

## Solid oral formulation of pudafensine

### Technical field

5 The present invention relates to solid formulations of pudafensine as disclosed herein or a pharmaceutically acceptable salt thereof.

### Background

10 Pudafensine (the compound Exo-7-[(8-azabicyclo[3.2.1]octan-3-yl)oxy]-3-methoxy-chromen-2-one also known as IP2015) is and mono-amine re-uptake inhibitor under clinical development. In the nervous system, the compound increases the level of neurotransmitters, which has utility in treatment of central nervous system disorders.

15 Given the compound's effect on the central nervous system, it is necessary that oral formulations exhibit a robust release profile. In some applications, it is desirable to obtain a complete release of the compound as fast as possible, in order to achieve the therapeutic effects as soon as possible.

20 Until now, no known solid formulations of the compound have shown to produce an effective release of the compound. The compound suffers from low solubility, which poses a challenge both in the manufacture of such formulations and for ensuring fast complete release upon oral administration of the compound.

25 Accordingly, there is a strong un-met need for solid forms that can ensure a consistent and fast release of pudafensine upon oral administration.

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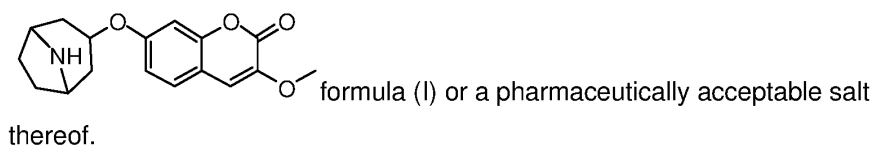
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### Summary

The inventors have surprisingly found that specific solid formulations of pudafensine can provide fast immediate release of the compound and high absorption in humans despite the drugs low solubility. The formulations according to the present disclosure are able to provide complete release of the compound in minutes, as demonstrated by the examples, and the drug is properly absorbed in humans and detected in plasma. This is highly advantageous in the clinical application of pudafensine since it allows a safe and robust administration of the compound with a fast release and on-set of the therapeutic effect.

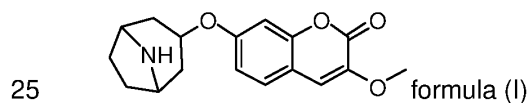
In one aspect, the present disclosure provides for composition comprising pellets, said pellets comprising or consisting of,

- a. a pellet core; and
- b. a drug layer covering the core, the drug layer comprising a compound of formula (I)



In one aspect, the present disclosure provides for a unit dosage form comprising the composition described herein.

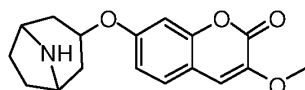
In one aspect, the present disclosure provides for method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)



in a subject, wherein the  $t_{\max}$  of the compound of formula I is between 3 and 5 hours, said method comprising oral administration of a composition as described herein.

In a final aspect, the present disclosure provides for method of preparing a composition comprising pellets, the method comprising:

- a) providing pellet core,
- b) providing a drug layer solution comprising a compound of formula (I)



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- formula (I), or a pharmaceutically acceptable salt thereof; and
- c) coating the drug layer solution on to the pellet core to form a drug layer.

### Description of Drawings

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Figure 1: Dissolution rate of IR pellets and IR capsules having 10 mg or 5 mg of pudafensine. **A, B**: IR pellets 10 mg pudafensine; **C**: IR pellets 5 mg pudafensine; **D**: IR capsules 5 mg pudafensine. Further experimental details are given in Example 2.

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Figure 2: Data from a Phase IIb study with the compound IP2015 in ED patients show their response to question Q3 of the international index of erectile function scale 15 (IIEF-15): When you attempted intercourse, how often were you able to penetrate (enter) your partner during the last week?

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Figure 3: Data from a Phase IIb study with the compound IP2015 in ED patients show their response to question Q4 in the International Index of erectile function scale 15 (IIEF-15): During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

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Figure 4: Data from a Phase IIb study with the compound IP2015 in ED patients show their overall response to questions of the International Index of erectile function scale 15 (IIEF-15).

### Definitions

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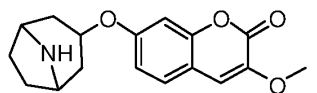
“C<sub>max</sub>” is a term used in pharmacokinetics to refer to the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administrated and prior to the administration of a second dose.

" $t_{\max}$ " is the term used in pharmacokinetics to describe the time at which the  $C_{\max}$  is observed.

As used herein the terms "inert core" and "inert sphere" refer to a pharmaceutically acceptable core for use in pharmaceutical formulations which core is inert. For example, the "inert core" or "inert sphere" refers to a pharmaceutically acceptable pellet that does not contain a drug substance.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

By "pudafensine," "IP2015" or "compound I" is meant the compound of formula I. The compound of formula I is:



The term "pharmaceutically acceptable salt" of a compound refers to a salt that is pharmaceutically acceptable, as defined herein, and preferably possesses the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids; or formed with organic acids; or salts formed when an acidic proton present in the parent compound either is replaced by a metal ion; or coordinates with an organic or inorganic base.

As used herein, "formulation" is the result of combining different substances, including the active ingredient, to produce a final product.

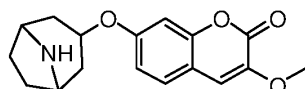
As used herein, the term 'weight of the pellets' refers to the total weight of the pellets including the drug layer within the composition, *e.g.*, the total weight of the components comprising the pellet core, drug layer, and any other layer on the pellet. In capsule formulations, this does not include the weight of the capsule shell.

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**Detailed description**

The present disclosure provides for composition comprising pellets, said pellets comprising or consisting of,

- 5                   a) a pellet core; and  
                  b) a drug layer covering the core, the drug layer comprising a compound of formula (I)



formula (I) or a pharmaceutically acceptable salt thereof.

10       A composition

Pellets offer a high degree of flexibility in the design and development of oral dosage forms. Microcrystalline cellulose pellets (MCC) and sugars are well-known materials in pellet technology to use as core materials. Water-insoluble inert pellet cores are made of microcrystalline cellulose or silica, while water-soluble inert pellet cores are composed of sugar, such as sucrose, xylitol, mannitol, lactose; starch or salts. Both material classes show desirable characteristics, such as a narrow particle size distribution, sphericity, and surface smoothness and may be used according to the invention. A person of skill in the art will be able to determine suitable materials and suppliers of spheres suitable as core for pellets of the compositions according to the present disclosure.

In one embodiment, the pellets comprise an inert pellet core. In one embodiment, the pellet core comprises or consist of microcrystalline cellulose (MCC). MCC is a commercially available chemical (CAS 9004-34-6) and its pellets are commercially available in multiple size ranges, for example Cellet® or Celphere™.

The size of the pellet core may be any suitable size, for example at least 100 µm. Different size of pellet cores may be used, for example pellet cores with sizes from 100 µm to 1500 µm, such as from 100 µm to 500 µm, such as from 500 µm to 1000 µm or from 1000 µm to 1500 µm.

Methods to coat pellet compositions are well known in the art. They can both start from a solution, dispersion or powder that is coated onto the pellets layer by layer. Well-established methods to coat pellets are for example: a fluidized bed technology, by compression coating, wüster coating, pan coating, centrifugal or rotor coating.

In one embodiment, the drug layer further comprises a binder. Binders are used to avoid the sticking of the drug on the pellets and provide a uniform coating on the pellets. The binder is mixed with the drug in a solution and then coated onto the inert pellets. It was surprisingly found that the presence of a binder, such as HPMC, in the coating solution  
5 allowed for homogeneous coating of pudafensine on to the inert pellet coat despite the compound's low solubility.

Known binders are for example sucrose, starch, hydroxypropyl methyl cellulose (HPMC) hydroxypropyl cellulose (HPC), gelatin or polyvinylpyrrolidone. Thus, in one  
10 embodiment, the binder is selected from: sucrose, starch, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), gelatin or polyvinylpyrrolidone (PVP); polyalkylene glycols or polyalkylene oxides, such as polyethylene oxide (PEO); or mixtures thereof.

15 In one embodiment, the drug layer comprises the binder in an amount from 0.5% to 10% by weight of the composition or by weight of the pellets, such as from 0.5% to 5%, such as from 1% to 5%, such as from 2% to 5%, such as 2%, 3%, 4% or 5% by weight of the composition or by weight of the pellets. Particularly, in one embodiment the drug layer comprises the binder, as described herein, in an amount from 0.5% to 10% by weight of  
20 the pellets, such as from 0.5% to 5%, such as 2%, 3%, 4% or 5% by weight of the pellets.

In one embodiment, the binder is hydroxypropyl methyl cellulose (HPMC). HPMC (CAS number 9004-65-3) is a cellulose derivative wherein some free hydroxyl groups in cellulose have been substituted with hydroxypropyl and methyl groups, different grades of HPMC having different multiple weight, degree hydroxypropyl or methyl groups and  
25 viscosities are commercially available and suitable for use in formulation development.

In one embodiment, the drug layer comprises HPMC in an amount from about 0.5% to about 10% by weight of the composition or by weight of the pellets. In one embodiment, the drug layer comprises HPMC in an amount from about 1% to 5% by weight of the composition or by weight of the pellets, such as about 2%, 3%, 4% or 5% by weight of  
30 the composition or by weight of the pellets. Particularly, in one embodiment the drug layer comprises HPMC, as described herein, in an amount from 0.5% to 10% by weight of the pellets, such as from 0.5% to 5%, such as 2%, 3%, 4% or 5% by weight of the pellets.

In one embodiment, the drug layer comprises additional excipients such as pH modifiers and/or stabilizers. The inventors unexpectedly found that the addition of sodium sulphite (also known as sodium sulphite or  $\text{Na}_2\text{SO}_3$ , CAS number 7757-83-7) in the drug layer increased the dissolution rate of pudafensine from the drug layer. Thus, in one  
5 embodiment the drug layer further comprises sodium sulphite. The examples demonstrate that the presence of sodium sulphite in the drug layer accelerated the dissolution rate of pudafensine from the formulation.

The pH modifier, the stabilizer or the sodium sulphite may be present for example in an  
10 amount from about 0.05 % to about 1.5 % by weight of the composition or the pellets, such as for example from 0.05 % to 0.5 % by weight, such as from 0.5 % to 1.0% by weight, such as for example 1.0 % to 1.5 % by weight of the composition or by weight of the pellets. In one embodiment, the stabilizer or the sodium sulphite is present in an amount from about 0.05% to about 1.5% by weight of the pellets.

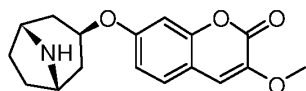
15 In one embodiment, the sodium sulphite is present in an amount of about 0.3 % to 0.8% by weight of the pellets. In one embodiment, the sodium sulphite is present in an amount of about 0.5% by weight of the pellets.

In one embodiment, the compound of formula I, or pharmaceutically acceptable salt thereof, is present in an amount from about 0.5% to about 5 % by weight of the total  
20 composition or by weight of the pellets. For example, the compound of formula I may be present in an amount from 0.5 % to 1 %, such as from 1 % to 2 %, such as from 2 % to 3 %, such as from 3 % to 4 %, such as from 4 % to 5 % by weight of the total composition or by weight of the pellets. In one embodiment, the compound of formula I may be  
25 present from 2.5% to 3.5% by weight of the composition or by weight of the pellets.

In one embodiment, the compound of formula I, or pharmaceutically acceptable salt thereof, is present in an amount from about 0.5% to about 5% by weight of the pellets. For example, the compound of formula I is present in an amount from 0.5 % to 1 %, such  
30 as from 1 % to 2 %, such as from 2 % to 3 %, such as from 3 % to 4 %, such as from 4 % to 5 % by weight of the pellets. In one embodiment, the compound of formula I is present in an amount from 2.5% to 3.5% by weight of the pellets.

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In one embodiment, the compound of formula I is according to formula Ia



formula (Ia),

or a pharmaceutically acceptable salt thereof.

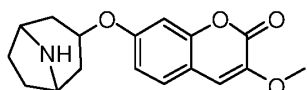
- 5 In one embodiment, the compound is Exo-7-[(8-azabicyclo[3.2.1]octan-3-yl)oxy]-3-methoxy-chromen-2-one or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) or formula (Ia) is a hydrochloride salt.

- 10 In one embodiment, the composition is an immediate release (IR) composition of the compound of formula I.

Thus, in one embodiment the present disclosure provides for a composition which is an immediate release composition of an active ingredient consisting of a compound of

- 15 formula I,

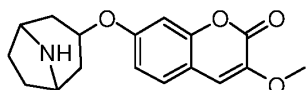


formula (I), or a pharmaceutically acceptable salt thereof,

the composition comprising pellets, said pellets comprising or consisting of:

- a) an inert pellet core comprising microcrystalline cellulose (MCC);  
 b) a drug layer comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount of about 0.5% to about 5% by weight of the total composition or by weight of the pellets and HPMC in an amount of 0.5% to about 5% by weight of the total composition or by weight of the pellets, which layer covers the inert core.
- 20

- 25 In one embodiment the present disclosure provides for a composition which is an immediate release composition of an active ingredient consisting of a compound of formula I,



formula (I), or a pharmaceutically acceptable salt thereof,

the composition comprising pellets, said pellets comprising or consisting of:

- 30 a) an inert pellet core comprising microcrystalline cellulose (MCC);

- b) a drug layer comprising: the compound of formula (I), or a pharmaceutically acceptable salt thereof, in an amount of about 0.5% to about 5% by weight of the pellets and HPMC in an amount of 0.5% to about 5% by weight of the pellets, which layer covers the inert core.

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In one embodiment, the drug layer further comprises other excipients such as pH modifiers or stabilizers, as described herein. In one embodiment, the drug layer further comprises sodium sulphite as described herein.

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In one embodiment, the drug layer further comprises HPMC as described herein.

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In one embodiment, the composition according to the present disclosure comprises an amount of the compound of formula I of about 0.5 mg to about 30 mg, such as from 1 mg to 20 mg, such as from 1 mg to about 16 mg, such as 1 mg to about 10 mg, such as from 2 mg to about 10 mg, such as from 3 mg to about 10 mg, such as from 4 mg to about 10 mg. For example, the composition may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg of the compound of formula I. In one embodiment, the composition comprises about 5 mg of the compound of formula I.

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#### Dosage form

The present disclosure provides for dosage form, such as a pharmaceutical dosage form, comprising the composition as described herein. In one embodiment, the dosage form is a unit dosage form. Methods to manufacturing dosage forms, including suitable excipients and materials will be known to the skilled artisan.

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The unit dosage form or the pharmaceutical dosage form is in one embodiment a solid dosage form. In one embodiment, the unit dosage form or the pharmaceutical dosage form is a capsule.

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Dosage forms are designed to facilitate the safe and effective delivery of active compounds to patients.

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Thus, in one embodiment, the composition according to the present disclosure is in the form of a unit dosage form or a pharmaceutical dosage form. In one embodiment, the composition according to the present disclosure is a capsule.

In one embodiment, the composition is for oral administration.

Immediate release

5 The inventors have surprisingly shown that the compositions according to the present disclosure provide for a fast and immediate release of pudafensine in the gastrointestinal tract after oral administration.

10 The examples demonstrate that the compositions according to the present disclosure provide for a fast release of pudafensine, with complete release upon 5 minutes in physiological conditions, allowing for a fast absorption of the drug despite its poor solubility.

In one embodiment, the composition provides a pharmacokinetic profile having a single mean average plasma concentration peak upon oral administration.

15 In one embodiment, the composition provides a  $C_{\max}$  of the compound of formula I after oral administration of 80% to 125% of the  $C_{\max}$  provided by an equivalent amount of the compound of formula I administered orally as an aqueous solution. In one embodiment, the composition provides for a  $C_{\max}$  of the compound of formula I upon oral administration from 5.0 ng/mL to 13.0 ng/mL, such as from 6.0 ng/mL to 10.0 ng/mL, or 7.0 ng/mL to 20 9.5 ng/mL.

25 In one embodiment, the composition provides in a mean  $C_{\max}$  of the compound of formula I from 6.0 ng/mL to 10.0 ng/mL, for example from 6.0 ng/mL to 7.0 ng/mL, or from 7.0 ng/mL to 8.0 ng/mL, or from 8.0 ng/mL to 9.0 ng/mL, or from 9.0 ng/mL to 10.0 ng/mL.

In one embodiment, the composition increases  $t_{\max}$  of the compound of formula I compared to an aqueous solution of the compound of formula I after oral administration by no more than 150 minutes.

30 In one embodiment, the composition provides a  $t_{\max}$  of the compound of formula I from about 2 to 8 hours, such as from 3 to 5 hours after oral administration, such as  $t_{\max}$  3, 4, or 5 hours.

35 The compositions according to the present disclosure provide for an immediate release of the compound of formula I. An immediate release may be characterized by the

dissolution rate of the active ingredient from the composition. A person of skill in the art is aware of methods to determine dissolution rate of solid dosage forms, such as according to the US Pharmacopeia, such as with a USP-I or a USP-II apparatus, with suitable methods of detection of the active ingredient such as HPLC or ELISA.

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In one embodiment, the composition releases the compound of formula I at a rate of more than 90% released in the first hour as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C.

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In one embodiment, the composition releases the compound of formula I at a rate of more than 90% release in the first 0.5 hours, such as more than 90% release in the first 10 minutes, such as more than 90% release in the first 5 minutes as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C.

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In one embodiment, the composition releases the compound of formula I at a rate of essentially 100%, or complete release, in the first 5 minutes as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C. Surprisingly, it was found that addition of sodium sulphite in the drug layer produced an increase in the release that allowed for complete release after 5 min in dissolution rate tests simulating stomach pH.

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The exposure of a substance may be measured as the “area under the curve” or “AUC” of the compound in the bloodstream. As it is well-known in the art, this may be calculated by plotting the concentration of the drug in the bloodstream against time and determining the integral of the resulting curve, also known as the “area under the curve” of “AUC”.

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The amount of drug in the bloodstream may be detected at different time-points by well known methods in the art such as HPLC, LC/MS, ELISA, or other suitable analytical methods. Methods to calculate the integral of the plot are also well known to some one of skill in the art. The integral of the plot, or area under the curve, may be calculated within a specific time interval, such as within the first 24, 48, or 72 hours. In general, the term “AUC<sub>0-t</sub>” refers to the area under the curve for the first “t” hours, for example as in “AUC<sub>0-24</sub>” referring to the area under the curve within the first 24 hours. The term “AUC<sub>0-inf</sub>” or “AUC<sub>inf</sub>” refers to the area under the curves where the last point for integration has been extrapolated to infinity.

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In one embodiment, the composition provides for a  $AUC_{0-72}$  of the compound of formula I of at least 90% of the  $AUC_{0-72}$  of an aqueous solution of an equivalent amount of the compound of formula I after oral administration.

5 In one embodiment, the composition provides for a  $AUC_{0-inf}$  of the compound of formula I of at least 90% of the  $AUC_{0-inf}$  of an aqueous solution of an equivalent amount of the compound of formula I after oral administration. In one embodiment, the composition provides for an  $AUC_{0-inf}$  of the compound of formula I upon oral administration from 150 to 550 h·ng/mL, such as  $AUC_{0-inf}$  from 180 to 480 h·ng/mL, or  $AUC_{0-inf}$  from 250 to 350  
10 h·ng/mL, such as  $AUC_{0-inf}$  of about 300 h·ng/mL.

In one embodiment, the composition provides for mean  $AUC_{0-inf}$  of the compound of formula I upon oral administration from 200 h·ng/mL to 400 h·ng/mL, such as mean  $AUC_{0-inf}$  from 250 h·ng/mL to 350 h·ng/mL.

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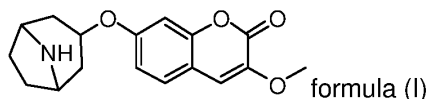
Thus, in one aspect the present disclosure provides for an immediate release composition of a compound of formula (I), said composition providing a pharmacokinetic profile upon administration characterized by having one or more of:

- a  $C_{max}$  of the compound of formula I from 5.0 ng/mL to 13.0 ng/mL, such as from  
20 6.0 ng/mL to 10.0 ng/mL, such as from 7.5 ng/mL to 9.0 ng/mL,
- a  $t_{max}$  of the compound of formula I from about 2 to 8 hours, such as from 3 to 5 hours,
- an  $AUC_{0-inf}$  of the compound of formula I from 180 to 480 h·ng/mL, such as  $AUC_{0-inf}$  from 250 to 350 h·ng/mL, such as  $AUC_{0-inf}$  of about 300 h·ng/mL.

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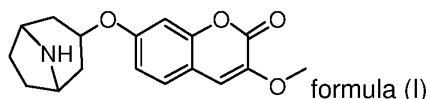
In one embodiment, said immediate release composition comprises the compound of formula (I), a pellet core, a binder, pH modifiers or stabilizers as described herein in the section "A composition".

30 In one aspect, the present disclosure provides for a method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)



in a subject, wherein the  $t_{max}$  of the compound of formula I is between 3 and 5 hours, said method comprising oral administration of a composition as described herein.

In one aspect, the present disclosure provides the composition as described herein for use in a method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)



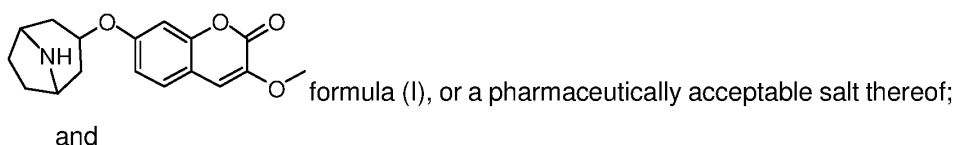
- 5 in a subject, wherein the  $t_{\max}$  of the compound of formula I is between 3 and 5 hours, said method comprising oral administration of a composition as described herein.

In one embodiment, the subject is a human.

10 Method of preparation

In a final aspect, the present disclosure provides for method of preparing a composition comprising pellets, the method comprising:

- a) providing pellet core,  
15 b) providing a drug layer solution comprising a compound of formula (I)



- c) coating the drug layer solution on to the pellet core to form a drug layer.

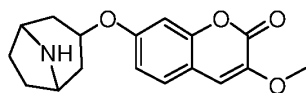
20 In one embodiment of the method, the pellet core, or the drug layer, are as described herein in the section "Composition".

In one embodiment of the method, the drug layer solution comprises a binder or a stabilizer according as described herein in the section "Composition".

25 In one embodiment of the method, the drug layer solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consist of an aqueous solution.



9. The composition according to any one of the preceding items, wherein said composition is an immediate release composition of an active ingredient consisting of a compound of formula I,



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formula (I), or a pharmaceutically acceptable salt thereof, the composition comprising pellets comprising or consisting of:

- a) an inert pellet core comprising microcrystalline cellulose (MCC);
- b) a drug layer comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount of about 0.5% to about 5% by weight of the total composition or by weight of the pellets and HPMC in an amount of 1% to about 5% by weight of the total composition or by weight of the pellets, which layer covers the inert core.

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10. The composition according to item 9, wherein the drug layer further comprises sodium sulphite.

11. The composition according to item 9, wherein the sodium sulphite is present in an amount from 0.05 % to 1% by weight.

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12. The composition according to any one of the preceding items, the composition provides a  $t_{max}$  of the compound of formula I from about 2 to 8 hours after oral administration.

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13. The composition according to any one of the preceding items, wherein the composition releases the compound of formula I at a rate of 100% release in the first 5 minutes as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C.

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14. The composition according to any one of the preceding items, wherein the composition provides for a  $AUC_{0-inf}$  of at least 90% of the  $AUC_{0-inf}$  of an aqueous solution of an equivalent amount of the compound of formula I after oral administration.

15. A unit dosage form comprising the composition according to any one of items 1 to 14.

Examples

Example 1: Preparation of formulations

Aim

To describe the preparation of compositions according to the present disclosure.

Materials and Methods

**Materials.** Microcrystalline cellulose spheres (Celphere CP-507 particle size range 500-710 µm), sodium sulphite anhydrous, hydroxypropylmethyl cellulose (HPMC, Methocel E5 premium LV) and pudafensine monohydrate monohydrochloride salt.

Sodium sulphite, HPMC 5cps and pudafensine are mixed in purified water then stirred to get uniform dispersion. Then the solution is coated onto the inert pellet core (Celphere CP-507) in a fluidized bed (GPCG 1.1 bowl, Gun nozzle size: 1.2 mm, ADP size: type B). Finally, the drug-layered pellets are filled into Swedish Orange Capsule size 0.

For pudafensine solutions, a drug in bottle product is prepared as following: pudafensine is dissolved in water for injection containing 50 mg/mL of hydroxypropyl 2-beta cyclodextrin (HPβCD)

The drug substance pudafensine was used as a monohydrate and monohydrochloride salt. Hence the quantity per bottle, or capsule or administration is calculated based on the amount of free base.

Results

IP2015 compositions where prepared according to the tables below.

Table 1. Composition of IP2015 immediate release (IR) pellets

|               |                       | IP2015 IR pellets                |               |                |
|---------------|-----------------------|----------------------------------|---------------|----------------|
| S. No         | Purpose               | Ingredients                      | Qty (g)       | % w/w          |
| Drug layering |                       |                                  |               |                |
| 1             | Core pellets          | Celphere CP-507                  | 1400.0        | 92.729         |
| 2             | Drug substance        | IP2015 <sup>a</sup>              | 48.37         | 3.204          |
| 3             | Binder                | HPMC E5 (Methocel E5 premium LV) | 53.40         | 3.537          |
| 4             | pH modifier/alkalizer | Sodium sulphite anhydrous        | 8.00          | 0.530          |
| 5             | Dispersant            | Purified Water                   | q.s           | q.s            |
|               |                       | <b>Total</b>                     | <b>1509.6</b> | <b>100.000</b> |

<sup>a</sup>The drug substance is a monohydrate and monohydrochloride salt. The quantity of free base may be calculated by analysis of anhydrous and solvent-free basis, by methods well known in the art. For the present batch 60 mg of free base correspond to 72 mg of drug substance.

Solubility tests

Solubility of IP2015 was determined in both aqueous and non-aqueous vehicles. In non-aqueous liquids, the solubility was visually confirmed in progressive dilutions. The solubility of IP2015 in pH specific aqueous solutions was evaluated, the solubility was visually confirmed, and the content was evaluated by HPLC.

Table 2. Solubility of IP2015 in different media.

| Vehicle                           | Solubility (mg/ml) | Inference (Ph.Eur)    |
|-----------------------------------|--------------------|-----------------------|
| Ethanol                           | <1                 | Very slightly soluble |
| N,N-dimethyl acetamide            | <1                 | Very slightly soluble |
| Dimethyl sulfoxide                | 5 to 10            | Slightly soluble      |
| N-methyl-2-pyrrolidone            | <1                 | Very slightly soluble |
| Propylene glycol                  | 1 to 5             | Slightly soluble      |
| Polyethylene glycol 400           | <1                 | Very slightly soluble |
| Glycerine                         | <1                 | Very slightly soluble |
| pH 1.2 HCl (0.1N)                 | 0.017              | Very slightly soluble |
| pH 3.0 Citrate buffer             | 0.839              | Very slightly soluble |
| pH 4.0 Citrate buffer             | 0.849              | Very slightly soluble |
| pH 3.0 Acetate buffer             | 1.173              | Slightly soluble      |
| pH 4.5 Acetate buffer             | 0.981              | Very slightly soluble |
| pH 5.8 Potassium Phosphate buffer | 0.104              | Very slightly soluble |
| pH 6.8 Potassium Phosphate buffer | 0.146              | Very slightly soluble |
| pH 7.5 Potassium Phosphate buffer | 0.084              | Very slightly soluble |
| Purified Water                    | 0.738              | Very slightly soluble |

Results

As seen from table 2, IP2015 has solubility lower than 1 mg/mL in aqueous solutions across physiological pH. It was unexpectedly found that the presence of the binder in the solution allowed for a homogeneous and consistent distribution of IP2015 in the drug layer. In contrast, when a solubility enhancer was used to improve the solubility of IP2015, such as hydroxypropyl 2-beta cyclodextrin (HPβCD), the concentration of the compound was not enough to form a good drug layer.

Example 2: IP2015 release in solution

Aim

To study the release of IP2015 for compositions according to the present disclosure.

Materials and Methods

The dissolution profile of IP2015 IR pellets (part finished IMP) and IP2015 IR capsules is determined using 0.1N HCl Buffer.

Dissolution conditions:

| Parameter       | Condition         |
|-----------------|-------------------|
| Media           | 0.1N HCl buffer   |
| Volume          | 900 mL            |
| Apparatus       | USP-I (Basket)    |
| RPM             | 50                |
| Temperature     | 37.0° + 0.5°C     |
| Sampling volume | 10 mL             |
| Time points     | 5, 10, 15, 30 min |

5       Dissolution samples are being analyzed with a gradient reverse phase HPLC method, The mobile phase is buffer solution (0.1% orthophosphoric acid and water): acetonitrile (85:15). The detection is by DAD.

10       To study the effect of sodium sulphite, two different samples of pellets were prepared according to example 1, with and without sodium sulphite. The dissolution rate of samples corresponding to 5 mg of IP2015 from the pellets without encapsulation was studied.

15       To study the effect of encapsulation, the dissolution rate of IP2015 from both encapsulated and non-encapsulated pellets was assessed using samples corresponding to 5 mg of IP2015, prepared according to example 1. For comparison, dissolution of non-encapsulated samples corresponding to 10 mg of IP2015 was also assessed.

Results

The dissolution profile of samples with and without sodium sulphite is shown in Table 3.

20       Table 3. Drug release from 5 mg IP2015 IR pellet samples with and without sodium sulphite.

| Time / min | Drug release (%)                     |                                         |
|------------|--------------------------------------|-----------------------------------------|
|            | with Na <sub>2</sub> SO <sub>3</sub> | without Na <sub>2</sub> SO <sub>3</sub> |
| 5          | 96                                   | 103                                     |
| 10         | 97                                   | 107                                     |
| 15         | 98                                   | 108                                     |
| 20         | 99                                   | 108                                     |
| 30         | 99                                   | 108                                     |
| 45         | 99                                   | 108                                     |
| 60         | 99                                   | 108                                     |

Impact of sodium sulphite on the dissolution profile was observed. The dissolution profiles of scale-up batches, which had sodium sulphite in the drug layering coating, showed a faster dissolution profile compared to a scale-up batch, which does not have sodium sulphite in the drug layer.

5

Figure 1 shows the release profile of IP2015 IR pellets and capsules . The dissolution profile is as expected. The IP2015 IR capsule fulfil the requirements for an immediate release oral dosage form with 80% released after 10 min and > 90% released after 20 min.

10

### *Conclusion*

It was surprisingly found that the presence of sodium sulphite enhances the dissolution rate from the IR compositions.

15

### Example 3: In vivo pharmacokinetics of IP2015 IR composition

#### *Aim*

To study the pharmacokinetic parameters of the compositions according to the present disclosure.

20

#### *Materials and methods*

The pharmacokinetic profiles of different formulations of IR Pellets and one solution formulation (DiB) of IP2015 as reference item were investigated in Göttingen minipigs, after single oral administration.

25

Animals were fasted prior to dosing. Each formulation was administered to the animals by a single administration; a wash-out period of 7 days was allowed after each day of dosing. A single dose of 0.5mg/kg was administered orally, by capsule, with a washout period of 7 days after each day of dosing. A single dose (0.25mL/kg) of reference item solution was administered orally, by gavage.

30

Assessment of mortality was conducted twice each day. All clinical signs were recorded at baseline and at the same time daily during the study (approximately 1-1.5, 2-2.5 and 3-3.5 hours after dosing). Fasted body weight was recorded on the day of allocation and the day before dosing.

On each day of dosing, blood samples were collected from the jugular vein (other veins were used, if necessary) at approximately the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours after the first administration.

At each sampling time, at least 1.0 mL of blood was collected and transferred into tubes containing K<sub>2</sub>EDTA anticoagulant and, centrifuged at room temperature, divided in two aliquots: [Aliquot A] of approximately 250 µL and the second [Aliquot B] with the plasma remaining) and frozen at -70 ± 10°C.

The concentration of IP2015 in minipig plasma was determined via LC-MS/MS method by The Bioanalytical Department, Syngene International Ltd. During analysis, standard and quality control samples were distributed throughout each batch of study samples analysed. Plasma concentration data was used for toxicokinetic evaluation.

PK parameters were determined from the individual minipig plasma concentration versus time data by a non-compartmental analysis with uniform weighting using Phoenix® WinNonlin® validated version 8.2. The PK parameters that were calculated includes the area under the plasma concentration-time curve until last quantifiable concentration (AUC<sub>last</sub>), AUC<sub>0-48h</sub>, peak plasma concentration (C<sub>max</sub>), time to reach peak plasma concentration (T<sub>max</sub>), C<sub>last</sub>, T<sub>last</sub>, AUC<sub>inf</sub> and terminal elimination half-life (t<sub>1/2</sub>). Plasma concentrations and TK parameters are presented in ng unit.

### Results

The results are displayed in Table 4 and Table 5.

Table 4. Mean pharmacokinetic parameters of IP2015 in different formulations.

|                                        | IR      | DiB     |
|----------------------------------------|---------|---------|
| <b>Dose</b> (mg/kg)                    | 0.5     | 0.5     |
| <b>C<sub>max</sub></b> (ng/mL)         | 17.026  | 25.135  |
| <b>T<sub>max</sub></b> (h)             | 3.33    | 2.5     |
| <b>AUC<sub>0-48h</sub></b> (h*ng/mL)   | 336.317 | 399.6   |
| <b>C<sub>last</sub></b>                | 2.226   | 2.416   |
| <b>T<sub>last</sub></b>                | 48      | 48      |
| <b>Half-life</b> (h)                   | 13.58   | 15.03   |
| <b>AUC<sub>last</sub></b> (h*ng/mL)    | 336.317 | 399.6   |
| <b>AUC<sub>INF_obs</sub></b> (h*ng/mL) | 390.254 | 459.579 |

Table 5. Systemic exposure ratios IR vs. DiB.

|                      | Ratio (IR / DiB) |
|----------------------|------------------|
| C <sub>max</sub>     | 0.68             |
| AUC <sub>0-48h</sub> | 0.84             |
| T <sub>max</sub>     | 1.3              |

5 Conclusion

It was observed that the compositions according to the present disclosure produces a slight increase in T<sub>max</sub>, and a decrease in C<sub>max</sub> but the exposure of IP2015 is maintained.

10 Example 4. Clinical trial studying pharmacokinetics of IP2015 formulations in human.  
Aim

To study the pharmacokinetics of immediate release (IR) compositions of IP2015 according to the present disclosure in humans.

Materials and Methods

15 The study is a 3-way crossover study in which pharmacokinetic parameters of IP2015 immediate release compositions according to the present disclosure were studied after oral administration. For comparison, the results were compared to a solution of IP2015. The compositions were prepared as described in example 1.

20 The study was a crossover study performed in 12 healthy subject that received single doses of 5 mg of IP2015 in different formulations with sufficient wash-out in between. After administration of the compositions, the plasma blood levels of IP2015 monitored at different timepoints.

Results

The results are shown in Table 6 and Table 7.

Table 6. Pharmacokinetic parameters of IR and DiB compositions.

|                               | IR composition |      |        |      | DiB |      |        |      |
|-------------------------------|----------------|------|--------|------|-----|------|--------|------|
|                               | N              | Min  | Median | Max  | N   | Min  | Median | Max  |
| T <sub>lag</sub> (h)          | 12             | 0    | 0      | 0    | 12  | 0    | 0      | 0    |
| t <sub>max</sub> (h)          | 12             | 1.97 | 4.98   | 7.95 | 12  | 0.98 | 3.5    | 6.07 |
| C <sub>max</sub> (ng/mL)      | 12             | 5.39 | 8.81   | 12.5 | 12  | 6.25 | 8.69   | 14.4 |
| AUC <sub>last</sub> (h*ng/mL) | 12             | 182  | 260    | 410  | 12  | 186  | 251    | 402  |
| AUC <sub>inf</sub> (h*ng/mL)  | 10             | 193  | 301    | 479  | 9   | 199  | 284    | 496  |
| AUC <sub>0-24</sub> (h*ng/mL) | 12             | 98.7 | 146    | 209  | 12  | 106  | 147    | 219  |

Table 7. Systemic exposure ratios IR vs. DiB

|                     | IR / DiB ratio |      |        |      |                  |
|---------------------|----------------|------|--------|------|------------------|
|                     | N              | Min  | Median | Max  | Geom. mean (CV%) |
| C <sub>max</sub>    | 12             | 0.84 | 1.03   | 1.23 | 1.011 (11.91 %)  |
| AUC <sub>last</sub> | 12             | 0.9  | 0.99   | 1.16 | 1.004 (8.05 %)   |
| AUC <sub>inf</sub>  | 8              | 0.88 | 1      | 1.18 | 1.012 (10.55 %)  |

Conclusion

It was observed that the compositions according to the present disclosure produces a slight increase in t<sub>max</sub>, and a decrease in C<sub>max</sub> but the exposure of IP2015 is maintained. Thus, the composition of the present disclosure provides for a fast release that closely matches the drug-in-bottle formulation.

Example 5. Clinical trial studying adverse events and efficacy of treatment of erectile dysfunction with IP2015 in humans

The study investigated the effects of repeat single oral doses of IP2015 on male subjects with erectile dysfunction (ED) on ability to develop and maintain an erection, as well as safety and tolerability of single oral doses of IP2015, effects on penile rigidity and tumescence during visual stimulation, effects on sperm count and motility, and any possible relationship between plasma levels of IP2015, its efficacy and safety.

Materials and Methods

Study design

130 subjects were divided into 3 groups upon which the study was conducted in parallel. Each subject was dosed on four occasions with either 5 mg IP2015, 10 mg IP2015 or matched placebo. In each group, subjects were randomized evenly to each of the three study treatments and received the same treatment at each visit.

The study lasted approximately 8 weeks and consisted of the following:

- A screening visit (up to 21 days prior to the baseline visit)
- A baseline visit (Day -7)
- Outpatient visits on Week 1 (Day 1), Week 2, Week 3 and Week 4
- A follow-up visit a minimum of 7 to 10 days after their final dose.

On Day -7, and at Week 1 (Day 1), Week 2, Week 3, Week 4 and Follow-up visits, all groups were asked to complete the IIEF-15 questionnaire. Group 2 was asked to complete a Visual Stimulation Assessment using a RigiScan Plus Monitor on Day -7, Week 1 (Day 1) and Week 4. Group 2 was also required to provide blood samples for pharmacokinetic assessment on Week 1 (Day 1) and Week 4. Group 3 was required to provide semen samples on Day -7 and Week 4.

#### Participants

The patients were otherwise healthy male subjects with ED as determined from an IIEF-5 score of  $\leq 16$ , with a body mass index of 18 to 35 kg/m<sup>2</sup> (inclusive), of any ethnic origin. Subjects were aged between 18 to 59 years, inclusive.

#### Dose and Mode of Administration

There were three potential study treatments of 5 mg IP2015, 10 mg IP2015 or matched placebo. In each group, subjects were randomized evenly to each of the three study treatments and received the same treatment on each visit. IP2015 or matched placebo was administered once in the morning of Week 1 (Day 1), Week 2, Week 3, and Week 4 as an oral solution in the fasted state. The dose was taken with 240 mL of water at room temperature. Subjects had fasted 2 hours prior to dosing until 4 hours post-dose. Water was allowed ad libitum except for 1 hour before and 1 hour after dosing.

#### Evaluation

Efficacy was assessed through the International Index of Erectile Function (IIEF)-15 questionnaire. The change from baseline in responses to questions of the IIEF-15 questionnaire, including questions regarding erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction domain scores, was determined at different time points of the study. RigiScan assessments during the stimulus assessment, and sperm count and motility by semen sample collection was used for efficacy evaluation. Safety was assessed through AE reporting, 12-lead ECG, vital signs, physical examinations, and clinical laboratory evaluations. Pharmacokinetics was assessed by blood sampling.

## Results

### Efficacy of IP2015

The results for Q3 in the IIEF-15: "When you attempted intercourse, how often were you able to penetrate (enter) your partner during the last week?" are shown in Figure 2. The results for Q3 were significant for treatment with 5 mg IP2015 at week 3 versus placebo ( $p=0.034$ ) and versus baseline ( $p=0.046$ ). In the overall score for Q3, there was also a tendency to difference versus placebo ( $p=0.07$ ) and versus baseline ( $p=0.07$ ).

The results for Q4 in the IIEF-15: "During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?" are shown in Figure 3. The results for Q4 show that there was a tendency to difference versus baseline ( $p=0.056$ ) for the 5 mg in the overall score, though there was no difference compared to placebo ( $p=0.44$ ).

The overall response to questions of IIEF-15 is shown in Figure 4, the results were significant for treatment with 5 mg IP2015 versus baseline at follow-up ( $p=0.0046$ ) and tendency versus placebo ( $p=0.07$ ) and the same was the case for the overall score for 5 mg versus baseline ( $p=0.0032$ ) and tendency versus placebo ( $p=0.10$ ).

In figures 2, 3 and 4, the results show the change from baseline for patients treated with four doses of placebo ( $n=45$ ), 5 mg ( $n=42$ ), and 10 mg ( $n=43$ ) IP2015 dosed in parallel at days 1, 8, 15, and 22. The results are means $\pm$ SE. The statistical differences were performed with Mixed Model Repeated Measures (MMRM).

### Adverse events

Treatment-emergent adverse effects for the low-dose (5 mg) IP2015 were comparable to the placebo group. The TEAEs were dose-dependent, mild and moderate and slightly increased in the high dose compared to the low dose of IP2015. No severe side effects were observed at any of the doses of IP2015 (Table 8).

The results for semen analysis were complete and the treatment did not have negative effects on sperm count, motility, or morphology.

Table 8. Treatment-emergent adverse events

| TEAE      | IP2015 5mg, N=42 | IP2015 10 mg, N=43 | Placebo, N=45   |
|-----------|------------------|--------------------|-----------------|
| Any TEAE  | 32 (76.2 %), 61  | 34 (79.1 %), 141   | 31 (68.9 %), 63 |
| Related*  | 10 (23.8 %), 19  | 23 (53.5 %), 84    | 8 (17.8 %), 11  |
| Mild      | 29 (69.0 %), 56  | 33 (76.7%), 132    | 27 (60.0%), 57  |
| Moderate  | 3 (7.1%), 5      | 7 (16.3%), 9       | 6 (13.3%), 6    |
| Severe    | 0                | 0                  | 0               |
| Headache  | 11 (26.2 %), 15  | 16 (37.2 %), 27    | 14 (31.1 %), 21 |
| Dizziness | 3 (7.1 %), 3     | 12 (27.9 %), 15    | 2 (4.4 %), 2    |
| Nausea    | 1 (2.4 %), 1     | 8 (18.6 %), 15     | 1 (2.2 %), 1    |

Conclusion

5 Overall, these results, show that 5 mg doses that IP2015 are effective in treating erectile  
dysfunction and are safely tolerated. There was a significant effect of the 5 mg dose of  
IP2015 (pudafensine) on the Q3 in the IIEF-15 score compared to baseline and placebo.  
There were tendencies regarding the overall IIEF-15 score showing a clinically significant  
score change of 2, which is significant for a low dose of IP2015 versus baseline and  
10 p=0.10 versus placebo.

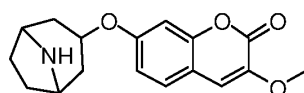
Treatment-emergent adverse effects for the 5 mg dose of IP2015 were comparable to  
the placebo group. The TEAEs were dose-dependent, only mild and moderate effects  
were observed. No severe TEAEs were present.

15 The higher efficacy and lower incidence of TEAEs at 5 mg of IP2015 compared to 10 mg  
demonstrates the need for the present solid dosage formulation that mimic the  
pharmacokinetics of the drug-in-bottle (DiB) used in this study without compromising  
exposure.

20

**Claims**

1. A composition comprising pellets, said pellets comprising or consisting of:
- a pellet core; and
  - a drug layer covering the core, the drug layer comprising a compound of formula (I)



formula (I) or a pharmaceutically acceptable salt thereof.

2. The composition according to claim 1, wherein the drug layer further comprises a binder selected from cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), or hydroxypropyl cellulose (HPC); gelatin; polyalkylene glycols, such as PEO; and polyvinyl pyrrolidone (PVP).
3. The composition according to claim 2, wherein the drug layer comprises the binder in an amount from 0.5 to 10% by weight of the pellets.
4. The composition according to any one of claims 2-3, wherein the binder is HPMC.
5. The composition according to any one of the preceding claims, wherein the drug layer comprises HPMC in an amount from about 1% to 5% by weight of the pellets.
6. The composition according to any one of the preceding claims, wherein the drug layer further comprises additional excipients selected from: pH modifiers and/or stabilizers.
7. The composition according to claim 6, wherein the pH modifier and/or stabilizer is present in an amount from 0.05% to 1% by weight of the pellets.
8. The composition according to any one of claims 6-7, wherein the stabilizer is sodium sulphite.

9. The composition according to any one of the preceding claims, wherein the drug layer comprises sodium sulphite in an amount from 0.05 % to 1% by weight of the pellets.

5

10. The composition according to any one of the preceding claims, wherein the pellet core comprises or consists of spheres made of a material selected from: microcrystalline cellulose (MCC); sugars, such as sucrose, xylitol, mannitol, and lactose; starch, silica, tartaric acid and calcium carbonate.

10

11. The composition according to any one of the preceding claims, wherein the pellet core comprises or consists of microcrystalline cellulose (MCC).

15

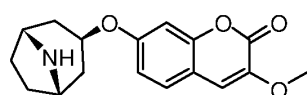
12. The composition according to any one of the preceding claims, wherein the drug layer comprises the compound of formula I, or a pharmaceutically acceptable salt thereof, in an amount of about 0.5% to about 5% by weight of the pellets.

20

13. The composition according to any one of the preceding claims, wherein the binder is present in an amount between 0.5% and 5% by weight of the pellets.

25

14. The composition according to any one of the preceding claims, wherein the compound of formula I is according to formula Ia



formula (Ia),

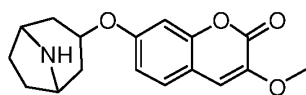
or a pharmaceutically acceptable salt thereof.

30

15. The composition according to any one of the preceding claims, wherein the compound is exo-7-[(8-azabicyclo[3.2.1]octan-3-yl)oxy]-3-methoxy-chromen-2-one or a pharmaceutically acceptable salt thereof.

16. The composition according to any one of the preceding claims, wherein the composition is an immediate release (IR) composition of the compound of formula I.

5 17. The composition according to any one of the preceding claims, wherein said composition is an immediate release composition of an active ingredient consisting of a compound of formula I,



10 thereof, the composition comprising pellets, said pellets comprising or consisting of:

- 15 a) an inert pellet core comprising microcrystalline cellulose (MCC);  
b) a drug layer comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount of about 0.5% to about 5% by weight of the pellets and HPMC in an amount of 0.5% to about 5% by weight of the pellets, wherein the drug layer covers the inert core.

18. The composition according to claim 17, wherein the drug layer further comprises additional excipients selected from: pH modifiers and/or stabilizers.

20 19. The composition according to any one of claims 17-18, wherein the drug layer further comprises sodium sulphite.

25 20. The composition according to any one of claims 17-19, wherein the drug layer comprises sodium sulphite in an amount from 0.05 % to 1% by weight of the pellets.

30 21. The composition according to any one of the preceding claims, wherein the composition comprises an amount of the compound of formula I of about 0.5 mg to 10 mg.

22. The composition according to any one of the preceding claims, wherein the composition is in the form of a pharmaceutical dosage form or a unit dosage form.

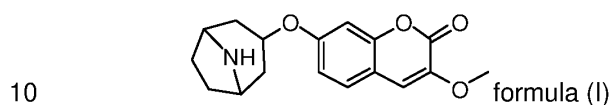
23. The composition according to any one of the preceding claims, wherein the composition is in the form of a solid dosage form.
- 5 24. The composition according to any one of claims 22-23, wherein the unit dosage form or pharmaceutical dosage form is a capsule.
25. The composition according to any one of the preceding claims, wherein the composition is for oral administration.
- 10 26. The composition according to any one of the preceding claims, wherein the composition provides a pharmacokinetic profile having a single mean average plasma concentration peak upon oral administration.
- 15 27. The composition according to any one of the preceding claims, wherein the composition provides a  $C_{\max}$  after oral administration of 80% to 125% of the  $C_{\max}$  provided by an equivalent amount of the compound of formula I administered orally as an aqueous solution.
- 20 28. The composition according to any one of the preceding claims, wherein the composition provides a  $C_{\max}$  of the compound of formula I upon oral administration from 5.0 ng/mL to 12.5 ng/mL, such as from 6.0 ng/mL to 10.0 ng/mL, such as from 7 ng/mL to 9 ng/mL.
- 25 29. The composition according to any one of the preceding claims, wherein the composition increases the  $t_{\max}$  of the compound of formula I compared to an aqueous solution of the compound of formula I after oral administration by at the most 150 minutes.
- 30 30. The composition according to any one of the preceding claims, wherein the composition provides a  $t_{\max}$  of the compound of formula I from about 2 to 8 hours, such as from 3 to 5 hours after oral administration.
- 35 31. The composition according to any one of the preceding claims, wherein the composition provides a  $t_{\max}$  of the compound of formula I from about 2 to 8 hours after oral administration.

32. The composition according to any one of the preceding claims, wherein the composition provides a  $t_{\max}$  of the compound of formula I from about 3 to 5 hours after oral administration.
- 5      33. The composition according to any one of the preceding claims, wherein the composition releases the compound of formula I at a rate of more than 90% released in the first hour as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C.
- 10      34. The compositions according to any one of the preceding claims, wherein the composition releases the compound of formula I at a rate of more than 90% release in the first 0.5 hours, such as more than 90% release in the first 10 minutes, such as more than 90% release in the first 5 minutes as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C.
- 15      35. The composition according to any one of the preceding claims, wherein the composition releases the compound of formula I at a rate of 100% release in the first 5 minutes as measured in a USP-I or a USP-II apparatus at pH 1.0 at 37 °C.
- 20      36. The composition according to any one of the preceding claims, wherein the composition provides for an  $AUC_{0-72}$  of the compound of formula I of at least 90% of the  $AUC_{0-72}$  of an aqueous solution of an equivalent amount of the compound of formula I after oral administration.
- 25      37. The composition according to any one of the preceding claims, wherein the composition provides for an  $AUC_{0-\infty}$  of the compound of formula I of at least 90% of the  $AUC_{0-\infty}$  of an aqueous solution of an equivalent amount of the compound of formula I after oral administration.
- 30      38. The composition according to any one of the preceding claims, wherein the composition provides for an  $AUC_{0-\infty}$  of the compound of formula I upon oral administration from 180 to 480 h·ng/mL, such as  $AUC_{0-\infty}$  from 250 to 350 h·ng/mL, such as  $AUC_{0-\infty}$  of about 300 h·ng/mL.
- 35      39. The composition according to any one of the preceding claims, wherein the composition comprises from about 0.1 mg to about 10 mg of the compound of formula (I).

40. The composition according to any one of the preceding claims, wherein the composition comprises 5mg of the compound of formula (I).

5 41. A unit dosage form comprising the composition according to any one of the preceding claims.

42. A method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)

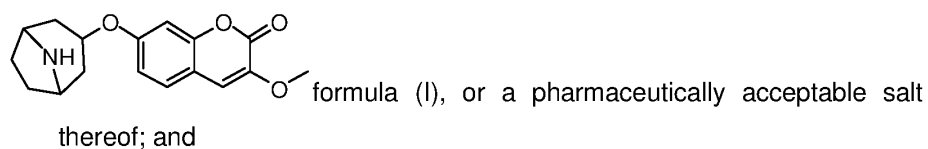


in a subject, wherein the  $t_{\max}$  of the compound of formula I is between 3 and 5 hours, said method comprising oral administration of a composition according to any one of the preceding claims.

15 43. The method according to claim 42, wherein the subject is a human.

44. A method of preparing a composition comprising pellets, the method comprising:

- 20 a) providing pellet core,  
b) providing a drug layer solution comprising a compound of formula (I)



- c) coating the drug layer solution on to the pellet core to form a drug layer.

25 45. The method according to claim 44, wherein:

- a. the pellet core is as described in any one of claims 10-11, and/or  
b. the drug layer solution comprises a binder, a pH modifier or stabilizer, and/or the compound of formula I as described in any one of claims 1-10 and 12-15.

30