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(54) Titre : UTILISATION DE BUPRENORPHINE POUR TRAITER L'INCONTINENCE D'URINE
(54) Title: USE OF BUPRENORPHINE FOR TREATMENT OF URINARY INCONTINENCE

(57) **Abrégé/Abstract:**

The invention relates to the utilization of buprenorphine in the production of a medicament for the treatment of increased urinary urgency, urinary frequency and/or urinary incontinence and to the corresponding medicaments and method for the treatment of urinary urgency, urinary frequency and/or urinary incontinence.



ABSTRACT

The invention relates to the utilization of buprenorphine in the production of a medicament for the treatment of increased urinary urgency, urinary frequency and/or urinary incontinence and to the corresponding medicaments and method for the treatment of urinary urgency, urinary frequency and/or urinary incontinence.

Use of buprenorphine for treatment of urinary incontinence

The invention relates to the use of buprenorphine for the preparation of a medicament for treatment of an increased
5 urge to urinate, an increased frequency of micturition and/or urinary incontinence and to corresponding medicaments and methods for treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence.

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Urinary incontinence is the involuntary discharge of urine. This occurs in an uncontrolled manner when the pressure within the urinary bladder exceeds the pressure needed to close the ureter. Causes can be on the one hand an
15 increased internal pressure in the bladder (e.g. due to detrusor instability) with the consequence of urgency incontinence, and on the other hand a reduced sphincter pressure (e.g. following giving birth or surgical interventions) with the consequence of stress incontinence.
20 The detrusor is the coarsely bundled multilayered bladder wall musculature, contraction of which leads to voiding of urine, and the sphincter is the closing muscle complex of the urethra. Mixed forms of these types of incontinence and so-called overflow incontinence (e.g. in cases of
25 benign prostate hyperplasia) or reflex incontinence (e.g. following damage to the spinal cord) occur. Further details in this respect are to be found in Chutka, D.S. and Takahashi, P.Y., 1998, Drugs 560: 587-595.

30 The urge to urinate is the state, aimed at voiding of urine (micturition), of increased bladder muscle tension as the bladder capacity is approached (or exceeded). The clinical picture of urgency incontinence here comprises 1. an increased urge to urinate, 2. an increased frequency of

micturition and 3. involuntary urinary incontinence as such. Causes can be, inter alia, inflammations of the urinary bladder and neurogenic bladder disorders, and also bladder tuberculosis. However, not all the causes have yet
5 been clarified. Another clinical picture which fits here is hyperactive bladder (overactive bladder).

An increased urge to urinate, an increased frequency of micturition and also urinary incontinence are perceived as
10 extremely unpleasant and there is a clear need among persons affected by these indications to achieve an improvement which is as long-term as possible.

An increased urge to urinate, an increased frequency of
15 micturition and in particular urinary incontinence are conventionally treated with medicaments using substances which are involved in the reflexes of the lower urinary tract (Wein, A.J., 1998, Urology 51 (suppl. 21): 43-47). These are usually medicaments which have an inhibiting
20 action on the detrusor muscle, which is responsible for the internal pressure in the bladder. These medicaments are e.g. parasympatholytics, such as oxybutynin, propiverine or tolterodine, tricyclic antidepressants, such as imipramine, or muscle relaxants, such as flavoxate. Other medicaments,
25 which in particular increase the resistance of the urethra or of the neck of the bladder, show affinities for α -adrenoreceptors, such as ephedrine, for β -adrenoreceptors, such as clenbutarol, or are hormones, such as oestradiol. Certain diarylmethylpiperazines and -piperidines are also
30 described for this indication in WO 93/15062. For tramadol also a positive effect on bladder function has been demonstrated in a rat model of rhythmic bladder contractions (Nippon-Shinyaku, WO 98/46216).

There is furthermore literature in which a known side effect of opioids, urinary retention, is investigated clinically (Cousins and Mather, 1984, Anesthesiol. 61, 276-310). Examples are weak opioids, such as diphenoxylate (Fowler et al., 1987 J. Urol 138:735-738), potent opioids, such as morphine (Malinovsky et al., 1998 loc. cit.; Kontani and Kawabata, (1988); Jpn J Pharmacol. Sep;48(1):31) and meperidine (Doyle and Briscoe, 1976 Br J Urol 48:329-335; Mohan et al., 1995, Int. J. Clin. Pharmacol. Therap. 33, 34-37) and very potent opioids, such as fentanyl (Malinovsky et al., 1998 loc. cit.; Drenger and Magora, 1989 Anesth Analg 69:348-353) or also mixed opioid agonists/antagonists, such as pentazocine (Shimizu et al. (2000) Br. J. Pharmacol. 131 (3): 610 - 616; Mohan et al., 1995, Int. J. Clin. Pharmacol. Therap. 33, 34-37) and nalbuphine (Malinovsky et al., 1998, loc. cit.)). Nevertheless, all these studies were carried out in analgesically active concentrations, since they were after all studies on humans, and in none of these cases has a positive effect ever been reported in the treatment of an increased urge to urinate or urinary incontinence. Rather, urinary retention is found here, which is, however, generally an entirely undesirable action and therefore makes these compounds appear unattractive.

In the case of the indications in question here, however, it should furthermore be remembered that it is in general a matter of very long-term uses of medicaments and, in contrast to many situations where analgesics are employed, those affected are faced with a situation which is very unpleasant but not intolerable. It is therefore to be ensured here - even more so than with analgesics - that

side effects are avoided if the person affected does not want to exchange one evil for another. Also, analgesic actions are also largely undesirable during permanent treatment of urinary incontinence.

5

The object of the present invention was therefore to discover substances which are helpful for treatment of an increased urge to urinate, an increased frequency of micturition or urinary incontinence and at the active doses
10 preferably simultaneously show fewer side effects and/or analgesic actions.

Surprisingly, it has now been found that buprenorphine already has a favourable action on bladder function, in
15 particular urgency incontinence or "overactive bladder", at low concentrations and is particularly suitable for treatment of corresponding clinical pictures.

The invention accordingly provides the use of
20 buprenorphine, also in the form of its racemates, enantiomers and diastereomers, in particular in the form of mixtures of its enantiomers or diastereomers or in the form of an individual enantiomer or diastereomer; its base and/or salts of physiologically acceptable acids, for the
25 preparation of a medicament for treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence, in particular urgency incontinence or "overactive bladder".

30 Surprisingly, it has been found that in a model with which the indications claimed, in particular urgency incontinence, can be simulated, buprenorphine is highly active. In the model, buprenorphines eliminates the

detrusor overactivity induced by oxy-haemoglobin and correspondingly influences bladder parameters in a positive manner. Precisely in a model which clearly shows the disease symptoms just such as urgency incontinence,
5 "overactive bladder" etc. buprenorphine has therefore proved suitable.

This action is also surprising in as much as there are also studies on buprenorphine in respect of urine retention and
10 the action on bladder and urethra activity (Murray K., 1983, Brit. Med. J. 286, 765-766; Drenger and Magora, 1989 Anesth Analg 69:348-353; Batra et al., 1996, Int. J. Clin. Pharmacol. Therap. 34, 309-311; Malinovsky et al., 1998 Anesth Analg 87:456-461), wherein, however, the sometimes
15 somewhat contradictory results contradict precisely a use of buprenorphine in urinary incontinence. Thus, Drenger and also Batra report that an epidural administration of buprenorphine in the analgesically active region of 4 µg/kg (Batra) or at 2 µg/kg (Drenger [on dogs]) has no
20 significant influence on bladder or urethra function and in the end, due to a lack of effect, both therefore recommend precisely the use of buprenorphine for pain treatment on patients in whom complications in the urinary system are to be avoided. It is all the more astonishing that precisely
25 buprenorphine shows a decidedly favourable action here in the treatment of urinary incontinence.

In the other extreme, Malinovsky reports (table 4, p. 460) that on administration of 0.3 mg i.v. to patients of about
30 70 kg body weight (4.3 µg/kg) urinary retention occurs in 5 out of 10 cases, and in the case described by Murray urinary retention also occurs after sublingual intake of 400 µg buprenorphine (~ 5.7 µg/kg). Apart from the fact

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that urinary retention is a clearly undesirable action, the data here are contradictory and the doses reported in which adverse actions are shown on the bladder as a result cover or overlap with those in which none at all are shown. It is particularly confusing here that an amount of 4 µg/kg administered i.t. (Batra et al.) has no influence on bladder function in spite of the considerably lower distribution compartment and therefore higher concentration at the site of action, although precisely IT administration of opioids is said to lead to significant urinary retention (Cousins and Mather 1984; Drenger and Mangora 1989), while 4.3 µg/kg i.v. is said to lead to 50% urinary retention (Malinovsky et al.). It was all the more astonishing that in spite of the negative literature indications on both sides, buprenorphine is active on urinary incontinence, and in particular in a model which simulates the disease.

Suitable salts in the context of this invention and in each of the uses claimed are salts of buprenorphine with inorganic or organic acids and/or a sugar substitute, such as saccharin, cyclamate or acesulfam. The free base, the hydrochloride, stearate, citrate or lactate is particularly preferred here, in particular the free base or the hydrochloride.

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In one embodiment of the invention the buprenorphine is in the form of its free base, the hydrochloride, the stearate, the citrate or lactate, in particular the free base or the hydrochloride.

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It is particularly preferred if the treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence with the medicaments prepared using, according to the invention, buprenorphine is
5 carried out with a buprenorphine dose below the lower limit of the conventional dose for pain treatment.

It is very particularly preferred here if the treatment is carried out with an amount of buprenorphine of $< 300 \mu\text{g}$ or $< 4.3 \mu\text{g/kg}$ of body weight, preferably between $300 \mu\text{g}$ and $1 \mu\text{g}$ or $4.3 \mu\text{g/kg}$ and $0.014 \mu\text{g/kg}$, in particular between
5 $250 \mu\text{g}$ and $5 \mu\text{g}$ or $3.6 \mu\text{g/kg}$ and $0.07 \mu\text{g/kg}$, particularly preferably between $200 \mu\text{g}$ and $10 \mu\text{g}$ or $2.8 \mu\text{g/kg}$ and $0.14 \mu\text{g/kg}$. It is furthermore preferable here that the stated amounts of buprenorphine are the maximum or minimum amounts of an individual dose and/or the maximum or minimum
10 amounts administered per day.

Dosages (i.m. or i.v.) of $0.3 - 0.6 \text{ mg}$ are stated as conventional in pain treatment (Martindale (ed. C. Parfitt), The complete drug reference, 32nd ed., 1999, p.
15 22 et seq.). Approx. $300 \mu\text{g}$ can accordingly be assumed here to be the lower limit of analgesic activity. The relative dosage in $\mu\text{g/kg}$ was calculated accordingly for a patient with an average body weight of 70 kg .

20 In view of the data, for example of Batra et al. 1996, who saw no significant effects on the bladder with buprenorphine in humans with a dosage of $4 \mu\text{g/kg}$, it was very surprising to discover that in spite of amounts of buprenorphine which already lie at this and furthermore
25 also at significantly below this lower analgesic dosage, an action of buprenorphine which alleviates urgency incontinence arises in an animal model.

It is furthermore particularly preferred if the medicament
30 prepared using, according to the invention, buprenorphine for treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence shows

a delayed release, and is preferably in the form of a sustained release formulation.

This is a very particularly preferred embodiment of the invention, since the treatment of urinary incontinence requires a very long-term treatment. It is therefore very favourable if the medicament shows a delayed release and the active compound is correspondingly released continuously over a relatively long period of time.

10

It is a preferred embodiment of the invention here, on the one hand, if the medicament is in the form of a delayed-release particle or implant, in particular an implant or particle of synthetic material, the synthetic material preferably being chosen from polylactide, polyglycollide or a polylactide/polyglycollide copolymer.

15

In this embodiment the buprenorphine is preferably bonded non-covalently to and in the particle or the implant, which, after administration, releases the active compound slowly, sometimes in the case of implants over months, and continuously in small amounts, usually with breakdown of the carrier matrix of the particle or implant. However, precisely because in the treatment of urgency incontinence symptoms, such as urinary incontinence, with buprenorphine only such surprisingly low doses are necessary and a continuously slow release is appropriate for treatment according to present knowledge, it has been found that this form of the invention is very favourable.

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On the other hand, it is therefore also a very particularly preferred embodiment of the invention if the medicament prepared is a transdermal therapeutic system in the form of

a patch for administration of buprenorphine to the skin. Also or precisely this form of the medicament prepared using, according to the invention, buprenorphine for treatment of an increased urge to urinate, an increased
5 frequency of micturition and/or urinary incontinence shows, according to present knowledge, particularly favourable properties in this indication or these indications. In a favourable manner, such patches continuously release, over a period of 3 or also 5 or more days, particular easily
10 adjustable amounts of buprenorphine, which can also be very low (which surprisingly are sufficient in this indication), which are then absorbed via the skin. Correspondingly suitable patches are known, inter alia, from
EP 0 430 019 B1, WO 98/36728 or WO96/19975

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It is preferred if the transdermal therapeutic system comprises a backing layer which is permeable to the active compound, an adhesive reservoir layer and a re-detachable protective layer. It is furthermore preferred here if the
20 reservoir layer contains 20-90 wt.% of polymer material, 0.1-30 wt.% of plasticizer, 0.1-20 wt.% of buprenorphine, also in the form of its racemates, enantiomers or diastereomers, in particular in the form of mixtures of its enantiomers or diastereomers or in the form of an
25 individual enantiomer or diastereomer; its base and/or salts of physiologically acceptable acids, preferably in the form of buprenorphine base, and 0.1-30 wt.% of a solvent for buprenorphine, the solvent for buprenorphine in the reservoir layer which remains in the system preferably
30 being a compound with at least one acid group.

A particularly preferred form of the medicament prepared using, according to the invention, buprenorphine for

treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence shows a release rate of the buprenorphine of between 1 µg/h and 40 µg/h, preferably between 2 µg/h and 35 µg/h, in particular between 5 µg/h and 20 µg/h, preferably between 5 µg/h and 10 µg/h. These are - as has emerged - particularly favourable release rates for these indications.

- 10 It is a further preferred embodiment of the medicament prepared using, according to the invention, buprenorphine for treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence in the form of a transdermal therapeutic system in the form of a
- 15 patch for administration of buprenorphine to the skin if the transdermal therapeutic system has a release rate of the buprenorphine of the first order over a dosage interval of 72 h, so that a maximum plasma concentration of between 20 pg/ml and 1,052 pg/ml is achieved, and if, during the
- 20 treatment, the transdermal therapeutic system remains on the skin of the patient for a further dosage interval of at least 2 days, during which the transdermal therapeutic system shows release kinetics of the buprenorphine of zero order, so that the patients experience analgesia during the
- 25 additional dosage interval of at least two days.

It is furthermore preferred here that during the additional dosage interval of at least 2 days a relative average release rate of between 0.3 µg/h and 21 µg/h, preferably

30 between 0.3 µg/h and 9 µg/h or between 13 µg/h and 21 µg/h, in particular between 0.3 µg/h and 0.6 µg/h, between 0.7 µg/h and 1 µg/h, between 2 µg/h and 4 µg/h, between

4 µg/h and 7 µg/h or between 5 µg/h and 9 µg/h is maintained.

- This form is also preferred if the corresponding
- 5 transdermal therapeutic system has a release rate of the buprenorphine of the first order over a dosage interval of 72 h, so that approx. 72 h after use of this transdermal therapeutic system an average plasma concentration of between 20 pg/ml and 1,052 pg/ml, preferably between
- 10 85 pg/ml and 263 pg/ml, in particular between 20 pg/ml and 66 pg/ml, between 42 pg/ml and 132 pg/ml, between 169 pg/ml and 526 pg/ml, between 254 pg/ml and 789 pg/ml or between 339 pg/ml and 1,052 pg/ml is achieved.
- 15 Corresponding transdermal therapeutic systems in which approx. 72 h after use of this transdermal therapeutic system an average plasma concentration of between 20 pg/ml and 1,052 pg/ml and during the additional dosage interval of at least 2 days a relative average release rate of
- 20 between 0.3 µg/h and 9 µg/h is present, or an average plasma concentration of between 85 pg/ml and 263 pg/ml and a relative average release rate of between 13 µg/h and 21 µg/h or an average plasma concentration of between 20 pg/ml and 66 pg/ml and a relative average release rate
- 25 of between 0.3 µg/h and 0.6 µg/h or an average plasma concentration of between 42 pg/ml and 132 pg/ml and a relative average release rate of between 0.7 µg/h and 1 µg/h or an average plasma concentration of between 169 pg/ml and 526 pg/ml and a relative average release rate
- 30 of between 2 µg/h and 4 µg/h or an average plasma concentration of between 254 pg/ml and 789 pg/ml and a relative average release rate of between 4 µg/h and 7 µg/h or an average plasma concentration of between 339 pg/ml and

1,052 pg/ml and a relative average release rate of between 5 µg/h and 9 µg/h, are also favourable.

This embodiment is furthermore preferred if the transdermal
5 therapeutic system remains on the skin of the patient for at least 5 days.

Although buprenorphine in the use according to the invention shows only mild side effects to none at all, it
10 may also be of advantage, for example to avoid certain forms of dependency, also to use morphine antagonists, in particular naloxone, naltrexone and/or levallorphan, in addition to these compounds.

15 The invention also relates to medicaments for the treatment of an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence which comprise, as the active compound, at least buprenorphine, also in the form of its racemates, enantiomers and diastereomers, in
20 particular in the form of mixtures of its enantiomers or diastereomers or in the form of an individual enantiomer or diastereomer; its bases and/or salts of physiologically tolerated acids, and optionally additives and/or auxiliary substances.

25

Generally, these medicaments according to the invention and also the medicaments described above prepared using, according to the invention, buprenorphine for treatment of
30 an increased urge to urinate, an increased frequency of micturition and/or urinary incontinence on the one hand can comprise additives and/or auxiliary substances and on the other hand can be present in the most diverse known medicament forms.

Suitable additives and/or auxiliary substances in the context of this invention are all the substances known to the expert from the prior art for achieving pharmaceutical formulations. Auxiliary substances can be, for example, water, ethanol, 2-propanol, glycerol, ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, glucose, fructose, lactose, sucrose, dextrose, molasses, starch, modified starch, gelatine, sorbitol, inositol, mannitol, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, cellulose acetate, shellac, cetyl alcohol, polyvinylpyrrolidone, paraffins, waxes, naturally occurring and synthetic gums, acacia gum, alginates, dextran, saturated and unsaturated fatty acids, stearic acid, magnesium stearate, zinc stearate, glyceryl stearate, sodium lauryl sulfate, edible oils, sesame oil, coconut oil, groundnut oil, soya bean oil, lecithin, sodium lactate, polyoxyethylene and -propylene fatty acid esters, sorbitan fatty acid esters, sorbic acid, benzoic acid, citric acid, ascorbic acid, tannic acid, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, magnesium oxide, zinc oxide, silicon dioxide, titanium oxide, titanium dioxide, magnesium sulfate, zinc sulfate, calcium sulfate, potash, calcium phosphate, dicalcium phosphate, potassium bromide, potassium iodide, talc, kaolin, pectin, crospovidone, agar and bentonite.

The choice of these auxiliary substances and the amounts thereof to be employed depend on whether the medicament is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally. Formulations in the form of tablets, chewable tablets, coated tablets,

capsules, granules, drops, juices or syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are suitable for parenteral, topical and inhalatory administration.

- 5 Suppositories for use in the rectum are a further possibility.

Buprenorphine can be released from certain formulation forms in a delayed manner. Examples are sustained release
10 tablet forms, but in particular also the use of buprenorphine in a depot in dissolved form, a barrier film or a patch, optionally with the addition of agents which promote penetration of the skin, as suitable examples for suitable percutaneous administration forms and also delayed
15 release particles or implants.

Examples of auxiliary substances and additives for oral administration forms are disintegrants, lubricants, binders, fillers, mould release agents, where appropriate
20 solvents, flavouring substances, sugar, in particular carrier agents, diluents, dyestuffs, antioxidants etc. Waxes or fatty acid esters, inter alia, can be used or suppositories, and carrier substances, preservatives, suspension auxiliaries etc. can be used for compositions
25 for parenteral administration.

A particularly preferred form of the medicament according to the invention exists if the medicament shows a delayed release, preferably is present in the form of a sustained
30 release formulation, in particular

is present in the form of a delayed release particle or implant, preferably an implant or particle of a

synthetic material, the synthetic material preferably being chosen from polylactide or a polylactide/polyglycollide copolymer

5 or

is a transdermal therapeutic system in the form of patch for administration of buprenorphine to the skin.

10 For the medicament according to the invention, the same preferred embodiments as have already been described above for medicaments prepared using, according to the invention, buprenorphine for treatment of an increased urge to urinate, an increased frequency of micturition and/or
15 urinary incontinence otherwise apply.

The medicaments and pharmaceutical compositions according to the invention can be prepared with the aid of means, devices, methods and processes which are well-known in the
20 prior art of pharmaceutical formulation, such as are described, for example, in "Remington's Pharmaceutical Sciences", eds. A.R. Gennaro, 17th ed., Mack Publishing Company, Easton, Pa. (1985), in particular in part 8, chapter 76 to 93. However, other types of preparation, in
25 particular for modern medicament forms, are also conceivable and known.

The invention furthermore also relates to a method for treatment of an increased urge to urinate, an increased
30 frequency of micturition or urinary incontinence in which buprenorphine, in the form of its racemates, enantiomers or diastereomers, in particular in the form of mixtures of its enantiomers or diastereomers or in the form of an

individual enantiomer or diastereomer; its bases and/or salts of physiologically acceptable acids, is used.

The following examples are intended to illustrate the invention without the subject matter of the invention being limited thereto.

Examples

10 Example 1: Test system of cystometry on conscious naïve rats

Cystometric studies were carried out on naïve, female Sprague-Dawley rats by the method of Ishizuka et. al. ((1997), Naunyn-Schmiedeberg's Arch. Pharmacol. 355: 787 - 793). Three days after implantation of bladder and venous catheters, the animals were examined in the conscious state, freely mobile. The bladder catheter was connected to a pressure transducer and an injection pump. The animals were placed in metabolism cages which allowed measurement of the volume of urine. Physiological saline solution was infused into the emptied bladder (10 ml/h) and the bladder pressure and micturition volume were recorded continuously. After a stabilization phase, a 20-minute phase which was characterized by normal, reproducible micturition cycles was recorded. The following parameters, inter alia, were determined:

- Threshold pressure (TP, bladder pressure immediately before micturition),
- Bladder capacity (BC, residual volume after preceding micturition plus volume of the infused solution during the filling phase),

- Intercontraction interval ((ICI), the interval of time between micturitions).

An increase in the threshold pressure (TP) indicates an important therapeutic action on one of the indications according to the invention. The intercontraction interval (ICI) is also an important parameter for measuring the physiological activity of a substance in the treatment of urinary incontinence, as is the bladder capacity (BC). On the basis of the very heterogeneous causes of the symptoms of these clinical pictures, for an activity it is not necessary to have a positive influence on all three parameters here. It is therefore entirely sufficient if a positive action is to be found in only one of these parameters for it to be possible to employ the substance in urinary incontinence, an increased frequency of micturition or an increased urge to urinate.

After three reproducible micturition cycles were recorded as the pre-value, 10 µg/kg buprenorphine in the vehicle = 0.9% NaCl were administered i.v. and the action on the cystometric parameters was recorded for 90 to 120 minutes. At the action maximum, the mean of 3 micturition cycles was determined and was stated as the percentage change with respect to the pre-value (table 1).

The concentration employed corresponds to the ED₅₀ in a known analgesia model for rats, the tail flick.

Buprenorphine	TP threshold pressure	BC bladder capacity	ICI intercontraction interval
0.01 mg/kg iv (n=6)	+69.9% **	+3.6%	+10.9%

Table 1: Influence on the cystometric parameters by buprenorphine (change from the pre-value [%]); n corresponds to the number of animals employed in the study. Significance (Student T test): *p < 0.05; ** p < .0.01;

5 *** p < 0.001.

Precisely on the TP buprenorphine shows a positive action on bladder regulation and is therefore suitable in principle for treatment of urinary incontinence.

10 Nevertheless, the concentration employed, which has an analgesic action, is evidently too high, since drip incontinence occurred in 2 of the 6 animals. At two lower concentrations, 0.001 mg/kg i.v. and 0.005 mg/kg i.v., an increase in the TP of +27.6% and +37.5% respectively
15 occurred at n = 6.

Example 2: Test system of cystometry on conscious damaged rats

20 This model simulates urgency incontinence in an animal model; the oxyhaemoglobin (OxyHb) employed induces bladder overactivity.

Cystometric studies were carried out on naïve, female
25 Sprague-Dawley rats by the method of Pandita et al. (J. Urol. 2000, 164:545-550). Three days after implantation of bladder and venous catheters, the animals were examined in the conscious state, freely mobile. The bladder catheter

was connected to a pressure transducer and an injection pump. The animals were placed in metabolism cages which allowed measurement of the volume of urine. Physiological saline solution was infused into the emptied bladder (10 ml/h) and the bladder pressure and micturition volume were recorded continuously. After a stabilization phase, a 20-minute phase which was characterized by normal, reproducible micturition cycles was recorded. The following parameters, inter alia, were determined:

10

- Threshold pressure (TP, bladder pressure immediately before micturition),
- Bladder capacity (BC, residual volume after preceding micturition plus volume of the infused solution during the filling phase),
- Intercontraction interval ((ICI), the interval of time between micturitions)
- Micturition pressure (MP, maximum bladder pressure during micturition).

20

An increase in the threshold pressure (TP) indicates an important therapeutic action on one of the indications according to the invention. The intercontraction interval (ICI) is also an important parameter for measuring the physiological activity of a substance in the treatment of urinary incontinence, as is the bladder capacity (BC). On the basis of the very heterogeneous causes of the symptoms of these clinical pictures, for an activity it is not necessary to have a positive influence on all the parameters here. It is therefore entirely sufficient if a positive action is to be found in only one of these parameters for it to be possible to employ the substance in

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urinary incontinence, an increased frequency of micturition or an increased urge to urinate.

After three reproducible micturition cycles were recorded
5 as the pre-value, 2.5×10^{-4} M oxyhaemoglobin in the vehicle =
0.9% NaCl were infused into the bladder. The action on the
cystometric parameters were recorded for about 20 minutes.
At the action maximum, the mean of 3 micturition cycles was
determined and was stated as the percentage change with
10 respect to the pre-value (table 2). Treatment with
oxyhaemoglobin induces a characteristic change in the
cystometric parameters with an increase in the micturition
pressure, a lowering of the bladder capacity and a
reduction in the intercontraction interval. These changes
15 represent the changes found in patients with urgency
incontinence.

Administration of 5 µg/kg buprenorphine in the vehicle =
0.9% NaCl i.v. before administration of oxyhaemoglobin is
20 capable of suppressing the changes induced by
oxyhaemoglobin and moreover of also inducing an increase in
the threshold pressure (table 2).

	MP Micturition pressure [cm H ₂ O]	TP threshold pressure [cm H ₂ O]	BC bladder capacity [ml]	ICI inter- contraction interval [min]
OxyHb				
2.5x10⁻⁴M iv (n = 5)	b: 59±8 a: 97±5 dif.: +64.4% **	b: 8.72±1.31 a: 9.84±1.56 dif.: +12.8%	b: 0.92±0.10 a: 0.65±0.06 dif.: -29.3% **	b: 4.96±0.33 a: 3.33±0.18 dif.: -32.9% **
OxyHb + buprenorphine				
OxyHb: 2.5x10⁻⁴M buprenorphine: 0.005 mg/kg iv (n=6)	b: 54±9 a: 37±8 dif.: -31.5% *	b: 9.07±1.29 a: 14.28±2.53 dif.: +57.4% *	b: 1.19±0.12 a: 1.17±0.13 dif.: -1.7%	b: 6.72±0.73 a: 6.70±0.88 dif.: -0.3%

Table 2: Influence on cystometric parameters by oxyhaemoglobin (OxyHb) with and without prior administration of buprenorphine. Average values with standard deviations before (b) and after (a) use of the substances and the change (dif.) compared with the pre-value [%] are stated; n corresponds to the number of animals employed in the study. Significance (Student T test): * p < 0.05; ** p < 0.01; *** p < 0.001.

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It can be seen that OxyHb has a significant adverse influence on bladder parameters in the sense of urgency incontinence. This adverse influence is eliminated and even improved by buprenorphine. The micturition pressure thus falls compared with the urgency incontinence induced by OxyHb, and even significantly compared with the untreated control. Furthermore, in this urgency incontinence model buprenorphine completely normalizes the intercontraction interval and the bladder capacity and also

has the effect of a significant and clear increase in the threshold pressure.

The evidence is thus provided that buprenorphine, in particular in the field of urgency incontinence, for which the OxyHb model is a standard model, shows an outstanding action, and in particular also in the event of damage, that is to say in the case of disease.

10 **Example 3: Transdermal formulation:**

A transdermal administration system is formulated in accordance with example 1 of WO 98/36728.

15 1.139 g of a polyacrylate solution of 47.83 wt.% with self-crosslinking acrylate copolymers comprising 2-ethyl acrylate, vinyl acetate, acrylic acid (solvent: ethyl acetate : heptane : isopropanol : toluene : acetylacetonate in a ratio of 37:26:26:4:1), 100 g laevulinic acid, 150 g
20 oleyl oleate, 100 g polyvinylpyrrolidone, 150 g ethanol, 200 g ethyl acetate and 100 g buprenorphine base were homogenised. The mixture was stirred for approx. 2 h and then inspected visually to determine whether all the solid substances had dissolved. Evaporation losses must be
25 checked by renewed weighing and if necessary the solvent must be compensated with the aid of ethyl acetate. Thereafter, the mixture is applied to a transparent polyester film 420 mm wide such that the weight per unit surface area of the dried layer is 80 g/m². The polyester
30 film serves as a protective layer and can be detached again by treatment with silicone. The solvent is removed by heated air passed over a damp zone. By this heat treatment, not only do the solvents evaporate, the

laevulinic acid also melts. Thereafter, the sealing film is covered with a polyester film 15 μ thick. An area of 16 cm^2 is cut out with the aid of a suitable cutting tool and the edges which have remained between the individual
5 objects are removed.

To achieve the nominal release rate of approx. 25 $\mu\text{g/h}$, the total amount of buprenorphine in the transdermal patch is approx. 10 mg, the active surface area are approx. 12.5 cm^2
10 and the size of the patch is, for example, approx. 30.6 cm^2 .

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CLAIMS:

1. A use of buprenorphine, a racemate thereof, an enantiomer thereof, a diastereomer thereof, a mixture of enantiomers thereof, a mixture of diastereomers thereof, a
5 base thereof or a salt thereof of a physiologically acceptable acid in preparation of a pharmaceutical composition for treatment of one or more of an increased urge to urinate, and increased frequency of micturition and urinary incontinence.
- 10 2. A use according to claim 1, wherein the buprenorphine is in the form of the mixture of enantiomers.
3. A use according to claim 1, wherein the buprenorphine is in the form of the mixture of diastereomers.
- 15 4. A use according to claim 1, wherein the buprenorphine is in the form of the enantiomer.
5. A use according to claim 1, wherein the buprenorphine is in the form of the diastereomer.
6. A use according to any one of claims 1 to 5,
20 wherein the one or more of the increased urge to urinate, the increased frequency of micturition and the urinary incontinence is urgency incontinence.
7. A use according to any one of claims 1 to 5,
25 wherein the one or more of the increased urge to urinate, the increased frequency of micturition and the urinary incontinence is overactive bladder.
8. A use according to any one of claims 1 to 7, wherein the buprenorphine is for administration in a dose

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below the lower limit of a conventional dose for pain treatment.

9. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of less than
5 300 μg .

10. A use according to claim 9, wherein the amount of less than 300 μg of buprenorphine is the maximum amount of an individual dose.

11. A use according to claim 9, wherein the amount of
10 less than 300 μg of buprenorphine is the maximum amount of a daily administration.

12. A use according to claim 9, wherein the amount of less than 300 μg of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily
15 administration.

13. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of between 300 μg and 1 μg .

14. A use according to claim 13, wherein the amount of
20 300 μg of buprenorphine is the maximum amount of an individual dose.

15. A use according to claim 13, wherein the amount of 300 μg of buprenorphine is the maximum amount of a daily administration.

25 16. A use according to claim 13, wherein the amount of 300 μg of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

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17. A use according to claim 13, wherein the amount of 1 μ g of buprenorphine is the minimum amount of an individual dose.

18. A use according to claim 13, wherein the amount of 5 1 μ g of buprenorphine is the minimum amount of a daily administration.

19. A use according to claim 13, wherein the amount of 1 μ g of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

10 20. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of between 250 μ g and 5 μ g.

21. A use according to claim 20, wherein the amount of 250 μ g of buprenorphine is the maximum amount of an 15 individual dose.

22. A use according to claim 20, wherein the amount of 250 μ g of buprenorphine is the maximum amount of a daily administration.

23. A use according to claim 20, wherein the amount of 20 250 μ g of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

24. A use according to claim 20, wherein the amount of 5 μ g of buprenorphine is the minimum amount of an individual 25 dose.

25. A use according to claim 20, wherein the amount of 5 μ g of buprenorphine is the minimum amount of a daily administration.

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26. A use according to claim 20, wherein the amount of 5 μ g of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

27. A use according to any one of claims 1 to 8,
5 wherein the buprenorphine is in an amount of between 200 μ g and 10' μ g.

28. A use according to claim 27, wherein the amount of 200 μ g of buprenorphine is the maximum amount of an individual dose.

10 29. A use according to claim 27, wherein the amount of 200 μ g of buprenorphine is the maximum amount of a daily administration.

30. A use according to claim 27, wherein the amount of 200 μ g of buprenorphine is the maximum amount of an
15 individual dose and the maximum amount of a daily administration.

31. A use according to claim 27, wherein the amount of 10 μ g of buprenorphine is the minimum amount of an individual dose.

20 32. A use according to claim 27, wherein the amount of 10 μ g of buprenorphine is the minimum amount of a daily administration.

33. A use according to claim 27, wherein the amount of 10 μ g of buprenorphine is the minimum amount of an individual
25 dose and the minimum amount of a daily administration.

34. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of less than 4.3 μ g/kg of body weight.

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35. A use according to claim 34, wherein the amount of less than $4.3\mu\text{g}/\text{kg}$ of body weight of buprenorphine is the maximum amount of an individual dose.

36. A use according to claim 34, wherein the amount of less than $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

37. A use according to claim 34, wherein the amount of less than $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

38. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of between $4.3\mu\text{g}/\text{kg}$ of body weight and $0.014\mu\text{g}/\text{kg}$ of body weight.

39. A use according to claim 38, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

40. A use according to claim 38, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

41. A use according to claim 38, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

42. A use according to claim 38, wherein the amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

43. A use according to claim 38, wherein the amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

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44. A use according to claim 38, wherein the amount of 0.014 μ g/kg body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

5 45. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of between 3.6 μ g/kg of body weight and 0.07 μ g/kg of body weight.

46. A use according to claim 45, wherein the amount of 3.6 μ g/kg body weight of buprenorphine is the maximum amount
10 of an individual dose.

47. A use according to claim 45, wherein the amount of 3.6 μ g/kg body weight of buprenorphine is the maximum amount of a daily administration.

48. A use according to claim 45, wherein the amount of
15 3.6 μ g/kg body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

49. A use according to claim 45, wherein the amount of 0.07 μ g/kg body weight of buprenorphine is the minimum amount
20 of an individual dose.

50. A use according to claim 45, wherein the amount of 0.07 μ g/kg body weight of buprenorphine is the minimum amount of a daily administration.

51. A use according to claim 45, wherein the amount of
25 0.07 μ g/kg body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

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52. A use according to any one of claims 1 to 8, wherein the buprenorphine is in an amount of between 2.8 $\mu\text{g/kg}$ of body weight and 0.14 $\mu\text{g/kg}$ of body weight.

53. A use according to claim 52, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

54. A use according to claim 52, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

10 55. A use according to claim 52, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

15 56. A use according to claim 52, wherein the amount of 0.14 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

57. A use according to claim 52, wherein the amount of 0.14 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

20 58. A use according to claim 52, wherein the amount of 0.14 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

25 59. A use according to any one of claims 1 to 58, wherein the buprenorphine is for delayed release.

60. A use according to any one of claims 1 to 58, wherein the buprenorphine is for delayed release in a sustained release formulation.

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61. A use according to any one of claims 1 to 58, wherein the buprenorphine is in the form of a delayed-release particle or implant.

62. A use according to claim 61, wherein the delayed-
5 release particle or implant comprises a synthetic material.

63. A use according to claim 62, wherein the synthetic material is a polylactide, a polyglycolide or a polylactide/polyglycolide copolymer.

64. A use according to any one of claims 1 to 58,
10 wherein the buprenorphine is in the form of transdermal therapeutic system in the form of a patch for administration of the buprenorphine to the skin.

65. A use according to claim 64, wherein the transdermal therapeutic system comprises a backing layer
15 which is permeable to the buprenorphine, an adhesive reservoir layer and a re-detachable protective layer.

66. A use according to claim 65, wherein the adhesive reservoir layer comprises 20 to 90 wt.% of polymer material, 0.1 to 30 wt.% of plasticizer, 0.1 to 20 wt.% of the
20 buprenorphine, and 0.1 to 30 wt.% of a solvent for the buprenorphine, wherein the solvent for the buprenorphine is for remaining in the system after administration of the buprenorphine.

67. A use according to claim 66, wherein the solvent
25 is a compound with at least one acid group.

68. A use according to any one of claims 1 to 67, wherein the buprenorphine is for administration at a release rate of between 1 $\mu\text{g/h}$ and 40 $\mu\text{g/h}$.

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69. A use according to any one of claims 1 to 67,
wherein the buprenorphine is for administration at a release
rate of between 2 $\mu\text{g/h}$ and 35 $\mu\text{g/h}$.

70. A use according to any one of claims 1 to 67,
5 wherein the buprenorphine is for administration at a release
rate of between 5 $\mu\text{g/h}$ and 20 $\mu\text{g/h}$.

71. A use according to any one of claims 1 to 67,
wherein the buprenorphine is for administration at a release
rate of between 5 $\mu\text{g/h}$ and 10 $\mu\text{g/h}$.

10 72. A use according to any one of claims 1 to 71,
wherein the buprenorphine is for coadministration with a
morphine antagonist.

73. A use according to claim 72, wherein the morphine
antagonist is one or more of naloxone, naltrexone and
15 levallorphan.

74. A use according to any one of claims 1 to 73,
wherein the buprenorphine is in the form of the free base,
the hydrochloride, the stearate, the citrate or the lactate.

75. A use according to any one of claims 1 to 73,
20 wherein the buprenorphine is in the form of the free base.

76. A use according to any one of claims 1 to 73,
wherein the buprenorphine is in the form of the
hydrochloride.

77. Buprenorphine, a racemate thereof, an enantiomer
25 thereof, a diastereomer thereof, a mixture of enantiomers
thereof, a mixture of diastereomers thereof, a base thereof
or a salt thereof of a physiologically acceptable acid for
treatment of one or more of an increased urge to urinate,

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and increased frequency of micturition and urinary incontinence.

78. Buprenorphine according to claim 77, wherein the buprenorphine is in the form of the mixture of enantiomers.

5 79. Buprenorphine according to claim 77, wherein the buprenorphine is in the form of the mixture of diastereomers.

80. Buprenorphine according to claim 77, wherein the buprenorphine is in the form of the enantiomer.

10 81. Buprenorphine according to claim 77, wherein the buprenorphine is in the form of the diastereomer.

82. Buprenorphine according to any one of claims 77 to 81, wherein the one or more of the increased urge to urinate, the increased frequency of micturition and the
15 urinary incontinence is urgency incontinence.

83. Buprenorphine according to any one of claims 77 to 82, wherein the one or more of the increased urge to urinate, the increased frequency of micturition and the urinary incontinence is overactive bladder.

20 84. Buprenorphine according to any one of claims 77 to 83, wherein the buprenorphine is for administration in a dose below the lower limit of a conventional dose for pain treatment.

85. Buprenorphine according to any one of claims 77
25 to 84, wherein the buprenorphine is in an amount of less than 300 μ g.

86. Buprenorphine according to claim 85, wherein the amount of less than 300 μ g of buprenorphine is the maximum amount of an individual dose.

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87. Buprenorphine according to claim 85, wherein the amount of less than 300 μ g of buprenorphine is the maximum amount of a daily administration.

88. Buprenorphine according to claim 85, wherein the
5 amount of less than 300 μ g of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

89. Buprenorphine according to any one of claims 77
to 84, wherein the buprenorphine is in an amount of between
10 300 μ g and 1 μ g.]

90. Buprenorphine according to claim 89, wherein the amount of 300 μ g of buprenorphine is the maximum amount of an individual dose.

91. Buprenorphine according to claim 89, wherein the
15 amount of 300 μ g of buprenorphine is the maximum amount of a daily administration.

92. Buprenorphine according to claim 89, wherein the amount of 300 μ g of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily
20 administration.

93. Buprenorphine according to claim 89, wherein the amount of 1 μ g of buprenorphine is the minimum amount of an individual dose.

94. Buprenorphine according to claim 89, wherein the
25 amount of 1 μ g of buprenorphine is the minimum amount of a daily administration.

95. Buprenorphine according to claim 89, wherein the amount of 1 μ g of buprenorphine is the minimum amount of an

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individual dose and the minimum amount of a daily administration.

96. Buprenorphine according to any one of claims 77 to 84, wherein the buprenorphine is in an amount of between 5 250 μg and 5 μg .

97. Buprenorphine according to claim 96, wherein the amount of 250 μg of buprenorphine is the maximum amount of an individual dose.

98. Buprenorphine according to claim 96, wherein the 10 amount of 250 μg of buprenorphine is the maximum amount of a daily administration.

99. Buprenorphine according to claim 96, wherein the amount of 250 μg of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily 15 administration.

100. Buprenorphine according to claim 96, wherein the amount of 5 μg of buprenorphine is the minimum amount of an individual dose.

101. Buprenorphine according to claim 96, wherein the 20 amount of 5 μg of buprenorphine is the minimum amount of a daily administration.

102. Buprenorphine according to claim 96, wherein the amount of 5 μg of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily 25 administration.

103. Buprenorphine according to any one of claims 77 to 84, wherein the buprenorphine is in an amount of between 200 μg and 10 μg .

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104. Buprenorphine according to claim 103, wherein the amount of 200 μ g of buprenorphine is the maximum amount of an individual dose.

105. Buprenorphine according to claim 103, wherein the
5 amount of 200 μ g of buprenorphine is the maximum amount of a daily administration.

106. Buprenorphine according to claim 103, wherein the amount of 200 μ g of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily
10 administration.

107. Buprenorphine according to claim 103, wherein the amount of 10 μ g of buprenorphine is the minimum amount of an individual dose.

108. Buprenorphine according to claim 103, wherein the
15 amount of 10 μ g of buprenorphine is the minimum amount of a daily administration.

109. Buprenorphine according to claim 103, wherein the amount of 10 μ g of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily
20 administration.

110. Buprenorphine according to any one of claims 77 to 84, wherein the buprenorphine is in an amount of less than 4.3 μ g/kg of body weight.

111. Buprenorphine according to claim 110, wherein the
25 amount of less than 4.3 μ g/kg of body weight of buprenorphine is the maximum amount of an individual dose.

112. Buprenorphine according to claim 110, wherein the amount of less than 4.3 μ g/kg body weight of buprenorphine is the maximum amount of a daily administration.

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113. Buprenorphine according to claim 110, wherein the amount of less than $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

5 114. Buprenorphine according to any one of claims 77 to 84, wherein the buprenorphine is in an amount of between $4.3\mu\text{g}/\text{kg}$ of body weight and $0.014\mu\text{g}/\text{kg}$ of body weight.

115. Buprenorphine according to claim 114, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the
10 maximum amount of an individual dose.

116. Buprenorphine according to claim 114, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

117. Buprenorphine according to claim 114, wherein the
15 amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

118. Buprenorphine according to claim 114, wherein the amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the
20 minimum amount of an individual dose.

119. Buprenorphine according to claim 114, wherein the amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

120. Buprenorphine according to claim 114, wherein the
25 amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

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121. Buprenorphine according to any one of claims 77 to 84, wherein the buprenorphine is in an amount of between 3.6 $\mu\text{g/kg}$ of body weight and 0.07 $\mu\text{g/kg}$ of body weight.

122. Buprenorphine according to claim 121, wherein the
5 amount of 3.6 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

123. Buprenorphine according to claim 121, wherein the amount of 3.6 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

10 124. Buprenorphine according to claim 121, wherein the amount of 3.6 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

125. Buprenorphine according to claim 121, wherein the
15 amount of 0.07 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

126. Buprenorphine according to claim 121, wherein the amount of 0.07 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

20 127. Buprenorphine according to claim 121, wherein the amount of 0.07 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

128. Buprenorphine according to any one of claims 77
25 to 84, wherein the buprenorphine is in an amount of between 2.8 $\mu\text{g/kg}$ of body weight and 0.14 $\mu\text{g/kg}$ of body weight.

129. Buprenorphine according to claim 128, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

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130. Buprenorphine according to claim 128, wherein the amount of $2.8\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

131. Buprenorphine according to claim 128, wherein the
5 amount of $2.8\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

132. Buprenorphine according to claim 128, wherein the
10 amount of $0.14\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

133. Buprenorphine according to claim 128, wherein the amount of $0.14\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

134. Buprenorphine according to claim 128, wherein the
15 amount of $0.14\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

135. Buprenorphine according to any one of claims 77 to 134, wherein the buprenorphine is for delayed release.

20 136. Buprenorphine according to any one of claims 77 to 134, wherein the buprenorphine is for delayed release in a sustained release formulation.

137. Buprenorphine according to any one of claims 77 to 134, wherein the buprenorphine is in the form of a
25 delayed-release particle or implant.

138. Buprenorphine according to claim 137, wherein the delayed-release particle or implant comprises a synthetic material.

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139. Buprenorphine according to claim 138, wherein the synthetic material is a polylactide, a polyglycolide or a polylactide/polyglycolide copolymer.

140. Buprenorphine according to any one of claims 77 to 134, wherein the buprenorphine is in the form of transdermal therapeutic system in the form of a patch for administration of the buprenorphine to the skin.

141. Buprenorphine according to claim 140, wherein the transdermal therapeutic system comprises a backing layer which is permeable to the buprenorphine, an adhesive reservoir layer and a re-detachable protective layer.

142. Buprenorphine according to claim 141, wherein the adhesive reservoir layer comprises 20 to 90 wt.% of polymer material, 0.1 to 30 wt.% of plasticizer, 0.1 to 20 wt.% of the buprenorphine, and 0.1 to 30 wt.% of a solvent for the buprenorphine, wherein the solvent for the buprenorphine is for remaining in the system after administration of the buprenorphine.

143. Buprenorphine according to claim 142, wherein the solvent is a compound with at least one acid group.

144. Buprenorphine according to any one of claims 77 to 143, wherein the buprenorphine is for administration at a release rate of between 1 $\mu\text{g/h}$ and 40 $\mu\text{g/h}$.

145. Buprenorphine according to any one of claims 77 to 143, wherein the buprenorphine is for administration at a release rate of between 2 $\mu\text{g/h}$ and 35 $\mu\text{g/h}$.

146. Buprenorphine according to any one of claims 77 to 143, wherein the buprenorphine is for administration at a release rate of between 5 $\mu\text{g/h}$ and 20 $\mu\text{g/h}$.

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147. Buprenorphine according to any one of claims 77 to 143, wherein the buprenorphine is for administration at a release rate of between 5 $\mu\text{g/h}$ and 10 $\mu\text{g/h}$.

148. Buprenorphine according to any one of claims 77 to 147, wherein the buprenorphine is for coadministration with a morphine antagonist.

149. Buprenorphine according to claim 148, wherein the morphine antagonist is one or more of naloxone, naltrexone and levallorphan.

150. Buprenorphine according to any one of claims 77 to 149, wherein the buprenorphine is in the form of the free base, the hydrochloride, the stearate, the citrate or the lactate.

151. Buprenorphine according to any one of claims 77 to 149, wherein the buprenorphine is in the form of the free base.

152. Buprenorphine according to any one of claims 77 to 149, wherein the buprenorphine is in the form of the hydrochloride.

153. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and buprenorphine, a racemate thereof, an enantiomer thereof, a diastereomer thereof, a mixture of enantiomers thereof, a mixture of diastereomers thereof, a base thereof or a salt thereof of a physiologically acceptable acid for treatment of one or more of an increased urge to urinate, and increased frequency of micturition and urinary incontinence.

154. A pharmaceutical composition according to claim 153, wherein the buprenorphine is in the form of the mixture of enantiomers.

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155. A pharmaceutical composition according to claim 153, wherein the buprenorphine is in the form of the mixture of diastereomers.

156. A pharmaceutical composition according to
5 claim 153, wherein the buprenorphine is in the form of the enantiomer.

157. A pharmaceutical composition according to claim 153, wherein the buprenorphine is in the form of the diastereomer.

10 158. A pharmaceutical composition according to any one of claims 153 to 157, wherein the one or more of the increased urge to urinate, the increased frequency of micturition and the urinary incontinence is urgency incontinence.

15 159. A pharmaceutical composition according to any one of claims 153 to 157, wherein the one or more of the increased urge to urinate, the increased frequency of micturition and the urinary incontinence is overactive bladder.

20 160. A pharmaceutical composition according to any one of claims 153 to 159, wherein the buprenorphine is for administration in a dose below the lower limit of a conventional dose for pain treatment.

25 161. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of less than 300 μg .

162. A pharmaceutical composition according to claim 161, wherein the amount of less than 300 μg of buprenorphine is the maximum amount of an individual dose.

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163. A pharmaceutical composition according to claim 161, wherein the amount of less than 300 μ g of buprenorphine is the maximum amount of a daily administration.

5 164. A pharmaceutical composition according to claim 161, wherein the amount of less than 300 μ g of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

165. A pharmaceutical composition according to any one
10 of claims 153 to 160, wherein the buprenorphine is in an amount of between 300 μ g and 1 μ g.

166. A pharmaceutical composition according to claim 165, wherein the amount of 300 μ g of buprenorphine is the maximum amount of an individual dose.

15 167. A pharmaceutical composition according to claim 165, wherein the amount of 300 μ g of buprenorphine is the maximum amount of a daily administration.

168. A pharmaceutical composition according to claim 165, wherein the amount of 300 μ g of buprenorphine is
20 the maximum amount of an individual dose and the maximum amount of a daily administration.

169. A pharmaceutical composition according to claim 165, wherein the amount of 1 μ g of buprenorphine is the minimum amount of an individual dose.

25 170. A pharmaceutical composition according to claim 165, wherein the amount of 1 μ g of buprenorphine is the minimum amount of a daily administration.

171. A pharmaceutical composition according to claim 165, wherein the amount of 1 μ g of buprenorphine is the

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minimum amount of an individual dose and the minimum amount of a daily administration.

172. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of between 250 μg and 5 μg .

173. A pharmaceutical composition according to claim 172, wherein the amount of 250 μg of buprenorphine is the maximum amount of an individual dose.

174. A pharmaceutical composition according to claim 172, wherein the amount of 250 μg of buprenorphine is the maximum amount of a daily administration.

175. A pharmaceutical composition according to claim 172, wherein the amount of 250 μg of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

176. A pharmaceutical composition according to claim 172, wherein the amount of 5 μg of buprenorphine is the minimum amount of an individual dose.

177. A pharmaceutical composition according to claim 172, wherein the amount of 5 μg of buprenorphine is the minimum amount of a daily administration.

178. A pharmaceutical composition according to claim 172, wherein the amount of 5 μg of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

179. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of between 200 μg and 10 μg .

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180. A pharmaceutical composition according to claim 179, wherein the amount of 200 μ g of buprenorphine is the maximum amount of an individual dose.

181. A pharmaceutical composition according to
5 claim 179, wherein the amount of 200 μ g of buprenorphine is the maximum amount of a daily administration.

182. A pharmaceutical composition according to claim 179, wherein the amount of 200 μ g of buprenorphine is the maximum amount of an individual dose and the maximum
10 amount of a daily administration.

183. A pharmaceutical composition according to claim 179, wherein the amount of 10 μ g of buprenorphine is the minimum amount of an individual dose.

184. A pharmaceutical composition according to
15 claim 179, wherein the amount of 10 μ g of buprenorphine is the minimum amount of a daily administration.

185. A pharmaceutical composition according to claim 179, wherein the amount of 10 μ g of buprenorphine is the minimum amount of an individual dose and the minimum
20 amount of a daily administration.

186. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of less than 4.3 μ g/kg of body weight.

187. A pharmaceutical composition according to
25 claim 186, wherein the amount of less than 4.3 μ g/kg of body weight of buprenorphine is the maximum amount of an individual dose.

188. A pharmaceutical composition according to claim 186, wherein the amount of less than 4.3 μ g/kg body

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weight of buprenorphine is the maximum amount of a daily administration.

189. A pharmaceutical composition according to claim 186, wherein the amount of less than $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

190. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of between $4.3\mu\text{g}/\text{kg}$ of body weight and $0.014\mu\text{g}/\text{kg}$ of body weight.

191. A pharmaceutical composition according to claim 190, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

15 192. A pharmaceutical composition according to claim 190, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of a daily administration.

20 193. A pharmaceutical composition according to claim 190, wherein the amount of $4.3\mu\text{g}/\text{kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

25 194. A pharmaceutical composition according to claim 190, wherein the amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

195. A pharmaceutical composition according to claim 190, wherein the amount of $0.014\mu\text{g}/\text{kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

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196. A pharmaceutical composition according to claim 190, wherein the amount of $0.014\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

5 197. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of between $3.6\mu\text{g/kg}$ of body weight and $0.07\mu\text{g/kg}$ of body weight.

198. A pharmaceutical composition according to
10 claim 197, wherein the amount of $3.6\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

199. A pharmaceutical composition according to claim 197, wherein the amount of $3.6\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of a daily
15 administration.

200. A pharmaceutical composition according to claim 197, wherein the amount of $3.6\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose and the maximum amount of a daily administration.

20 201. A pharmaceutical composition according to claim 197, wherein the amount of $0.07\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

202. A pharmaceutical composition according to claim 197, wherein the amount of $0.07\mu\text{g/kg}$ body weight of
25 buprenorphine is the minimum amount of a daily administration.

203. A pharmaceutical composition according to claim 197, wherein the amount of $0.07\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose
30 and the minimum amount of a daily administration.

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204. A pharmaceutical composition according to any one of claims 153 to 160, wherein the buprenorphine is in an amount of between 2.8 $\mu\text{g/kg}$ of body weight and 0.14 $\mu\text{g/kg}$ of body weight.

5 205. A pharmaceutical composition according to claim 204, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose.

206. A pharmaceutical composition according to claim 204, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of
10 buprenorphine is the maximum amount of a daily administration.

207. A pharmaceutical composition according to claim 204, wherein the amount of 2.8 $\mu\text{g/kg}$ body weight of buprenorphine is the maximum amount of an individual dose
15 and the maximum amount of a daily administration.

208. A pharmaceutical composition according to claim 204, wherein the amount of 0.14 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of an individual dose.

209. A pharmaceutical composition according to
20 claim 204, wherein the amount of 0.14 $\mu\text{g/kg}$ body weight of buprenorphine is the minimum amount of a daily administration.

210. A pharmaceutical composition according to claim 204, wherein the amount of 0.14 $\mu\text{g/kg}$ body weight of
25 buprenorphine is the minimum amount of an individual dose and the minimum amount of a daily administration.

211. A pharmaceutical composition according to any one of claims 153 to 210, wherein the buprenorphine is for delayed release.

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212. A pharmaceutical composition according to any one of claims 153 to 210, wherein the buprenorphine is for delayed release in a sustained release formulation.

213. A pharmaceutical composition according to any one
5 of claims 153 to 210, wherein the buprenorphine is in the form of a delayed-release particle or implant.

214. A pharmaceutical composition according to claim 213, wherein the delayed-release particle or implant comprises a synthetic material.

10 215. A pharmaceutical composition according to claim 214, wherein the synthetic material is a polylactide, a polyglycolide or a polylactide/polyglycolide copolymer.

216. A pharmaceutical composition according to any one of claims 153 to 210, wherein the buprenorphine is in the
15 form of transdermal therapeutic system in the form of a patch for administration of the buprenorphine to the skin.

217. A pharmaceutical composition according to claim 216, wherein the transdermal therapeutic system comprises a backing layer which is permeable to the
20 buprenorphine, an adhesive reservoir layer and a re-detachable protective layer.

218. A pharmaceutical composition according to claim 217, wherein the adhesive reservoir layer comprises 20 to 90 wt.% of polymer material, 0.1 to 30 wt.% of
25 plasticizer, 0.1 to 20 wt.% of the buprenorphine, and 0.1 to 30 wt.% of a solvent for the buprenorphine, wherein the solvent for the buprenorphine is for remaining in the system after administration of the buprenorphine.

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219. A pharmaceutical composition according to claim 218, wherein the solvent is a compound with at least one acid group.

220. A pharmaceutical composition according to any one
5 of claims 153 to 219, wherein the buprenorphine is for administration at a release rate of between 1 $\mu\text{g/h}$ and 40 $\mu\text{g/h}$.

221. A pharmaceutical composition according to any one
10 of claims 153 to 219, wherein the buprenorphine is for administration at a release rate of between 2 $\mu\text{g/h}$ and 35 $\mu\text{g/h}$.

222. A pharmaceutical composition according to any one
of claims 153 to 219, wherein the buprenorphine is for
administration at a release rate of between 5 $\mu\text{g/h}$ and
15 20 $\mu\text{g/h}$.

223. A pharmaceutical composition according to any one
of claims 153 to 219, wherein the buprenorphine is for
administration at a release rate of between 5 $\mu\text{g/h}$ and
10 $\mu\text{g/h}$.

20 224. A pharmaceutical composition according to any one
of claims 153 to 223, wherein the buprenorphine is for
coadministration with a morphine antagonist.

225. A pharmaceutical composition according to
claim 224, wherein the morphine antagonist is one or more of
25 naloxone, naltrexone and levallorphan.

226. A pharmaceutical composition according to any one
of claims 153 to 225, wherein the buprenorphine is in the
form of the free base, the hydrochloride, the stearate, the
citrate or the lactate.

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227. A pharmaceutical composition according to any one of claims 153 to 225, wherein the buprenorphine is in the form of the free base.

228. A pharmaceutical composition according to any one
5 of claims 153 to 225, wherein the buprenorphine is in the form of the hydrochloride.

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