Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2488220 C 2011/02/01

(11)(21) **2 488 220**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(86) Date de dépôt PCT/PCT Filing Date: 2003/05/26
(87) Date publication PCT/PCT Publication Date: 2003/12/04
(45) Date de délivrance/Issue Date: 2011/02/01
(85) Entrée phase nationale/National Entry: 2004/11/26
(86) N° demande PCT/PCT Application No.: EP 2003/005488
(87) N° publication PCT/PCT Publication No.: 2003/099267
(30) Priorité/Priority: 2002/05/29 (DE102 24 108.2)

(51) Cl.Int./Int.Cl. *A61K 31/13* (2006.01), *A61K 9/16* (2006.01), *A61K 9/20* (2006.01)

(72) Inventeurs/Inventors:
BARTHOLOMAUSE, JOHANNES, DE;
ZIEGLER, IRIS, DE

(73) Propriétaire/Owner:
GRUENENTHAL GMBH, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : MEDICAMENT CONTENANT DU 1-DIMETHYLAMINO-3-(3-METHOXYPHENYL)-2-METHYLPENTAN-3-OL, LIBERANT LE PRINCIPE ACTIF DE MANIERE RETARDEE

(54) Title: MEDICAMENT WITH DELAYED ACTIVE CONSTITUENT RELEASE CONTAINING 1-DIMETHYLAMINO-3-(3-METHOXYPHENYL)-2-METHYLPENTAN-3-OL

(57) Abrégé/Abstract:
The invention relates to a pharmaceutical formulation with delayed release of active constituent, which contains 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or one of its pharmaceutically acceptable salts in a matrix, with delayed release of active constituent, wherein the matrix contains 1 to 80 wt.% of one or more hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix- forming agents and has the following in vitro dissolution rate: 3-35 wt.% (referred to 100 wt.% of active constituent) of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 0.5 hour, 5-50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 1 hour, 10-75 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 2 hours, 15-82 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 3 hours, 30-97 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 6 hours, more than 50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 12 hours, more than 70 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 18 hours, and more than 80 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 24 hours.

Abstract

The invention relates to a pharmaceutical formulation with delayed release of active constituent, which contains 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or one of its pharmaceutically acceptable salts in a matrix, with delayed release of active constituent, wherein the matrix contains 1 to 80 wt.% of one or more hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix-forming agents and has the following *in vitro* dissolution rate: 3-35 wt.% (referred to 100 wt.% of active constituent) of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 0.5 hour, 5-50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 1 hour, 10-75 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 2 hours, 15-82 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 3 hours, 30-97 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 6 hours, more than 50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 12 hours, more than 70 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 18 hours, and more than 80 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 24 hours.

Medicament with delayed active constituent release containing 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol

The present invention relates to a pharmaceutical formulation with delayed active constituent release that contains 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or one of its pharmaceutically acceptable salts in a matrix.

1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol is known from EP 0 693 475 B1 as an analgesically active medicament and may be administered orally. The usual formulations for oral administration of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol lead to a rapid release of the active constituent in the gastrointestinal tract, resulting in a rapid onset of the analgesic effect. At the same time it is observed that the effect rapidly wears off. Accordingly the treatment of severe chronic pain using 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol has hitherto required the medicament to be administered at relatively short intervals, for example 4 to 6 times a day, in order thereby to ensure a sufficient concentration of active constituent in the patient's blood plasma. The necessity of a frequent dosage easily leads however to mistakes in administration of the medicament as well as to undesired plasma concentration fluctuations, which has a deleterious effect as regards patient compliance and therapeutic usefulness, especially in the treatment of chronic pain conditions. A pharmaceutical application form with delayed release (retard formulation) for oral administration of the active constituent 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol is therefore desirable.

In the prior art retard formulations are generally known for a large number of various active constituents. Conventional retard forms include, *inter alia*, coated retard forms and matrix retard forms.

In the case of coated retard forms such as are described for example in DE 36 25 458 A1, the core of a pharmaceutical composition containing an active constituent is provided with a coating of one or more hydrophilic and/or hydrophobic polymers that delays the release of the active constituent.

In matrix retard forms the active constituent is contained in a matrix formed from one or more carrier materials, which controls the release of the active constituent. Thus for example, DE 33 09 516 A1 discloses a process for the production of matrix formulations with hydroxypropylmethyl-cellulose (HPMC) as carrier material and to some extent a delayed release of the active constituent, wherein the active material does not comprise more than one third of the weight of the formulation and consists of at least one hydroxypropylmethylcellulose that has a methoxy content of 16-24 wt.%, an hydroxypropyl content of 4-32 wt.% and a number average molecular weight of at least 50,000. The formulations disclosed in DE 33 09 516 A1 contain HPMCs with viscosities (in 2 wt.% aqueous solution at 20°C) between 15 and 30,000 cPs (15 to 30,000 mPa·s). A release behaviour independent of the pH value of the dissolution medium is not disclosed in DE 33 09 516 A1.

An object of the present invention is accordingly to provide a pharmaceutical formulation with delayed active

constituent release containing 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol.

This object is achieved by a pharmaceutical formulation with delayed release that contains 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof in a matrix with delayed release of active constituent, wherein the matrix contains 1 to 80 wt.%, preferably 5 to 80 wt.%, of one or more hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix-forming agents, and has the following *in vitro* release rate measured using the Ph. Eur. paddle method at 75 rpm in a buffer (according to Ph. Eur.) at a pH value of 6.8 at 37°C and with UV spectrometric detection:

3-35 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol (referred to 100 wt.% of active constituent) released after 0.5 hour,

5-50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 1 hour

10-75 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 2 hours

15-82 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 3 hours

30-97 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 6 hours

more than 50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 12 hours,

more than 70 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 18 hours,

more than 80 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 24 hours.

According to one aspect of the present invention, there is provided a pharmaceutical formulation with delayed release, comprising, as active constituent, 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof in a matrix with delayed release of the active constituent; wherein the matrix comprises 1 to 80 wt.% of at least one pharmaceutically acceptable hydrophilic or hydrophobic matrix-forming polymer and exhibiting the following *in vitro* release rates measured using the Ph. Eur. paddle method at 75 rpm in a buffer (according to Ph. Eur.) at a pH value of 6.8 at 37°C and with UV spectrometric detection: 3-35 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 0.5 hour, 5-50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 1 hour, 10-75 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 2 hours, 15-82 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 3 hours, 30-97 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 6 hours, more than 50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 12 hours, more than 70 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 18 hours, more than 80 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 24 hours, wherein the wt.% is a wt.% of total active constituent.

According to another aspect of the present invention, there is provided a tablet for twice daily oral administration of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof comprising a pharmaceutical formulation as described herein.

According to still another aspect of the present invention, there is provided a use of a pharmaceutical formulation as described herein for treating increased urinary urgency or urinary incontinence.

According to yet another aspect of the present invention, there is provided a use of a tablet as described herein for treating increased urinary urgency or urinary incontinence.

According to a further aspect of the present invention, there is provided a use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof for treating increased urinary urgency or urinary incontinence, wherein 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as described herein.

According to yet a further aspect of the present invention, there is provided a use of a pharmaceutical formulation as described herein for treating pain.

According to still a further aspect of the present invention, there is provided a use of a tablet as described herein for treating pain.

According to another aspect of the present invention, there is provided a use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof for treating pain wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as described herein.

It has surprisingly been found that the formulation according to the invention provides for the delayed release of the active constituent 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol when administered orally and is thus suitable for administration at intervals of at least 12 hours. The formulation according to the invention accordingly provides a treatment for pain as well as a treatment for increased urinary urgency or urinary incontinence, in particular urgency incontinence and stress incontinence, in connection with which 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol need be administered only once daily, for example at intervals of 24 hours, or twice daily, for example at intervals of 12 hours, in order to ensure a sufficient plasma concentration of the active constituent. A corresponding effect duration and the maintenance of a sufficient blood plasma level is confirmed by simulation studies and experimental investigations.

It is particularly surprising in this connection that the formulation according to the invention not only guarantees, due to the delayed release, a long-lasting therapeutic effectiveness over a relatively long period (at least 12 hours), but at the same time on first administration of the medicament permits a rapid build up of the active constituent in the plasma, which leads to a rapid pain relief in the patient (rapid onset effect). Thus, on administration of the formulation according to the invention to a patient suffering pain, the pain can be rapidly alleviated without the analgesic effect also rapidly attenuating. The formulation according to the

invention thus combines properties of a formulation with immediate release of active constituent - rapid relief of pain due to sufficiently high active substance concentration shortly after administration of the medicament - with properties of a formulation with delayed release - long-lasting analgesic effect on account of a sufficiently high active constituent level over a prolonged time. The patient suffering from pain can thus effectively alleviate his/her pain by taking the analgesic in the formulation according to the invention and at the same time can, without further measures and simply by regular administration of the medicament at intervals of 12 (or 24) hours, effectively relieve the pain for a relatively long period.

It is also convenient that, due to the constant and sufficiently high active constituent level of the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol compound over a fairly long time that is achieved by the formulations and at the same time without further measures and simply by administration at intervals of 12 (or 24) hours, it is possible effectively to treat, alleviate or relieve over a relatively long time increased urinary urgency or urinary incontinence, in particular urgency incontinence and stress incontinence.

The active constituent of the formulation according to the invention is contained in a matrix with delayed release. It is however also conceivable for the active constituent to be contained in a matrix exhibiting a conventional release behaviour and to achieve the delayed release by a retard coating.

In the case where the formulation according to the invention contains a matrix with delayed release, the matrix comprises 1-80 wt.% of one or more hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix-forming agents, for example gums, cellulose ethers, cellulose esters, acrylic resins, materials derived from proteins, fats, waxes, fatty alcohols or fatty acid esters. When using hydrophilic polymers as matrix-forming agent it is preferred that the matrix contains 5 to 80 wt.% of matrix-forming agent.

The present invention also provides a pharmaceutical formulation that contains 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof in a matrix with delayed active constituent release, the matrix containing 1 to 80 wt.%, in particular 5 to 80 wt.%, of one or more hydrophilic or hydrophobic polymers as pharmaceutically acceptable matrix-forming agent, and which is characterised in that it comprises as pharmaceutically acceptable matrix-forming agent cellulose ethers and/or cellulose esters that have a viscosity of 3000 to 150,000 mPa·s in a 2 wt.% aqueous solution at 20°C. (The viscosity determination is carried out by means of capillary viscosimetry according to Pharm. Eu.) The compositions have the release profile according to the invention specified above.

Preferably cellulose ethers and/or cellulose esters that in a 2 wt.% aqueous solution at 20°C have a viscosity between 10,000 mPa·s, in particular 50,000 mPa·s, and 150,000 mPa·s, are used as pharmaceutically acceptable matrix-forming agents.

Particularly suitable pharmaceutically acceptable matrix-forming agents are selected from the group comprising hydroxypropylmethylcelluloses (HPMC), hydroxyethylcelluloses, hydroxypropylcelluloses (HPC), methylcelluloses, ethylcelluloses and carboxymethylcelluloses, and in particular are selected from the group comprising HPMCs, hydroxyethylcelluloses and HPCs. Most particularly preferred are HPMCs with a viscosity of ca. 100,000 mPa·s measured in a 2 wt.% aqueous solution at 20°C.

The active constituent 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol may be present as such, i.e. as free base, but may also be present in the form of a pharmaceutically acceptable salt, for example as the hydrochloride. The preparation of the free base is known from EP 0 693 475 A1. Insofar as the preparation of pharmaceutically acceptable salts - such as the hydrochloride - is also not disclosed in EP 0 693 475 A1, these may be obtained from the free base by means of methods generally known in the prior art.

1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol has two asymmetry centres, with the result that the compound may be present in the form of four different stereoisomers. In the formulation according to the invention 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol may be present as a mixture of all four diastereomers in an arbitrary mixture ratio, but also as a mixture of two or three of the four stereoisomers, or in stereoisomer-pure form. Preferred stereoisomers are in this connection (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol and (-)-(1S,2S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol, which may be present in the formulation

according to the invention as a mixture, in particular as a 1:1 mixture (racemate), or particularly preferably in isomer-pure form. The term "active constituent" is therefore understood for the purposes of the present invention to denote 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol compound as a mixture of various of its stereoisomers or as one of its pure stereoisomers, in each case as a free base or in the form of a pharmaceutically acceptable salt.

In the medicaments according to the invention the content of delayed release active constituent is preferably between 0.5 and 85 wt.% and the content of pharmaceutically acceptable matrix-forming agent is between 8 and 40 wt.%. Particularly preferred are medicaments with a content of delayed release active constituent of between 3 and 70 wt.%, in particular between 8 and 66 wt.%, and a content of pharmaceutically acceptable matrix-forming agent of between 10 and 35 wt.%, in particular between 10 and 30 wt.%. If the enantiomer-pure (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol (or a mixture of the (+) and (-) enantiomers with a large excess of the (+) enantiomer) is used as active constituent, it is particularly preferred if the content of active constituent is at the lower level, i.e. is between 0.5 and 25 wt.% (referred to the total weight). If the enantiomer-pure (-)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol (or a mixture of the (+) and (-) enantiomers with a large excess of the (-) enantiomer) is used as active constituent, it is particularly preferred if the content of active constituent is between 16 and 66 wt.%.

Further constituents of the matrix of the formulation according to the invention may optionally include digestible long-chain (i.e. with 8 to 50 C atoms, preferably 12 to 40 C atoms) unsubstituted or substituted hydrocarbons, such as for example fatty alcohols, fatty acid glyceryl esters, mineral oils and vegetable oils, as well as waxes, hydrocarbons with a melting point between 25° and 90°C being preferred. In particular fatty alcohols are preferred, most particularly preferred being lauryl alcohol, myristyl alcohol, stearyl alcohol, cetyl alcohol and cetylstearyl alcohol. Their content in the matrix is 0 to 60 wt.%. Alternatively or in addition polyethylene glycols may also be contained in the matrix in an amount of 0 to 60 wt.%.

The pharmaceutical formulations according to the invention may in addition contain as further constituents pharmaceutically conventional auxiliary substances such as fillers, for example lactose, microcrystalline cellulose (MCC) or calcium hydrogen phosphate, as well as slip agents, intestinal lubricants and flow regulating agents, for example talcum, magnesium stearate, stearic acid and/or highly dispersed silicon dioxide, whose total weight in the tablet is between 0 and 80 wt.%, preferably between 5 and 65 wt.%.

In many cases the release rate of an active constituent from an application form depends on the pH of the release medium. This may vary in a pH range from below 1 to about 8 during passage of the medicament through the gastrointestinal tract. These variations may differ from person to person taking the medicament. Also, there may be a different pH value/time profile during passage through the gastrointestinal tract in one and the same person from

one administration to the next. If the release rate of the active constituent from the medicament depends on the pH, this can lead to different release rates *in vivo* and thus to different bioavailability behaviours. The release profiles of the active constituent (in the form of the base or one of its pharmaceutically acceptable salts) from a pharmaceutical formulation according to the invention are however surprisingly independent of the pH value, such as may physiologically occur during passage through the gastrointestinal tract. The release profiles at an ambient pH value of 1.2, 4.0 and 6.8 are identical to one another and also when compared to the release during a pH value/time profile from pH 1.2 through pH 2.3 and pH 6.8 up to pH 7.2.

It has been found that for achieving the delayed release of active constituent from the formulation according to the invention, preferably present in tablet form, it is immaterial whether, under otherwise identical dimensions and identical composition of the tablet as regards the active constituent, the matrix-forming agent and the optional constituents, a water-soluble filler, for example lactose, is used as filler, or an insoluble filler that does not swell in the aqueous medium, for example calcium hydrogen phosphate, is used as filler, or an insoluble filler that swells in aqueous medium, for example microcrystalline cellulose, is used as filler. All such medicaments exhibit a release behaviour corresponding to one another.

It is furthermore surprising that in the compositions according to the invention, for a given amount of active constituent the amount of matrix-forming agent and the amount of optional constituents may in each case vary over

a relatively large range without the therapeutic effectiveness of at least 12 hourly or twice daily administration being compromised (as long as the quantitative limits for active constituent, matrix-forming agent and the further, optional constituents are maintained). An effectiveness of at least 12 hours is ensured for example with a content of active constituent of ca. 32.25 wt.% (referred to the weight of the total composition) in a composition comprising ca. 12.9 wt.% of HPMC with a viscosity of 100,000 mPa·s as matrix-forming agent and a content of for example MCC as filler of ca. 52.6 wt.%, as well as in a composition comprising ca. 25.8 wt.% of the same HPMC and ca. 39.7 wt.% of MCC (or lactose monohydrate) with otherwise the same amounts of slip agent, intestinal lubricant and flow regulating agent. The same also applies to compositions according to the invention with a higher or lower content of active constituent within the specified limits.

Also extremely surprising is the observation that when administering the pharmaceutical formulations according to the invention with delayed release of active constituent to human experimental subjects, despite the high first-pass effect for the active constituent an unaltered bioavailability is achieved, contrary to expectations, compared to formulations with immediate release of active constituent.

Those compositions according to the invention are furthermore preferred whose t_{max} value in the plasma concentration/time diagram *in vivo* is between 2 and 10 hours, in particular between 3.5 and 6 hours and most particularly preferably between 4 and 5.5 hours after oral

administration of the composition, i.e. whose peak plasma level occurs in the aforementioned timeframes.

The formulation according to the invention contains the active constituent 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol as such and/or as a pharmaceutically acceptable salt in an amount of normally 2.5 to 800 mg, in particular 5 to 400 mg, most particularly preferably 10 to 250 mg (weight of the active constituent 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol as hydrochloride) per dosage unit, wherein the release behaviour of the formulation according to the invention is not influenced by the exact amount of the active constituent as long as the quantitative limits specified above are maintained. It is preferred if the more active (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol is present in an amount of 2.5 to 80 mg, in particular 5 to 40 mg and most particularly preferably in an amount of 10 to 25 mg of active constituent (referred to the hydrochloride) in the formulations according to the invention, and specifically with the proviso that the quantitative limits specified above are maintained.

Pharmaceutically acceptable (or tolerable) salts of the active constituent are, within the context of the present invention, those salts of the active constituent that are physiologically compatible in pharmaceutical use, in particular for use in mammals and/or humans. Such pharmaceutically acceptable salts may be formed for example with inorganic or organic acids.

The pharmaceutical formulations according to the invention may exist in the form of simple tablets as well as coated tablets, for example as film tablets or sugar-coated

tablets. Usually the tablets are round and biconvex; oblong tablet shapes that allow the tablet to be divided are also possible. Furthermore granules, spheroids, pellets or microcapsules are also possible, which may be packed in sachets or capsules or compressed into dispersible tablets.

One or more coating layers may be used for the coated tablets. Suitable as coating material are known hydroxypropylmethylcelluloses with a low viscosity of ca. 1 to 100 mPa·s and low molecular weight of <10,000 (e.g. Pharmacoat 606 with a viscosity of 6 mPa·s in a 2 wt.% aqueous solution at 20°C), which only slightly affect the release profile of the medicaments according to the invention. Diffusion coatings known to the person skilled in the art, for example based on swellable but water-insoluble poly(meth)acrylates, lead to a modulation of the delay of the release of active constituent from pharmaceutical formulations according to the invention. The tablet core containing the active constituent and releasing the latter in a delayed manner, with an active constituent content preferably between 0.5 and 85 wt.%, particularly preferably between 3 and 70 wt.% and most particularly preferably between 8 and 66 wt.%, may be coated by various methods known to the person skilled in the art, for example sugar coating, spraying from solutions or suspensions or by powder application methods, with additional active constituent that is not released in a delayed manner like the initial dose, although this is not absolutely necessary for the desired delayed release with simultaneous rapid build up of the active constituent for the rapid relief of pain on first administration of the pharmaceutical formulation according to the invention.

Further modifications include multilayer tablets and laminated tablets, in which 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or one of its pharmaceutically acceptable salts in one or more layers of the multilayer tablet with a content of active constituent preferably between 0.5 and 85 wt.%, particularly preferably between 3 and 70 wt.% and most particularly preferably between 8 and 66 wt.%, and in the core of the laminated tablet with a content of active constituent preferably between 0.5 and 85 wt.%, particularly preferably between 3 and 70 wt.% and most particularly preferably between 8 and 66 wt.%, is released in a delayed manner by a pharmaceutically acceptable matrix-forming agent, and the release of the active constituents in one or more layers of the multilayer tablet or the outer lamination layer of the laminated tablets takes place in an unretarded manner. Multilayer tablets and laminated tablets may contain one or more coatings free of active constituent.

Instead of a retard matrix it is also possible to use in the pharmaceutical formulation with delayed release a normal release matrix with a coating that delays the release of the active constituent. In this connection the active constituent may for example be contained in a conventional matrix of microcrystalline cellulose and optionally further pharmaceutical auxiliary substances such as binders, fillers, slip agents, intestinal lubricants and flow regulating agents, which are coated or covered with a material that controls the delayed release of the active constituent in aqueous medium. Suitable coating agents are for example water-insoluble waxes and polymers such as polymethacrylates (Eudragit or the like) or water-insoluble celluloses, in particular ethyl cellulose. Optionally the coating material may also contain water-soluble polymers

such as polyvinylpyrrolidone, water-soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose, other water-soluble agents such as Polysorbate 80, or hydrophilic pore-forming agents such as polyethylene glycol, lactose or mannitol.

The compositions according to the invention may for example be produced by the following general methods:

the constituents of the composition (active constituent, matrix-forming agent and optional constituents) are weighed out in turn and then screened on a conventional screening machine. The Quadro™ Comil™ U10 screening machine may for example be used for this purpose, a normal screen size being ca. 0.813 mm. The screened material is then mixed in a container mixer, for example in a Bohle container mixer, under the following typical operating conditions: duration ca. 15 minutes ± 45 sec. at a rotational speed of 20 ± 1 rpm. The powder mixture that is obtained is then compressed into tablets in a pelletising machine. A Korsch EKO pelletising machine with a round 10 mm diameter stamp having the contour of sugar-coated pills may for example be used for this purpose. Alternatively a compaction of the powder mixture and subsequent screening (Comil 3 mm friction slicing screen followed by 1.2 mm round hole screen) of the mouldings may be carried out, wherein the resultant granules are then compressed as described above with the addition of lubricant (e.g. magnesium stearate) on for example an EKO pelletising machine with 10 mm round stamps. The granulation may also be carried out by wet granulation based on aqueous or organic solvents; aqueous solvents with or without suitable binders are preferred. The production process may be adapted without any

difficulty to the respective requirements and to the desired application form according to procedures that are well known in the prior art.

The production of pharmaceutical formulations according to the invention is characterised by a high reproducibility of the release properties of the resultant compositions that contain 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or one of its pharmaceutically acceptable salts. The release profile of medicaments according to the invention was found to be stable over a storage time of at least one year under the conventional storage conditions according to the ICH Q1AR Stability Testing Guideline.

A single or double daily administration of a pharmaceutical formulation according to the invention to the patient ensures a good therapeutic effectiveness not only in chronically severe pain but also a good therapeutic effectiveness in the treatment of increased urinary urgency or urinary incontinence, in particular stress incontinence and urgency incontinence.

Accordingly, the present invention also provides for the use of a pharmaceutical formulation according to the invention or a tablet according to the invention for the production of a medicament for treating pain, in particular chronic, visceral, neuropathic or acute pain or inflammation pain.

The invention furthermore provides for the use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol for the production of a medicament for treating pain, in particular chronic, visceral, neuropathic or acute pain or inflammation pain, in which 1-dimethylamino-3-(3-

methoxyphenyl)-2-methylpentan-3-ol is contained in a pharmaceutical formulation according to the invention.

A further object of the present invention was to discover substances or pharmaceutical formulations or medicaments that are helpful in the treatment of increased urinary urgency or urinary incontinence, and that in particular release effective doses that exhibit fewer side effects and/or analgesic effects than medicaments known from the prior art.

Urinary incontinence is the involuntary voiding of urine. This occurs in an uncontrolled manner if the pressure within the bladder exceeds the pressure that is necessary to close the ureter. Causes may include on the one hand an increased internal bladder pressure (for example due to detrusor instability) resulting in urgency incontinence, and on the other hand a reduced sphincter pressure (for example after childbirth or surgical intervention), resulting in stress incontinence. The detrusor is the collective term for the coarse bundles of multilayer muscles of the bladder wall, whose contraction leads to release of urine; the sphincter is the constrictor muscle of the urethra. Mixed forms of these types of incontinence as well as so-called overflow incontinence (e.g. in benign prostatic hyperplasia) or reflex incontinence (e.g. after spinal cord injury) occur. Further details can be found in Chutka, D.S. and Takahashi, P.Y., 1998, Drugs 550: 587-595.

Urinary urgency is the state of increased bladder muscle tension leading to voiding of urine (micturition) when the bladder is almost full (or when its capacity is exceeded). This muscle tone acts as a stimulus to pass urine. Increased urinary urgency is understood in this connection

to mean in particular the occurrence of premature or more frequent and sometimes even painful urinary urgency up to so-called dysuria. This consequently leads to a significantly increased frequency of micturition. Causes may include, *inter alia*, inflammation of the bladder and neurogenic bladder disorders, as well as also bladder tuberculosis. However, all causes have not yet been elucidated.

Increased urinary urgency and also urinary incontinence are regarded as extremely unpleasant and there is therefore a clear need to achieve the greatest possible long-term improvement in patients affected by these medical conditions.

Increased urinary urgency and in particular urinary incontinence are normally treated with substances that act on the reflexes of the lower urinary tract (Wein A.J., 1998, Urology 51 (Suppl. 21): 43-47). In general these are medicaments that have a blocking effect on the detrusor muscle, which is responsible for the internal bladder pressure. These medicaments include for example parasympatholytics such as oxybutynin, propiverine or tolterodine, tricyclic antidepressants such as imipramine, or muscle relaxants such as flavoxate. Other medicaments that in particular increase the resistance of the urethra or cervix of the bladder have similarities with α-adrenoreceptors such as ephedrine, with β-adrenoreceptors such as clenbutarol, or are hormones such as oestradiol. Also, certain opioids, diarylmethylpiperazines and diarylmethylpiperidines have been described for this medical condition in WO 93/15062.

In the medical conditions that are of interest here, it should be noted that in general these involve the very long-term use of medicaments and, in contrast to many situations in which analgesics are used, patients suffer very unpleasant but not intolerable discomfort. Accordingly in this case - even more than with analgesics - care should be taken to avoid side effects if the patient does not wish to exchange one discomfort for another. Furthermore, in the long-term treatment of urinary incontinence analgesic effects are also largely undesirable.

Yet another object of the present invention was accordingly to find substances or pharmaceutical formulations or medicaments that are helpful in the treatment of increased urinary urgency or urinary incontinence.

It was now surprisingly found that 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol and in particular the pharmaceutical formulations according to the invention containing 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol have an outstanding effect on bladder function and accordingly are ideally suitable for treating the corresponding medical conditions.

The present invention accordingly also provides for the use of a pharmaceutical formulation according to the invention or a tablet according to the invention for producing a medicament for treating increased urinary urgency or urinary incontinence.

The invention in addition provides for the use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol for the production of a medicament for treating increased

urinary urgency or urinary incontinence, in which 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol is contained in a pharmaceutical formulation according to the invention.

Examples

The examples serve to illustrate the present invention and preferred embodiments, but are not intended to restrict the scope thereof.

Example 1

Matrix tablets with the following composition per tablet

1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	5 mg
Hydroxypropylmethylcellulose (Metolose 90 SH 100,000 from the Shinetsu company), 100,000 mPa·s	80 mg
Microcrystalline cellulose (Avicel™PH 101 from the FMC company)	50 mg
Lactose monohydrate (Lactose 200 from the Meggie company)	169 mg
Highly dispersed silicon dioxide	3 mg
Magnesium stearate	3 mg
Total amount	310 mg

were produced in the following way in a batch size of 2000 tablets:

All constituents were weighed out and screened on a Quadro Comil U10 screening machine using a screen size of 0.813 mm, mixed in a container mixer (Bohle LM 40) for 15 minutes ± 15 sec. at a rotational speed of 20 ± 1 rpm, and compressed on a Korsch EKO eccentric press into tablets with a diameter of 10 mm having the contours of sugar-

coated pills, a convex radius of 8 mm and a mean tablet weight of 310 mg.

The *in vitro* release was measured using the Ph. Eur. paddle method at 75 rpm in 900 ml of buffer pH 6.8 according to Ph. Eur. at 37°C and with UV spectrometric detection, and is given in the following table.

Time [min]	**Released total amount of the active constituent [%]**
0	0
30	17
240	75
480	95
720	100

Example 2

Matrix tables with the following composition per tablet

1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	50 mg
Hydroxypropylmethylcellulose (Metolose 90 SH 100,000 from the Shinetsu company), 100,000 mPa·s	80 mg
Microcrystalline cellulose (Avicel PH 101 from the FMC company)	174 mg
Highly dispersed silicon dioxide	3 mg
Magnesium stearate	3 mg
Total amount	310 mg

were produced in the following way in a batch size of 2000 tablets:

All constituents were weighed out and screened on a Quadro Comil U10 screening machine using a screen size of

0.813 mm, mixed in a container mixer (Bohle LM 40) for 15 minutes ± 15 sec. at a rotational speed of 20 ± 1 rpm, and compressed on a Korsch EKO eccentric press into tablets with a diameter of 10 mm having the contours of sugar-coated pills, a convex radius of 8 mm and a mean tablet weight of 310 mg.

The *in vitro* release was measured using the Ph. Eur. paddle method at 75 rpm in 900 ml of buffer pH 6.8 according to Ph. Eur. at 37°C and with UV spectrometric detection, and is given in the following table.

Time [min]	**Released total amount of the active constituent [%]**
0	0
30	20
240	63
480	81
720	91

Example 3

Matrix tables with the following composition per tablet

1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	100 mg
Hydroxypropylmethylcellulose (Metolose 90 SH 100,000 from the Shinetsu company), 100,000 mPa·s	80 mg
Microcrystalline cellulose (Avicel PH 101 from the FMC company)	94 mg
Lactose monohydrate (Lactose 200 from the Meggie company)	30 mg
Highly dispersed silicon dioxide	3 mg
Magnesium stearate	3 mg
Total amount	310 mg

were produced in the following way in a batch size of 2000 tablets:

All constituents were weighed out and screened on a Quadro Comil U10 screening machine using a screen size of 0.813 mm, mixed in a container mixer (Bohle LM 40) for 15 minutes ± 15 sec. at a rotational speed of 20 ± 1 rpm, and compressed on a Korsch EKO eccentric press into tablets with a diameter of 10 mm having the contours of sugar-coated pills, a convex radius of 8 mm and a mean tablet weight of 310 mg.

The *in vitro* release was measured using the Ph. Eur. paddle method at 75 rpm in 900 ml of buffer pH 6.8 according to Ph. Eur. at 37°C and with UV spectrometric detection, and is given in the following table.

Time [min]	Released total amount of the active constituent [%]
0	0
30	22
240	69
480	88
720	96

Tablets according to Example 3 were stored for 3 months at 40°C and 75% relative atmospheric humidity, for 9 months at 25°C and 9 months at 30°C (storage conditions according to ICH. The *in vitro* release was then redetermined using the Ph. Eur. paddle method at 75 rpm in 900 ml buffer pH 6.8 according to Ph. Eur. at 37°C and with UV spectrometric detection, and is shown in the following table:

Time [min]	Storage Conditions		
	9 Months/25°C	9 Months/30°C	3 Months/40°C 75% relative humidity
	Released total amount of the active constituent [%]		
0	0	0	0
30	21	21	21
240	73	72	77
480	93	92	94
720	100	99	100

Example 4

Matrix tablets with the following composition per tablet

(-)-(1R,2R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	100 mg
Cellactose (Meggie)	72.5 mg
Hydroxyethylcellulose (Natrosol 250 HX from the Hercules company)	12.5 mg
Cutina HR (Henkel)	150 mg
Talcum	3 mg
Magnesium stearate	2 mg
Total amount	340 mg

were produced in the following way in a batch size of 200 tablets:

The active constituent, Cellactose™, Natrosol™ and Cutina™ were mixed, then heated in a drying cabinet to 80°C, and granulated in a Kenwood™ Chef kitchen mixer. The cooled granules were sieved through a 1 mm screen. After mixing with magnesium stearate and talcum, the granules were compressed in an EKO eccentric press (Korsch) into 6 x 15 mm large oblong tablets with a fracture notch.

The *in vitro* release was measured as in Example 1.

Time [min]	Released total amount of the active constituent [%]
0	0
30	10
240	53
480	69
720	80
900	98

Example 5

Pellets with the following composition

(-)-(1R,2R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	100 mg
Low-substituted hydroxypropylcellulose (L-HPC LH 31 from the Shinetsu company)	75 mg
Aquacoat (aqueous ethylcellulose dispersion from the FMC company) (calculated as dry substance)	20 mg
Microcrystalline cellulose (Avicel PH 101 from the FMC company)	75 mg
Dibutyl sebacate (DBS)	4 mg
Tween 80	0.4 mg
Total amount	274.4 mg

were produced in the following way:

The active constituent, Avicel and L-HPC were mixed in a planetary mixer (Kenwood K mixer) for 10 minutes and then granulated with water. The moist granules were extruded in a Nica extruder with a 0.8 x 0.8 mm matrix and then rounded for 10 minutes in a Nica spheroniser at 500 rpm (load 1 kg). The pellets were dried overnight in a drying cabinet at 50°C and then graded in screening fractions. Pellets of size 0.6-1.0 mm (yield ca. 95%) were coated in the WSG (smooth GPCG1 with Wurster insert) at feed air temperatures of 60°C (product temperature 40°C) with an aqueous dispersion of Aquacoat™ and DBS (20%, calculated in terms of Aquacoat solids content), so as to produce a weight increase of 9.8% (referred to the initial weight). The dispersion was produced according to the manufacturer's data (FA, FMC), and the DBS together with Tween 80 were homogenised in part of the water and then added to the diluted Aquacoat dispersion. The ready-for-use dispersion

had a solids content of 20 wt.% and was stirred for at least 3 hours. The coated pellets were dried in the WSG and heat treated in the drying cabinet (2 hours at 60°C). The release was determined similarly to Example 1, but according to the basket method at 100 rpm.

Time [min]	Released total amount of the active constituent [%]
0	0
30	2
240	29
480	67
720	78
900	89
1080	101

Example 6: List of tested substances:

A list of the compounds tested for their effectiveness is given below:

Name	Cmpd. No.
(2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	1
(+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	2
(-)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol; hydrochloride	21

Example 8: Cystometry test system on conscious fresh rats

Cystometry investigations were carried out on fresh female Sprague-Dawley rats according to 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 investigated in the conscious state while freely moving. The bladder catheter was connected to a pressure gauge and an injection pump. The animals were placed in metabolic cages that enabled the volume of urine to be measured. Physiological saline solution was infused (10 ml/hour) into the emptied bladder and the bladder pressure and volume of urine were continuously recorded. After a stabilisation phase a 20-minute phase was recorded that was characterised by normal, reproducible micturition cycles. The following parameters among others were measured:

- threshold pressure TP, bladder pressure immediately before micturition,
- bladder capacity BC, residual volume after prior micturition plus volume of infused solution during the filling phase,
- intercontraction interval ICI, i.e. the time interval between consecutive micturition.

An increase in the threshold pressure (TP) indicates an important therapeutic effect in one of the medical conditions covered by the invention. Also, the intercontraction interval (ICI) is an important parameter for measuring the physiological effectiveness of a substance in the treatment of urinary incontinence, as is the bladder capacity (BC). In this connection, on account

of the widely differing causes of the symptoms of these disease patterns it is not necessary to influence positively all three parameters in order for a medicament to be effective. It is therefore perfectly adequate if a positive effect is demonstrated in only one of these parameters in order for the medicament to be of use in urinary incontinence or increased urinary urgency.

After recording three reproducible micturition cycles to provide a baseline value, the test substances (**1** (1.0 mg/kg), **2** (0.1; 0.3 and 0.5 mg/kg) and **21** (0.5 mg/kg), in a vehicle comprising 0.9% NaCl were applied intravenously and the effect on the cystometric parameters was recorded at 90 to 120 minutes. In the effect maximum the mean value of 3 micturition cycles was determined and recorded as a percentage change compared to the baseline value (Table 1).

Compound: (Concentration)	**TP** Threshold Pressure	**BC** Bladder Capacity	**ICI** Inter-Contraction Interval
1 1.0 mg/kg iv (n=9)	+94%**	+31%***	+42%
2 0.1 mg/kg iv (n=5)	+28.5%**	+7.8%	+15.6%
0.3 mg/kg iv (n=8)	+122%**	+33%*	+28%*
0.5 mg/kg iv (n=9)	+77.5%**	+20.6%*	+28.6%**
21 0.5 mg/kg iv (n=8)	-1.1%	+3%	+10%

Table 1: Influencing of the cystometric parameters by the test substances (change compared to the baseline value (%)); n corresponds to the number of experimental animals;

significance (Student T Test): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

The investigated substances exhibit a positive effect on the bladder regulation and are therefore suitable for treating urinary incontinence.

It was found *inter alia* that, of the enantiomers of the racemic compound 1, the (+) enantiomer (compound 2) is very effective (and thus is a particularly preferred compound of the invention), while the (-) enantiomer (compound 21) does not exhibit such a marked effect.

CLAIMS:

1. A pharmaceutical formulation with delayed release, comprising, as active constituent, 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof in a matrix with delayed release of the active constituent; wherein the matrix comprises 1 to 80 wt.% of at least one pharmaceutically acceptable hydrophilic or hydrophobic matrix-forming polymer and

exhibiting the following *in vitro* release rates measured using the Ph. Eur. paddle method at 75 rpm in a buffer (according to Ph. Eur.) at a pH value of 6.8 at 37°C and with UV spectrometric detection:

3-35 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol released after 0.5 hour,

5-50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 1 hour,

10-75 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 2 hours,

15-82 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 3 hours,

30-97 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 6 hours,

more than 50 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 12 hours,

more than 70 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 18 hours,

more than 80 wt.% of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or pharmaceutically acceptable salt thereof released after 24 hours, wherein the wt.% is a wt% of total active constituent.

2. A pharmaceutical formulation according to claim 1, wherein said at least one matrix-forming polymer comprises a cellulose ether or a cellulose ester that has a viscosity of 3000 to 150,000 mPa·s in a 2 wt.% aqueous solution at 20°C.

3. A pharmaceutical formulation according to claim 1, wherein said at least one matrix-forming polymer comprises a cellulose ether or cellulose ester that has a viscosity of 10,000 to 150,000 mPa·s in a 2 wt.% aqueous solution at 20°C.

4. A pharmaceutical formulation according to claim 1, wherein said at least one matrix-forming polymer comprises a cellulose ether or cellulose ester that has a viscosity of 50,000 to 150,000 mPa·s in a 2 wt.% aqueous solution at 20°C.

5. A pharmaceutical formulation according to claim 1, wherein said at least one matrix-forming polymer comprises at least one substance selected from the group consisting of hydroxypropylmethylcelluloses (HPMC), hydroxyethylcelluloses, hydroxypropylcelluloses (HPC), methylcelluloses, ethylcelluloses and carboxymethylcelluloses.

6. A pharmaceutical formulation according to claim 1, wherein said at least one matrix-forming polymer comprises at least one substance selected from the group consisting of hydroxypropylmethylcelluloses, hydroxyethylcelluloses and hydroxypropylcelluloses.

7. A pharmaceutical formulation according to any one of claims 1 to 6, the content of the delayed release active constituent is between 0.5 and 85 wt.% of the formulation and the content of the at least one matrix-forming polymer is between 8 and 40 wt.% of the formulation.

8. A pharmaceutical formulation according to any one of claims 1 to 6, the content of the delayed release active constituent is between 3 and 70 wt.% of the formulation and the content of the at least one matrix-forming polymer is between 10 and 35 wt.% of the formulation.

9. A pharmaceutical formulation according to any one of claims 1 to 6, the content of the delayed release active constituent is between 8 and 66 wt.% of the formulation and the content of the at least one matrix-forming polymer is between 10 and 30 wt.% of the formulation.

10. A pharmaceutical formulation according to any one of claims 1 to 9, wherein the peak plasma level of the active constituent *in vivo* is reached after 2 hours to 10 hours.

11. A pharmaceutical formulation according to any one of claims 1 to 9, wherein the peak plasma level of the active constituent *in vivo* is reached after 3.5 hours to 6 hours.

12. A pharmaceutical formulation according to any one of claims 1 to 9, wherein the active constituent comprises (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof.

13. A tablet for twice daily oral administration of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof comprising a pharmaceutical formulation as defined in any one of claims 1 to 12.

14. A use of a pharmaceutical formulation as defined in any one of claims 1 to 12 in production of a medicament for treating increased urinary urgency or urinary incontinence.

15. A use of a pharmaceutical formulation as defined in any one of claims 1 to 12 for treating increased urinary urgency or urinary incontinence.

16. A pharmaceutical formulation as defined in any one of claims 1 to 12 for treating increased urinary urgency or urinary incontinence.

17. A use of a tablet as defined in claim 13 in production of a medicament for treating increased urinary urgency or urinary incontinence.

18. A use of a tablet as defined in claim 13 for treating increased urinary urgency or urinary incontinence.

19. A tablet as defined in claim 13 for treating increased urinary urgency or urinary incontinence.

20. A use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof in the production of a medicament for treating increased urinary urgency or urinary incontinence, wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as defined in any one of claims 1 to 12.

21. A use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof for treating increased urinary urgency or urinary incontinence, wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as defined in any one of claims 1 to 12.

22. 1-Dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof for treating increased urinary urgency or urinary incontinence, wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as defined in any one of claims 1 to 12.

23. A use of a pharmaceutical formulation as defined in any one of claims 1 to 12 in production of a medicament for treating pain.

24. A use according to claim 23, wherein the pain is chronic pain, visceral pain, neuropathic pain, acute pain or inflammation pain.

25. A use of a pharmaceutical formulation as defined in any one of claims 1 to 12 for treating pain.

26. A use according to claim 25, wherein the pain is chronic pain, visceral pain, neuropathic pain, acute pain or inflammation pain.

27. A pharmaceutical formulation as defined in any one of claims 1 to 12 for treating pain.

28. A pharmaceutical formulation according to claim 27, wherein the pain is chronic pain, visceral pain, neuropathic pain, acute pain or inflammation pain.

29. A use of a tablet as defined in claim 13 in production of a medicament for treating pain.

30. A use according to claim 29, wherein the pain is chronic pain, visceral pain, neuropathic pain, acute pain or inflammation pain.

31. A use of a tablet as defined in claim 13 for treating pain.

32. A use according to claim 31, wherein the pain is chronic pain, visceral pain, neuropathic pain, acute pain or inflammation pain.

33. A tablet as defined in claim 13 for treating pain.

34. A tablet according to claim 33, wherein the pain is chronic pain, visceral pain, neuropathic pain, acute pain or inflammation pain.

35. A use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof in production of a medicament for treating pain, wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as defined in any one of claims 1 to 12.

36. A use of 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof for treating pain, wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as defined in any one of claims 1 to 12.

37. 1-Dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or a pharmaceutically acceptable salt thereof for treating pain, wherein the 1-dimethylamino-3-(3-methoxyphenyl)-2-methylpentan-3-ol or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical formulation as defined in any one of claims 1 to 12.