Nal. stand for oxycodone and naloxone and indicate the active compound which has been measured.

10

Example 7: Pharmacokinetic and bioavailability characteristics of different strengths of a fixed combination of oxycodone and naloxone and a combination of Oxygesic® plus Naloxone CR

15 1. Objective

The objectives of this study were to (i) evaluate the pharmacokinetic and bioavailability parameters of oxycodone and naloxone and their main metabolites when administered as a controlled-release fixed combination tablet formulation; (ii)

20 assess the interchangeability between the 3 different strengths of the fixed combination, OXN 10/5, OXN 20/10 and OXN 40/20; and (iii) compare the pharmacokinetics and bioavailability of the fixed combination formulation with marketed Oxygesic® given together with Naloxone CR tablets;

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2. Test population

A total of 28 healthy adult, male and female subjects were randomized to receive the study drugs with the aim that 24 subjects would complete the study and provide valid pharmacokinetic data.

Inclusion Criteria

Subjects who were included in the study were those who met all of the following criteria:

- Males or females of any ethnic group;
- Aged between ≥ 18 and ≤ 45 years;
- 15 • BMI within the range 19 - 29 kg/m², and within the weight range 60 - 100 kg for males and 55 - 90 kg for females;
- Females must be non-nursing, non-pregnant, and provide a negative urine β -hCG pregnancy test within 24 hours before receiving the study medication. Female subjects of childbearing potential must be using a reliable form of contraception (e.g. intrauterine device, oral contraceptive, barrier method).
- 20 Female subjects who were postmenopausal must have been postmenopausal for ≥ 1 year and, in the absence of HRT, have elevated serum FSH;
- Generally good health, evidenced by a lack of significantly abnormal findings on medical history, physical examination, clinical laboratory tests, vital signs, and ECG. Vital signs (after 3 minutes resting in a supine position) must be
- 25 within the following ranges: oral body temperature between 35.0 - 37.5 °C; systolic blood pressure, 90 - 140 mmHg; diastolic blood pressure, 50 - 90 mmHg; and pulse rate, 40 - 100 bpm. Blood pressure and pulse were taken again after 3 minutes in a standing position. After 3 minutes standing from a

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supine position, there should be no more than a 20 mmHg drop in systolic blood pressure, 10 mmHg drop in diastolic blood pressure, and no greater than 20 bpm increase in pulse rate; Written informed consent obtained; Willing to eat all the food supplied during the study.

5

Exclusion Criteria

Subjects who were excluded from the study were those who met any of the following criteria:

10

- Exposure to any investigational drug or placebo within 3 months of their first dose of study medication;
- Any significant illness within the 30 days before their first dose of study medication;

15

- Any clinically significant abnormalities identified at prestudy screening for medical history, physical examination or laboratory analyses;
- Use of any prescription medication (except HRT for postmenopausal females and contraceptive medication) in the 21 days, or over the counter medication including acid controllers, vitamins, herbal products and/or mineral supplements in the 7 days, before their first dose of study medication;

20

- Concurrent medical condition known to interfere with gastrointestinal drug absorption (e.g. delayed gastric emptying, mal absorption syndromes), distribution (e.g. obesity), metabolism or excretion (e.g. hepatitis, glomerulonephritis);

25

- History of, or concurrent medical condition, which in the opinion of the Investigator would compromise the ability of the subject to safely complete the study;
- History of seizure disorders for which subjects required pharmacologic treatment;

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- Current history of smoking more than 5 cigarettes a day;
- Subjects with evidence of active or past history of substance or alcohol abuse, according to DSM-IV criteria³, or subjects who, In the investigator's opinion, have demonstrated addictive or substance abuse behaviors;
- 5 • Subjects who reported regular consumption of 2 or more alcoholic drinks per day or have blood alcohol levels of $\geq 0.5\%$ at screening;
- Donation of more than 500 mL of blood or blood products or other major blood loss in the 3 months before their first dose of study medication;
- At risk of transmitting infection via blood samples such as producing a
10 positive HIV test at screening or having participated in a high risk activity for contracting HIV; producing a positive Hepatitis B surface antigen test at screening; producing a positive Hepatitis C antibody test at screening;
- Any positive results in the prestudy screen for ethanol, opiates, barbiturates, amphetamines, cocaine metabolites, methadone, propoxyphene,
15 phencyclidine, benzodiazepines, and cannabinoids in the specimen of urine collected at screening;
- Known sensitivity to oxycodone, naloxone, or related compounds;
- Contraindications and precautions as detailed in the datasheet for Oxygesic®;
- 20 • Refusal to allow their primary care physician (if applicable) to be informed;
- The Investigator believed the subject to be unsuitable for a reason not specifically stated in the exclusion criteria.

The demographic data are shown in Table 11.

Table 11: Subject Demographics and Other Baseline Characteristics: Safety Population

	Male (N = 22)	Female (N = 6)	Overall (N = 28)
5 Characteristics			
Race, n (%)			
Caucasian	22 (100%)	6 (100%)	28 (100%)
Age (y)			
10 Mean $\pm$ SD	32.6 $\pm$ 5.28	31.0 $\pm$ 6.32	32.3 $\pm$ 5.44
Range (min, max)	25,41	24,42	24,42
Height (cm)			
Mean $\pm$ SD	179.1 $\pm$ 4.84	168.0 $\pm$ 8.72	176.7 $\pm$ 7.33
15 Range (min, max)	165,187	159,181	159,187
Weight (kg)			
Mean $\pm$ SD	77.8 $\pm$ 9.04	67.0 $\pm$ 3.03	75.5 $\pm$ 9.25
Range (min, max)	62,97	63,71	62,97
Body Mass Index (kg/m ²)			
20 Mean $\pm$ SD	24.2 $\pm$ 2.56	23.9 $\pm$ 2.50	24.2 $\pm$ 2.50
Range (min, max)	20,29	20,27	20,29

3. Study Design, Test Treatment Dose and Mode of Administration

25 *Preparation of tested products*

A melt extrusion oxycodone/naloxone controlled-release tablet formulation with an oxycodone:naloxone ratio of 2:1 was produced. There are three dose strengths available, namely OXN 10/5, OXN 20/10, and OXN 40/20, where the first number is the mg amount of oxycodone hydrochloride and the second number is the mg amount of naloxone hydrochloride (see Table 12). OXN 20/10 and OXN 40/20 are from the same granulate, while OXN 10/5 has a slightly different formula in regard to the ratio of active ingredients to excipients.

Oxycodone/naloxone tablets (OXN Tablets) according to this example contain a fixed combination of oxycodone and naloxone in the ratio of 2:1. Tablets formulations are summarized below (see Table 12).

- 5 The 20/10 mg and 40/20 mg tablets are manufactured from the same granulation with these two tablet strengths being compositionally proportional. Oxycodone/Naloxone prolonged release tablets (OXN) tablets according to this example are controlled release tablets using a matrix of stearyl alcohol and ethylcellulose as the retardant. The tablets contain the combination of oxycodone hydrochloride and naloxone
- 10 hydrochloride in the strengths 10/5 mg, 20/10 mg and 40/20 mg (both as the hydrochloride). The complete statement of the components and quantitative composition of Oxycodone/Naloxone prolonged release tablets is given below in Table 12.
- 15 Table 12: Oxycodone/Naloxone prolonged release tablets.

Component	Quantity (mg/tablet)			Function	Reference to Standard
	OXN 10/5	OXN 20/10	OXN 40/20		
Oxycodone hydrochloride ¹⁾	10.50	21.00	42.00	Active	USP*/ H.S.E.
<i>corresponding to</i>					
<i>Oxycodone hydrochloride anhydrous</i>	<i>10.00</i>	<i>20.00</i>	<i>40.00</i>		
<i>Oxycodone base</i>	<i>9.00</i>	<i>18.00</i>	<i>36.00</i>		
Naloxone hydrochloride Dihydrate	5.45	10.90	21.80	Active	Ph. Eur.*
<i>corresponding to</i>					
<i>Naloxone hydrochloride anhydrous</i>	<i>5.00</i>	<i>10.00</i>	<i>20.00</i>		
<i>Naloxone base</i>	<i>4.50</i>	<i>9.00</i>	<i>18.00</i>		
Povidone K30	5.00	7.25	14.50	Binder	Ph. Eur.*

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Ethylcellulose N 45	10.00	12.00	24.00	Retardant	Ph. Eur.*
Stearyl alcohol	25.00	29.50	59.00	Retardant	Ph. Eur.*
Lactose monohydrate	64.25	54.50	109.00	Diluent	Ph. Eur.*
Purified talc	2.50	2.50	5.00	Glidant	Ph. Eur.*
Magnesium stearate	1.25	1.25	2.50	Lubricant	Ph. Eur.*
Total core	123.95	138.90	277.80		
Film Coat °					
Opadry II HP white – 85F18422	3.72			Coating	supplier specification
Opadry II HP pink – 85F24151		4.17		Coating	supplier specification
Opadry II HP yellow 85F32109			8.33	Coating	supplier specification
Purified talc	0.12	0.14	0.28	Gloss	Ph. Eur.*
Total filmtablet	127,79	143.21	286.41		* current Edition

¹⁾ calculated based on expected moisture content

° qualitative composition : see Table 12

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Table 13: Qualitative composition of the film coat

Opadry II HP	white 85F1842 2	pink 85F2415 1	yellow 85F3210 9	Reference to Standard
Polyvinylalcohol part. hydrolized	+	+	+	Ph. Eur. *
Titanium dioxide (E 171)	+	+	+	Ph. Eur. *
Macrogol 3350	+	+	+	Ph. Eur. *
Talcum	+	+	+	Ph. Eur. *
Iron oxide red (E 172)		+		NF* /EC Directive
Iron oxide yellow (E 172)			+	NF* /EC Directive
				* current Edition

5 Study Design

The study was an open-label, single dose, 4-treatment, 4-period, randomized across over study and healthy subjects. The treatments were given orally in the fasted state as follows:

10

- Treatment A: 4 x tablets of Oxn 10/5
- Treatment B: 2 x tablets of Oxn 20/10
- Treatment C: 1 x tablets of Oxn 40/20

15 The reference treatment was an Oxygesic® 20 mg tablet. Naloxone was used in the form of Naloxone 10 mg CR spray granulation tablet. Reference treatment was thus

- Treatment D: 2 tablets of Oxygesic® 20 mg and two tablets of Naloxone CR 10 mg.

20

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Duration of treatment included 21 days screening period and four study periods each with a single dose of study drug followed by a seven day wash-out period. There were post study medical 7 to 10 days after dosing of study period 4 and there were 7 to 10 days after discontinuation from the study. The total duration was 49 to 52 days.

5

The treatment schedule was a single dose of study drug in each of the four study periods. Each dose of study drug was separated by a 7 day wash-out period.

10 The enrolled population was defined as the subject population that provided the written informed consent to anticipate in the study. The full analysis population for pharmacokinetics was defined as those subjects, who had at least one valid pharmacokinetic parameter calculated on at least one treatment.

4. Pharmacokinetic Assessments

15

Drug Concentration Measurements

Blood samples for determining oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6 β -naloxol and naloxone-3-glucuronide concentrations were obtained for each subject during each of the 4 study periods immediately before dosing; and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48, 72 and 96 hours (22 blood samples per study period) after dosing. Blood was also drawn where possible at the first report of a serious or severe unexpected adverse event and at its resolution.

25

At each time of plasma determination, 6 mL venous blood was drawn from a forearm vein into a tube containing K2 EDTA anticoagulant. All samples were processed according to common sample handling procedures.

Pharmacokinetic Parameters

The following pharmacokinetic parameters were calculated from the plasma concentrations of oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6 β -naloxol and naloxone-3-glucuronide:

- Area under the plasma concentration time curve calculated to the last measurable concentration (AUC_t);
- Area under the plasma concentration-time curve, from the time of administration to infinity (AUC_{INF});
- Maximum observed plasma concentration (C_{max});
- Time point of maximum observed plasma concentration (t_{max});
- Terminal phase rate constant (Lambda_Z);
- Apparent terminal phase half life (t_{1/2Z}).

For oxycodone, noroxycodone, oxymorphone, noroxymorphone, and naloxone-3-glucuronide, AUC values were given in ng·h/mL, and C_{max} values in ng/mL. For naloxone and 6 β -naloxol, AUC values, due to the low concentrations, were given in pg·h/mL and C_{max} values in pg/mL.

AUC_t, AUC_{INF} and C_{max} were regarded as the primary parameters.

AUC_t were calculated using the linear trapezoidal method. Where possible, Lambda_Z was estimated using those points determined to be in the terminal log-linear phase. t_{1/2Z} was determined from the ratio of ln 2 to Lambda_Z. The areas under the plasma concentration-time curve between the last measured point and infinity were calculated from the ratio of the final observed plasma concentration (C_{last}) to Lambda_Z. This was then added to the AUC_t to yield AUC_{INF}.

All pharmacokinetic calculations were performed with WinNonlin Enterprise Edition, Version 4.1.

Statistical Methods

5

$C_{\max}$ and AUCINF of oxycodone were important in order to assess the equivalence of the 4 treatments. AUCt was calculated using the linear trapezoidal method. Where possible, LambdaZ was estimated using those points determined to be in the terminal log-linear phase. $t_{1/2}$ were determined from the ratio of $\ln 2$ to LambdaZ. The areas
10 under the plasma concentration-time curve between the last measured point and infinity were calculated from the ratio of the final observed plasma concentration (C_{last}) to LambdaZ. This was added to the AUCt to yield the area under the plasma concentration-time curve between the time of administration and infinity (AUCINF).

15 The dose adjusted relative systemic availabilities (Frelt, and FrelINF) and the $C_{\max}$ ratio were obtained from the ratio of AUCt, AUCINF and $C_{\max}$ values, respectively, for differences defined in the following comparisons of interest:

fixed combination A vs. open combination D

20 fixed combination B vs. open combination D

fixed combination C vs. open combination D

fixed combination A vs. fixed combination B

fixed combination A vs. fixed combination C

fixed combination B vs. fixed combination C

25

The full analysis population for pharmacokinetics were used for these analyses.

The metabolite: parent drug AUCt and AUCINF ratios were estimated for each treatment, where possible.

30

5. Clinical Pharmacology Results

Mean observed plasma concentration – time curves for oxycodone, naloxone-3-glucuronide, naloxone, noroxycodone, oxymorphone, noroxymorphone and 6-β-naloxol are presented in Figures 1 to 7.

Pharmacokinetic parameters for oxycodone, naloxone-3-glucuronide and naloxone are presented in Tables 14 to 19 respectively.

10 Table 14: Summary of Pharmacokinetic Parameters for Oxycodone by Treatment: Full Analysis Population for Pharmacokinetics

Pharmacokinetic parameter	4 x OXN 10/5	2 x OXN 20/10	1 x OXN 40/20	2 x Oxygesic 20 + 2 x Naloxone 10
AUCt (ng.h/mL)				
N	24	23	23	23
Arithmetic Mean	473.49	491.22	488.89	502.28
(SD)	(72.160)	(82.181)	(91.040)	(84.128)
Geometric Mean	468.29	484.58	481.08	495.72
AUCINF (ng.h/mL)				
N	24	22	22	22
Arithmetic Mean	475.06	497.17	491.22	509.11
(SD)	(72.182)	(81.687)	(93.458)	(82.963)
Geometric Mean	469.87	490.65	483.04	502.80
Cmax (ng/mL)				
N	24	23	23	23
Arithmetic Mean	34.91	35.73	34.46	40.45
(SD)	(4.361)	(4.931)	(5.025)	(4.706)
Geometric Mean	34.66	35.41	34.12	40.19
tmax (h)				
N	24	23	23	23
Median	3.5	4.0	3.0	2.5
(Min,Max)	(1.0, 6.0)	(2.0, 8.0)	(1.0, 6.0)	(0.5, 8.0)
t1/2Z				
N	24	22	22	22
Arithmetic Mean	4.69	4.87	4.83	5.01
(SD)	(0.775)	(0.995)	(0.975)	(0.802)

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Table 15: Oxycodone Summary of Ratios for AUCt, AUCINF, C_{max} and Differences for t_{max} and Half-Life - Full Analysis Population for Pharmacokinetics

Pharmacokinetic metric	4 x OXN 10/5 / 2 x Oxygesic 20 + 2 x Naloxone 10	2 x OXN 20/10 / 2 x Oxygesic 20 + 2 x Naloxone 10	1 x OXN 40/20 / 2 x Oxygesic 20 + 2 x Naloxone 10	4 x OXN 10/5 / 2 x OXN 20/10	4 x OXN 10/5 / 1 x OXN 40/20	2 x OXN 20/10 / 1 x OXN 40/20
AUCt (ng.h/mL)						
Ratio (%)	94.9	98.2	98.0	96.7	96.8	100.2
90%CI	91.5, 98.5	94.5, 102.0	94.4, 101.7	93.1, 100.4	93.3, 100.5	96.5, 104.0
AUCINF (ng.h/mL)						
Ratio (%)	94.5	98.2	97.8	96.2	96.5	100.4
90%CI	90.9, 98.1	94.5, 102.1	94.1, 101.7	92.6, 99.9	92.9, 100.3	96.5, 104.3
Cmax (ng/mL)						
Ratio (%)	86.2	88.4	85.8	97.5	100.5	103.1
90%CI	82.2, 90.4	84.2, 92.8	81.8, 90.0	92.9, 102.3	95.8, 105.4	98.2, 108.1
tmax (h)						
Difference	0.49	1.11	0.14	-0.63	0.35	0.97
90%CI	-0.19, 1.16	0.42, 1.80	-0.54, 0.82	-1.31, 0.05	-0.33, 1.02	0.29, 1.66
t1/2Z (h)						
Difference	-0.27	-0.11	-0.11	-0.16	-0.16	0.00
90%CI	-0.60, 0.05	-0.44, 0.23	-0.44, 0.22	-0.49, 0.16	-0.49, 0.16	-0.33, 0.33

5 Table 16: Summary of Pharmacokinetic Parameters for Naloxone-3-glucuronide by Treatment: Full Analysis Population for Pharmacokinetics

Pharmacokinetic parameter	4 x OXN 10/5	2 x OXN 20/10	1 x OXN 40/20	2 x Oxygesic 20 + 2 x Naloxone 10
AUCt (pg.h/mL)				
N	24	23	23	23
Arithmetic Mean	539.93	522.45	520.10	523.37
(SD)	(142.241)	(128.569)	(133.175)	(119.752)
Geometric Mean	520.14	506.63	502.26	509.38
AUCINF (pg.h/mL)				
N	22	21	22	22
Arithmetic Mean	562.53	520.97	527.94	537.25
(SD)	(130.732)	(133.172)	(135.424)	110.829
Geometric Mean	546.73	504.34	509.62	525.91
Cmax (pg/mL)				
N	24	23	23	23
Arithmetic Mean	62.01	63.62	61.95	63.55

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(SD)	(15.961)	(19.511)	(18.369)	(16.748)
Geometric Mean	59.93	60.70	59.34	61.55
t_{max} (h)				
N	24	23	23	23
Median	1.0	0.5	1.0	1.0
(Min,Max)	(0.5, 3.0)	(0.5, 6.0)	(0.5, 3.0)	(0.5, 6.0)
t_{1/2Z}				
N	22	21	22	22
Arithmetic Mean	8.48	7.93	7.81	7.66
(SD)	(3.066)	(2.402)	(2.742)	(1.717)

Table 17: Naloxone-3-Glucuronide Summary of Ratios for AUC_t, AUC_{INF}, C_{max} and Differences for T_{max} and Half-Life - Full Analysis Population for Pharmacokinetics

Pharmacokinetic metric	4 x OXN 10/5 / 2 x Oxygesic 20 + 2 x Naloxone 10	2 x OXN 20/10 / 2 x Oxygesic 20 + 2 x Naloxone 10	1 x OXN 40/20 / 2 x Oxygesic 20 + 2 x Naloxone 10	4 x OXN 10/5 / 2 x OXN 20/10	4 x OXN 10/5 / 1 x OXN 40/20	2 x OXN 20/10 / 1 x OXN 40/20
AUC_t (pg.h/mL)						
Ratio (%)	101.0	98.8	98.6	102.2	102.4	100.2
90%CI	95.6, 106.8	93.4, 104.5	93.3, 104.3	96.7, 108.1	97.0, 108.2	94.8, 105.9
AUC_{INF}(pg.h/mL)						
Ratio (%)	102.1	98.2	99.0	104.0	103.1	99.2
90%CI	96.3, 108.3	92.3, 104.2	93.4, 105.0	97.9, 110.5	97.3, 109.3	93.5, 105.2
C_{max} (pg/mL)						
Ratio (%)	95.4	96.5	95.1	98.8	100.3	101.5
90%CI	88.5, 102.8	89.4, 104.1	88.2, 102.5	91.7, 106.6	93.1, 108.0	94.1, 109.3
t_{max} (h)						
Difference	-0.34	-0.16	-0.42	-0.18	0.08	0.26
90%CI	-0.84, 0.17	-0.67, 0.35	-0.93, 0.10	-0.69, 0.33	-0.43, 0.59	-0.26, 0.77
t_{1/2Z} (h)						
Difference	0.87	0.37	0.32	0.50	0.56	0.06
90%CI	-0.02, 1.77	-0.53, 1.28	-0.58, 1.21	-0.41, 1.41	-0.33, 1.45	-0.85, 0.96

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Table 18: Summary of Pharmacokinetic Parameters for Naloxone by Treatment:
Full Analysis Population for Pharmacokinetics.

Pharmacokinetic parameter	4 x OXN 10/5	2 x OXN 20/10	1 x OXN 40/20	2 x Oxygesic 20 + 2 x Naloxone 10
AUCt (pg.h/mL)				
N	24	23	23	23
Arithmetic Mean	0.84	0.89	0.87	0.97
(SD)	(0.656)	(0.749)	(0.718)	(0.976)
Geometric Mean	0.67	0.70	0.68	0.72
AUCINF(pg.h/mL)				
N	2	6	0	1
Arithmetic Mean	-	1.64	-	-
(SD)	-	(1.043)	-	-
Geometric Mean	-	1.45	-	-
Cmax (pg/mL)				
N	24	23	23	23
Arithmetic Mean	0.07	0.08	0.08	0.08
(SD)	(0.065)	(0.106)	(0.071)	(0.101)
Geometric Mean	0.06	0.06	0.06	0.06
tmax (h)				
N	24	23	23	23
Median	4.0	5.0	2.0	1.0
(Min,Max)	(0.5, 12.0)	(0.5, 24.0)	(0.5, 12.0)	(0.5, 24.0)
t1/2Z				
N	4	9	4	4
Arithmetic Mean	9.89	12.85	13.83	11.02
(SD)	(3.137)	(11.924)	(1.879)	(1.075)

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Table 19: Naloxone Summary of Ratios for AUCt, AUCINF, C_{max} and Differences for T_{max} and Half-Life - Full Analysis Population for Pharmacokinetics.

Pharmaco kinetic metric	4 x OXN 10/5 / 2 x Oxygesic 20 + 2 x Naloxone 10	2 x OXN 20/10 / 2 x Oxygesic 20 + 2 x Naloxone 10	1 x OXN 40/20 / 2 x Oxygesic 20 + 2 x Naloxone 10	4 x OXN 10/5 / 2 x OXN 20/10	4 x OXN 10/5 / 1 x OXN 40/20	2 x OXN 20/10 / 1 x OXN 40/20
AUCt (pg.h/mL)						
Ratio (%)	94.2	99.4	94.1	94.7	100.1	105.7
90%CI	82.0, 108.2	86.3, 114.5	81.8, 108.1	82.4, 108.9	87.3, 114.9	92.0, 121.5
AUCINF (pg.h/mL)						
Ratio (%)	-	-	-	-	-	-
90%CI	--	--	--	--	--	--
Cmax (pg/mL)						
Ratio (%)	102.4	108.8	104.1	94.1	98.4	104.5
90%CI	88.0, 119.2	93.1, 127.0	89.3, 121.2	80.8, 109.7	84.6, 114.4	89.7, 121.8
tmax (h)						
Difference	-0.71	0.12	-2.03	-0.83	1.32	2.15
90%CI	-2.96, 1.54	-2.17, 2.42	-4.31, 0.24	-3.10, 1.44	-0.93, 3.57	-0.12, 4.43
t1/2Z (h)						
Difference	-3.55	0.79	2.30	-4.35	-5.85	-1.51
90%CI	-12.92, 5.82	-23.09, 24.67	-22.06, 26.67	-28.49, 19.80	-30.48, 18.77	-8.80, 5.78

5

6. Data Analysis

a) Oxycodone Results

- AUCt

- 10 The AUCt values obtained for oxycodone were very consistent between the treatments. Each of the treatments had a mean AUCt value of between 473 ng.h/mL (4 x OXN 10/5) and 502 ng.h/mL (2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg).

- 15 In terms of AUCt, each of the fixed combination tablets provided an equivalent availability of oxycodone to the reference treatment, and to each other. All of the

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relative bioavailability calculations had 90% confidence intervals that were within the 80 - 125% limits of acceptability for bioequivalence.

- $t_{1/2Z}$

5 The $t_{1/2Z}$ values obtained for oxycodone were consistent between the treatments. Each of the treatments had a mean $t_{1/2Z}$ value of between 4.69 h (4 x OXN 10/5), and 5.01 h (2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg). There were no statistical differences between the $t_{1/2Z}$ values for the treatments for any of the comparisons that were made.

10

- AUCINF

The AUCINF values obtained for oxycodone were very consistent between the treatments. Each of the treatments had a mean AUCINF value of between 475 ng.h/mL (4 x OXN 10/5) and 509 ng.h/mL (2 x Oxygesic 20 mg & 2 x naloxone
15 CR 10 mg).

In terms of AUCINF, each of the fixed combination tablets provided an equivalent availability of oxycodone to the reference treatment, and to each other. All of the relative bioavailability calculations had 90% confidence intervals that were within
20 the 80 - 125% limits of acceptability for bioequivalence.

- C_{max}

The C_{max} values obtained for oxycodone were consistent between the fixed combination treatments, and ranged from 34.46 ng/mL (1 x OXN 40/20) to
25 35.73 ng/mL (2 x OXN 20/10). The mean C_{max} value for 2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg was slightly higher at 40.45 ng/mL.

The C_{max} ratios comparing the fixed combination tablets with each other ranged from 97.5% to 103.1%, and each had 90% confidence intervals within 80 - 125%. The
30 higher mean C_{max} value for 2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg meant

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that the $C_{\max}$ ratios comparing the fixed combination tablet with the reference product were lower, ranging from 85.8% to 88.4%. However, these $C_{\max}$ ratios were still associated with 90% confidence intervals that were within 80 - 125%.

5 - $t_{\max}$

The median $t_{\max}$ values for the fixed combination tablets ranged from 3 h (1 x OXN 40/20) to 4 h (2 x OXN 20/10). The difference between these two treatments, although apparently small, was statistically significant. The median $t_{\max}$ for 2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg was 2.5 h, and there was a statistically
10 significant difference between this reference treatment and 2 x OXN 20/10.

b) Naloxone-3-Glucuronide Results

- AUCt

15 The AUCt values obtained for naloxone-3-glucuronide were very consistent between the treatments. Each treatment had a mean AUCt value of between 520 ng.h/mL (1 x OXN 40/20) and 540 ng.h/mL (4 x OXN 10/5).

In terms of AUCt, each of the fixed combination tablets provided an equivalent
20 availability of naloxone-3-glucuronide to the reference treatment, and to each other. All of the relative bioavailability calculations had 90% confidence intervals that were within the 80 - 125% limits of acceptability for bioequivalence.

- $t_{1/2Z}$

25 The $t_{1/2Z}$ values obtained for naloxone-3-glucuronide were consistent between the treatments. Each of the treatments had a mean $t_{1/2Z}$ value of between 7.66 h (2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg) and 8.48 h (4 x OXN 10/5). There were no statistical differences between the $t_{1/2Z}$ values for the treatments for any of the comparisons that were made.

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- AUCINF

The AUCINF values obtained for naloxone-3-glucuronide were very consistent between the treatments. Each of the treatments had a mean AUCINF value of between 521 ng.h/mL (2 x OXN 20/10) and 563 ng.h/mL (4 x OXN 10/5).

5

In terms of AUCINF, each of the fixed combination tablets provided an equivalent availability of naloxone-3-glucuronide to the reference treatment, and to each other. All of the bioavailability calculations had 90% confidence intervals that were within the 80 - 125% limits of acceptability for bioequivalence.

10

- C_{max}

The C_{max} values obtained for naloxone-3-glucuronide were consistent between the treatments. Each of the treatments had a mean C_{max} value that range from 61.95 ng.mL (1 x OXN 40/20) to 63.62 ng.mL (2 x OXN 20/10).

15

Each of the fixed combination tablets provided an equivalent naloxone-3-glucuronide C_{max} to the reference treatment, and to each other. All of the C_{max} ratio calculations had 90% confidence intervals that were within the 80 - 125% limits of acceptability for bioequivalence.

20

- t_{max}

The median t_{max} values for all the treatments ranged from 0.5 h (2 x OXN 20/10) to 1 h (4 x OXN 10/5, 1 x OXN 40/20 and 2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg). There were no significant differences between the median t_{max} values for any of the treatments.

25

- Naloxone-3-glucuronide : naloxone AUCt ratios

The mean naloxone-3-glucuronide : naloxone AUCt ratios ranged from 852.25 (2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg) to 933.46 (4 x OXN 10/5).

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- Naloxone-3-glucuronide : naloxone AUCINF ratios

The lack of AUCINF estimates for naloxone meant that mean naloxone-3-glucuronide : naloxone AUCINF ratios were only able to be calculated for 2 x OXN 20/10 tablets. These provided a mean naloxone-3-glucuronide : naloxone AUCINF ratio of 414.56, based on 5 subjects' data.

c) Naloxone Results

Naloxone concentrations were low, as was anticipated; therefore these results did not support a full pharmacokinetic assessment.

- AUCt

The AUCt values obtained for naloxone were consistent between the treatments. Each of the treatments had a mean AUCt value of between 0.84 ng.h/mL (2 x OXN 20/10) and 0.97 ng.h/mL (2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg).

In terms of AUCt, each of the fixed combination tablets provided an equivalent availability of naloxone to the reference treatment, and to each other. All of the bioavailability calculations had 90% confidence intervals that were within the 80 - 125% limits of acceptability for bioequivalence.

- t_{1/2Z}

It was not possible to calculate t_{1/2Z} values for naloxone for all of the subjects with confidence, because the plasma concentrations in the terminal part of the profile did not always approximate to a straight line when plotted on a semi-logarithmic scale.

The mean values were based on numbers of subjects ranging from 4 to 9.

The mean t_{1/2Z} values obtained for naloxone ranged from between 9.89 h (4 x OXN 10/5) to 13.83 h (1 x OXN 40/20). There were a wide range of t_{1/2Z} values contributing to the means, however, there were no statistical differences between the t_{1/2Z} values for the treatments for any of the comparisons that were made.

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- AUCINF

AUCINF values were calculated for those subjects with an estimable $t_{1/2Z}$ value. Some of the AUCINF values were not reportable because the extrapolated portion of the AUC accounted for more than 20% of the AUCINF value. A mean AUCINF value, of 1.64 ng.h/mL, was reportable for 2 x OXN 20/10 tablets only. None of the other treatments had sufficient data to report a mean AUCINF value. There were insufficient data to make comparisons between the treatments.

10 - C_{max}

Each of the treatments had a mean C_{max} value of between 0.07 ng/mL (4 x OXN 10/5) and 0.08 ng/mL (2 x OXN 20/10, 1 x OXN 40/20 and 2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg).

15 Each of the fixed combination tablets provided an equivalent naloxone C_{max} to each other. All of the C_{max} ratios comparing the fixed combination tablets had 90% confidence intervals that were within the 80 - 125% limits of acceptability for bioequivalence.

20 When the fixed combination tablets were compared with the reference product, the 2 x OXN 20/10 tablets versus 2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg had a 90% confidence interval that was above the 80 - 125% limit of acceptability for bioequivalence. The remaining fixed combination tablets provided an equivalent naloxone C_{max} to the reference product.

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- t_{max}

The median t_{max} values for the treatments ranged from 1 h (2 x Oxygesic 20 mg & 2 x naloxone CR 10 mg) to 5 h (2 x OXN 20/10). There were a wide range of t_{max} values for each of the treatments. There were no significant differences between the median t_{max} values for any of the treatments.

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7. Clinical Pharmacology Discussion and Conclusions

Low oral bioavailability prevents the complete pharmacokinetic assessment of
5 naloxone. This was confirmed as the low plasma concentrations meant that it was
not possible to estimate AUC_{INF} values for naloxone for most of the subjects.
Naloxone-3-glucuronide was present in the plasma in much higher concentrations,
and AUC_{INF} estimates were obtained for naloxone-3-glucuronide for the majority of
10 subjects. The conclusions for the naloxone component of the fixed combination
tablets were based on naloxone-3-glucuronide parameters.

a) Oxycodone

The mean plasma oxycodone concentration-time curves for 2 x Oxygesic 20 mg & 2
15 x naloxone CR 10 mg and the fixed combination tablets were almost superimposable.

A bioequivalence assessment was made for oxycodone. Each of the bioequivalence
comparisons had 90% confidence intervals that were within the limits of
acceptability for bioequivalence for Frelt, Frel_{INF} and C_{max} ratio. The oxycodone
20 results indicate that each of the fixed combination tablet strengths were
bioequivalent, both to each other and also to Oxygesic given together with naloxone
CR tablet. There were no statistical differences between any of the t_{max} or t_{1/2Z}
values for any of the treatments, further confirming the similarity of the products.

25 The plasma oxycodone concentrations achieved after administration of the reference
product were similar to dose-adjusted oxycodone concentrations seen after
administration of OxyContin in a previous study. The mean C_{max} values for the fixed
combination tablets were slightly lower, but when these were compared with the
reference product, the C_{max} ratios had confidence intervals that were within the limits
30 of acceptability for bioequivalence.

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b) Naloxone

The mean plasma naloxone concentrations were low, less than 0.1 ng/mL, and
5 appeared to be biphasic, with a second peak occurring at between 8 to 16 hours.

Even though all of the subjects did have quantifiable plasma naloxone
concentrations, individual subjects' plasma naloxone concentrations were low and
highly variable. The maximum observed plasma naloxone concentrations were 0.07
10 to 0.08 ng/mL.

The pharmacokinetic profiles of naloxone from earlier studies were examined. On
average, the mean C_{max} values from these studies, dose-adjusted to a single dose of 1
mg, ranged between 4 and 15 pg/mL confirming that the low plasma naloxone
15 concentrations observed here were consistent with those levels measured in earlier
studies.

A bioequivalence assessment was made for naloxone. The variability of the plasma
naloxone concentrations did not allow for an estimate of AUC_{INF}, or therefore
20 Frel_{INF} values. The bioavailability estimate was based on Frelt values. Each of the
bioavailability comparisons had 90% confidence intervals that were within the limits
of acceptability for bioequivalence. The mean C_{max} values for naloxone were
comparable, and five out of the six bioavailability comparisons had 90% confidence
intervals that met the criteria for bioequivalence.

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The t_{max} and $t_{1/2Z}$ values for the treatments were variable, however there were no
significant differences between any of the treatments for these two parameters.

As expected, the levels of naloxone-3-glucuronide seen in the plasma after
30 administration of the fixed combination tablets and Oxygesic plus naloxone, were

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much higher than the levels of naloxone that were achieved, resulting in naloxone-3-glucuronide : naloxone AUCt ratios of around 900. 6 β -naloxol was also measured in higher quantities than naloxone, resulting in 6 β -naloxol : naloxone AUCt ratios of around 22. These metabolite : parent AUCt ratios were consistent across the fixed
5 combination tablets and the reference treatment.

c) Naloxone-3-glucuronide

The mean plasma naloxone-3-glucuronide levels were higher than naloxone, and it
10 was possible to make a bioavailability assessment based on FrelINF values.

A bioequivalence assessment was made for naloxone-3-glucuronide. Each of the bioequivalence comparisons had 90% confidence intervals that were within the limits of acceptability for bioequivalence for Frelt, FrelINF and C_{max} ratio. The naloxone-
15 3-glucuronide results indicate that each of the fixed combination tablet strengths were bioequivalent to each other, and to Oxygesic plus naloxone. There were no statistical differences between any of the t_{max} or t_{1/2Z} values for any of the treatments, further confirming the similarity of the products.

20 Such formulations were then tested in clinical studies and pharmacovigilance studies versus a controlled release oxycodone hydrochloride formulation, Oxygesic® for analgesic efficacy. These clinical trials and pharmacovigilance studies involving more than 1000 patients have shown that for treatment with the oxycodone/naloxone combination, typical opioid-induced side effects such as urinary disorders including
25 urinary retention are reduced to rare frequency. This illustrates that naloxone is capable of treating urinary retention.

Claims:

1. Use of at least one opioid antagonist or a pharmaceutically acceptable salt thereof in the manufacture of an oral dosage form for treating urinary retention.
2. Use according to claim 1, wherein said opioid antagonist is selected from the group comprising naloxone, naltrexone, nalbuphine and pharmaceutically acceptable salts thereof.
3. Use according to claim 2, wherein said opioid antagonist is naloxone hydrochloride.
4. Use according to any one of claims 1 to 3, wherein said dosage form is an immediate release dosage form.
5. Use according to any one of claims 1 to 3, wherein said dosage form is a controlled release dosage form.
6. Use according to claim 5, wherein said controlled release dosage form comprises a controlled release matrix.
7. Use according to claim 5, wherein said controlled release dosage form comprises a controlled release coating.
8. Use according to any one of claims 5 to 7, wherein said dosage form comprises naloxone or a pharmaceutically acceptable salt thereof and wherein said dosage form releases naloxone or a pharmaceutically acceptable salt thereof when measured according to the European Pharmacopoeia paddle test at a rate of:
 - 10 -30 % by weight of naloxone or said salt thereof at 15 min,
 - 30 -50 % by weight of naloxone or said salt thereof at 1 h,
 - 45 -65 % by weight of naloxone or said salt thereof at 2 h,
 - 60 -85 % by weight of naloxone or said salt thereof at 4 h,
 - 70 -95 % by weight of naloxone or said salt thereof at 7 h, and
 - 80% by weight of naloxone or said salt thereof at 10 h.
9. Use according to any one of claims 1 to 8, wherein said dosage form comprises at least one additional pharmaceutically active agent.
10. Use according to claim 9, wherein said additional pharmaceutically active agent is an opioid agonist.
11. Use according to claim 10, wherein said opioid agonist is selected from the group comprising oxycodone, morphine, hydromorphone, oxymorphone or a pharmaceutically acceptable salt thereof.
12. Use according to claim 11, wherein said opioid agonist is oxycodone hydrochloride.
13. Use according to any one of claims 1 to 12, wherein said dosage form comprises naloxone hydrochloride and oxycodone hydrochloride as the sole pharmaceutically active agents in a 1:2 ratio by weight.
14. Use of at least oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in the manufacture of an oral dosage form for treatment of pain in patients which otherwise have to discontinue opioid-based pain therapy for development of urinary retention, wherein said dosage form is a controlled release dosage form.
15. Use according to claim 14, wherein said dosage form comprises oxycodone hydrochloride and naloxone hydrochloride.

16. Use according to claim 15, wherein said dosage form comprises oxycodone hydrochloride and naloxone hydrochloride in a 2:1 ratio by weight.

17. Use according to any one of claims 14 to 16, wherein oxycodone or a pharmaceutically acceptable salt thereof is comprised in said dosage form in an amount of 5 to 160 mg per unit dose and naloxone or a pharmaceutically acceptable salt thereof is comprised in said dosage form in an amount of 2.5 to 80 mg per unit dose.

18. Use according to claim 14, wherein said controlled release dosage form comprises a controlled release matrix.

19. Use according to claim 14, wherein said controlled release dosage form comprises a controlled release coating.

20. Use according to any one of claims 14 to 19, wherein said dosage form comprises oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and wherein said dosage form releases oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof when measured according to the European Pharmacopoeia paddle test at a rate of:

10 -30 % by weight of oxycodone or said salt thereof at 15 min,
30 -50 % by weight of oxycodone or said salt thereof at 1 h,
45 -65 % by weight of oxycodone or said salt thereof at 2 h,
60 -85 % by weight of oxycodone or said salt thereof at 4 h,
70 -95 % by weight of oxycodone or said salt thereof at 7 h, and
80% by weight of oxycodone or said salt thereof at 10 h, and
10 -30 % by weight of naloxone or said salt thereof at 15 min,
30 -50 % by weight of naloxone or said salt thereof at 1 h,
45 -65 % by weight of naloxone or said salt thereof at 2 h,
60 -85 % by weight of naloxone or said salt thereof at 4 h,
70 -95 % by weight of naloxone or said salt thereof at 7 h, and
80% by weight of naloxone or said salt thereof at 10 h.

21. An oral dosage form as defined in any one of claims 14 to 20, when used in treatment of pain in patients which otherwise have to discontinue opioid-based pain therapy for development of urinary retention.