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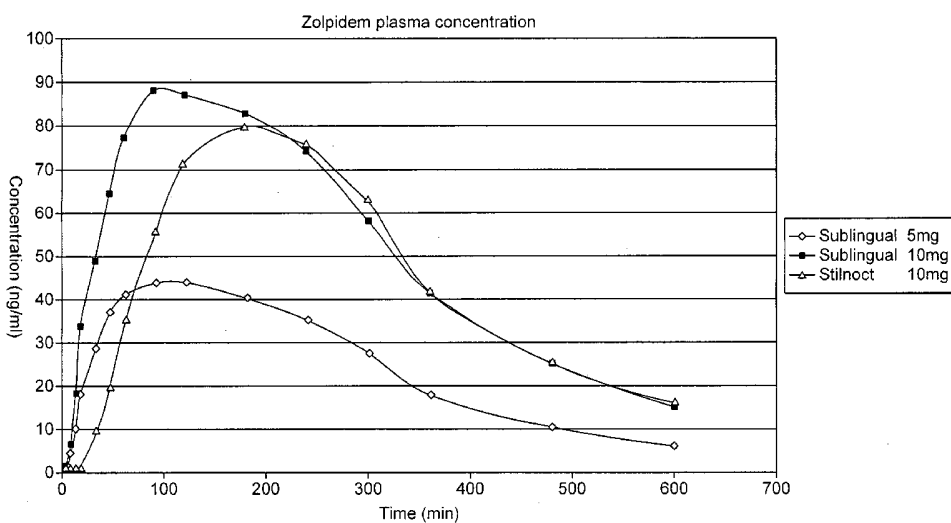
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(54) Title: NEW PHARMACEUTICAL FORMULATIONS USEFUL IN THE TREATMENT OF INSOMNIA



(57) Abstract: There is provided a formulation suitable for transmucosal administration comprising a short acting hypnotic drug, which formulation provides a measurable plasma concentration of drug within 10 minutes of administration. The formulation is capable of providing sleep on demand, and preferably comprises particles of drug, for example zolpidem or a pharmaceutically-acceptable salt thereof and a mucoadhesion promoting agent, such as sodium carboxymethylcellulose, which particles of drug and mucoadhesive are presented upon the surface of larger carrier particles.

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NEW PHARMACEUTICAL FORMULATIONS USEFUL IN THE TREATMENT OF INSOMNIA

This invention relates to new, fast acting pharmaceutical formulations comprising
5 short acting hypnotic agents that are useful in the short-term treatment of
insomnia, such as transient insomnia.

Insomnia is a common disorder characterised by difficulty in the initiation and/or
maintenance of sleep. Insomnia periodically affects 30% of adults. Furthermore,
10 more than 90% of the total population have trouble with sleep at some point
during their lives.

Inadequate sleep impairs quality of life and ability to function normally in a
general sense. It often results in adverse personal, medical or psychiatric
15 consequences, in addition to increasing the risk of accidents.

The disorder can be transient or chronic. Although isolated incidents of short-
term insomnia may be caused by, for example, grief, stress, or short-term exposure
to substances that are known to impair sleep, many patients who suffer from
20 transient insomnia may experience the disorder regularly and/or periodically on a
short-term basis.

In the treatment of short-term insomnia, consideration needs to be given to the
potential side effects of the medicament employed, including any associated drug
25 dependency. The practitioner also needs to be aware of the potential for
undesirable absorption of drug taking place several hours after administration,
which may give rise to decreased alertness and impaired psychomotor function
during normal activity the following day. In this respect, wherever possible, it is
important to expose patients only to short-term, or "on-demand", use of the lowest
30 effective dose of any particular drug.

Zolpidem (*N,N*-dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acet-
amide) is a short-acting sedative that is used in the short-term management of

insomnia. The drug possesses a short half-life and produces no active metabolites. It appears to act by binding to the benzodiazepine receptor component of the GABA receptor complex and accordingly possesses similar properties to the benzodiazepines. However, zolpidem has the general advantage of minimal
5 anxiolytic, myorelaxant and convulsant properties.

Currently-available zolpidem formulations comprise doses of between 5 and 10 mg of the drug in the form of its hemitartrate salt (see, for example, *British National Formulary*, Volume 48, pages 174 and 175). These compositions are
10 administered orally, typically before retiring, and rapidly disintegrate in the gastrointestinal tract to provide for systemic absorption of drug.

Although zolpidem is rapidly absorbed from the gastrointestinal tract, its bioavailability is reported to be 70% following oral administration. Peak plasma
15 concentrations are thereby typically reached within 1 and 5 hours of oral administration using current formulations.

In view of this, onset of action can be delayed in many patients, leading to a frustrating lack of “on demand” sleep, in addition, in many cases, to undesirable
20 residual effects (such as those mentioned hereinbefore) the following day. Equally importantly, in view of the first-pass and/or pre-systemic metabolism that is typically connected with oral administration, the use of currently-marketed zolpidem formulations is characterised by considerable inter- and intra-individual variability in terms of both onset of action and residual effects (see, for example,
25 Holm *et al*, *Drugs* (2000) **59**, 865; Darcourt *et al*, *J. Pharmacol.*, (1999) **13**, 81; Terzano *et al*, *Drug Safety* (2003) **26**, 261; Salvà and Costa, *Clin. Pharmacokinet.* (1995) **29**, 142; Drover *et al*, *Clin. Ther.* (2000) **22**, 1443; and “*Guidance for Industry; Labelling Guidance for Zolpidem Tablets*”, US Department of Health and Human Service (1997)).

30

Thus, there is a clear unmet clinical need for an improved formulation comprising a short acting hypnotic agent, such as zolpidem, which exhibits, in a consistent fashion, a more rapid, and preferably almost instantaneous, onset of action (e.g.

within minutes rather than hours), as well as fewer residual effects the following day.

A biphasic peroral dosage form comprising zolpidem has recently been described
5 in *inter alia* US patent No. 6,514,531 B1. This system provides for an initial
immediate release phase to induce sleep as rapidly as is possible with existing
commercial formulations. This is followed by a controlled-release phase with the
objective of maintaining sleep following induction. Other biphasic tablets
10 comprising zolpidem are disclosed in European patent application EP 1 260 216
A1.

US patent No. 6,638,535 B2 also discloses sustained release pellets comprising
short acting hypnotic agents, such as zolpidem, zopiclone and zaleplon which
provides for an *in vitro* release of less than 60% of active ingredient within the
15 first 5 minutes of the *in vitro* test.

International patent application WO 00/16750 discloses a drug delivery system for
the treatment of acute disorders by mucosal administration, in which the active
ingredient is in microparticulate form and is adhered to the surface of larger
20 carrier particles in the presence of a bioadhesion and/or mucoadhesion promoting
agent.

International patent application WO 03/059349 discloses oral dosage forms
comprising *inter alia* zolpidem, in addition to a solubility enhancer (e.g. a
25 surfactant) and a spheronization agent (e.g. a distilled monoglyceride).

The skilled person would expect that transmucosal administration of an active
ingredient across the pulmonary, nasal or oral mucosa (e.g. sublingual
administration) would give rise to an enhanced rate of absorption of that active
30 into plasma (as compared to an oral formulation), and thereby result in a vastly
increased bioavailability at an early stage following administration. In the
treatment of insomnia with a short acting hypnotic agent such as zolpidem, such
an enhanced rate of absorption might be expected to give rise to potential safety

problems in patients that are sensitive to the drug, potentially giving rise to undesirable pharmacological effects, such as a more rapid onset of sleep than is convenient (e.g. when preparing for sleep; see, for example col. 2, lines 9 to 18 of US 6,638,535 B2). Moreover, the skilled person would also expect such a rapid
5 absorption to compromise the duration of action of the relevant drug, and thereby the ability to maintain sleep during the night, especially given that short acting compounds are known to rapidly eliminated from plasma (see, for example, col. 2, lines 19 to 31 of US 6,638,535 B2).

10 Surprisingly, we have found that safe and reliable “on demand” sleep induction (and maintenance) may be provided by way of a formulation as described hereinafter.

According to a first aspect of the invention, there is provided a pharmaceutical
15 formulation suitable for transmucosal administration comprising a short acting hypnotic drug, which formulation provides a measurable plasma concentration of that drug within 10 minutes of administration.

The measurement of drug plasma concentration may be achieved by techniques
20 that are well known in the art, for example as described hereinafter.

However, as a guide, we have found that formulations suitable for transmucosal administration are capable of providing a measurable plasma concentration of drug within 10 minutes of administration if, when measured in a standard *in vitro*
25 dissolution (paddle) apparatus according to the United States Pharmacopoeia, using a phosphate buffer at pH 6.8 (USP) as dissolution medium, at least 50% of the active ingredient is released within 5 minutes, preferably within 4 minutes, for example within 3, or even 2, minutes. By the term “released” we mean that the active ingredient is released from the formulation and dissolved in the dissolution
30 medium.

We have found that formulations according to the present invention are capable of providing first measurable plasma drug concentrations with a surprising degree of

consistency, as expressed as the coefficient of variation (CV; a statistical measure of the deviation of a variable from its mean) for the time to first measurable plasma concentration. Observed CV values may be less than 50%, for example less than 40% for this variable.

5

Thus, as formulations according to the present invention consistently provide measurable plasma concentrations of drug within 10 minutes they are effectively capable of providing for consistent "on demand" sleep induction.

10 According to a further aspect of the invention, there is provided a transmucosal formulation suitable for providing sleep on demand, which formulation comprises a short acting hypnotic drug.

By "sleep on demand", we include that the formulation consistently induces sleep, 15 i.e. in at least 90% of cases (on an intra- and/or inter-patient basis), within 60 minutes, preferably within 45 minutes, more preferably within 30 minutes and especially within 20 (e.g. 15) minutes.

We have also found, very surprisingly, that formulations according to the present 20 invention are capable of providing rates of absorption of drug following administration that are not substantially different to those that are observed in currently-available oral formulations. In view of this, formulations according to the present invention are capable of reducing or preventing inconveniently rapid onset of sleep, or other undesirable pharmacological effects that might be 25 associated with rapid absorption, for example, in patients that are particularly sensitive to the relevant drug, as discussed hereinbefore.

In this respect, there is also provided a transmucosal formulation suitable for providing sleep on demand, which formulation comprises a short acting hypnotic 30 drug, wherein the formulation provides for a time difference between:

- (a) the first measurable; and
- (b) the maximum measured

plasma concentration of drug following administration of the formulation, which time difference is within the range of about 50 minutes to about 250 minutes, preferably about 55 minutes to about 230 minutes, more preferably about 70 minutes to about 180 minutes and particularly about 80 to about 160 minutes.

5

Equally surprisingly, we have also found that formulations according to the present invention are capable of providing levels of drug at an appropriate time after administration and following sleep induction that are not substantially different to those that are observed in currently-available oral formulations. In view of this, formulations according to the present invention are capable of maintaining a drug-induced sleep throughout the night.

In this respect, there is also provided a transmucosal formulation suitable for providing sleep on demand, which formulation comprises a short acting hypnotic drug, wherein the formulation provides for a plasma concentration of drug that is capable of maintaining sleep at least about 3 hours after administration of the formulation, preferably at least about 4 hours, more preferably at least about 5 hours and particularly at least about 6 hours, after administration. In otherwise healthy adult patients below the age of 60, plasma concentrations of drug that are capable of maintaining sleep are for example in the range of about 40 to about 100 ng/mL of plasma, for example about 50 to about 90 ng/mL, such as about 60 to about 85 ng/mL.

Furthermore, formulations according to the present invention are capable of providing levels of drug at an appropriate time after administration that do not give rise to the undesirable residual effects mentioned hereinbefore the following day.

In this respect, there is also provided a transmucosal formulation suitable for providing sleep on demand, which formulation comprises a short acting hypnotic drug, wherein the formulation provides for a plasma concentration of drug that that does not result in decreased alertness and/or impairment of psychomotor function in a patient following sleep at least about 8 hours, such as about 7 hours

after administration. In otherwise healthy adult patients below the age of 60, plasma concentrations of drug that are not capable of producing such effects, which effects may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, such effects), are, for example, less than about 40 ng/mL of plasma, for example less than about 30
5 ng/mL, such as less than about 25 ng/mL.

It will be appreciated by the skilled person that the aforementioned plasma concentration ranges of active ingredient are exemplary of the average case and are likely to vary with the severity of the insomnia that is to be treated, as well as
10 the age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. There can, of course, be individual instances where plasma concentrations that are outside the ranges specified above may give rise to the stated effects, and such are within the scope of this invention. For example, for
15 children or elderly patients, the aforementioned plasma concentration ranges may be approximately halved in order to produce (or not produce) the relevant effect.

Transmucosal drug delivery may be provided over the pulmonary, the nasal or, more preferably, the oral, mucosa. Pulmonary transmucosal drug delivery may be
20 provided, for example, by way of an inhaler comprising a powder formulation that includes the active ingredient. Nasal transmucosal drug delivery may be provided, for example, by way of a nasal spray comprising a powder formulation that includes the active ingredient. Oral transmucosal delivery may be provided, for example, by way of a spray comprising a powder formulation that includes the
25 active ingredient for spraying, for example, under the tongue, or by way of effervescent formulations or freeze-dried rapid melting tablet formulations, all of which are known to those skilled in the art.

However, we prefer that formulations according to the present invention are in the
30 form of sublingual tablets. Sublingual tablets that provide for sleep on demand may be prepared as described hereinafter.

According to a further aspect of the invention there is provided a sublingual tablet formulation that is suitable for providing sleep on demand, which formulation comprises particles of:

- (a) a short acting hypnotic drug; and
 - 5 (b) a mucoadhesion promoting agent,
- which particles of components (a) and (b) are each presented, at least in part, upon the surfaces of larger carrier particles.

It will be clear to the skilled person that formulations according to the present invention will comprise a pharmacologically effective amount of short acting
10 hypnotic drug (i.e. the “active” ingredient of the formulation). The term “pharmacologically effective amount” refers to an amount of active ingredient, which is capable of conferring the desired therapeutic effect on a treated patient, whether administered alone or in combination with another active ingredient.
15 Such an effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, an effect).

Short acting hypnotic drugs that may be employed in formulations according to the present invention include zopiclone, zaleplon, indeplon or, preferably,
20 zolpidem, and pharmaceutically acceptable salts of all of these. Also included are diastereomeric (e.g. enantiomeric) forms, as well as active metabolites, of these compounds/salts.

Preferred salts of zolpidem that may be employed include hydrochloride salts,
25 methanesulphonate salts, tosylate salts, fumarate salts, sulphate salts and tartrate salts, such as the hydrogen tartrate or the hemitartrate salt.

The active ingredient is preferably presented in the form of microparticles, preferably with a weight based mean diameter of between about 0.5 μm and about
30 15 μm , such as about 1 μm and about 10 μm . The term “weight based mean diameter” will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by

weight, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the weight fraction, as obtained e.g. by sieving.

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

The amount of active ingredient that may be employed in a sublingual tablet may be determined by the physician, or the skilled person, in relation to what will be most suitable for an individual patient. This is likely to vary with the severity of
10 the condition that is to be treated, as well as the age, weight, sex, renal function, hepatic function and response of the particular patient to be treated.

Suitable quantities of active ingredient that may be employed in tablet formulations may be in the range 2 to 20% by weight based upon the total weight
15 of the formulation. More preferably, formulations may contain between 4 and 17% by weight of active ingredient, and especially from about 5 to about 15%. The amount of active ingredient may also be expressed as the absolute amount in a tablet formulation. In such a case, the total amount of active ingredient that may be present may be sufficient to provide a dose of drug per tablet that is in the
20 range 3 to 15 mg, such as 4 to 13 mg and in particular between about 5 and about 12 mg.

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

Tablet formulations described herein comprise one or more mucoadhesion promoting agent and may thus facilitate the partial or complete adhesion of active ingredients to a biological surface, such as a mucosal membrane.
30

In the context of the present invention, the terms "mucoadhesive" and "mucoadhesion" refer to adhesion or adherence of a substance to a mucous membrane within the body. The skilled person will appreciate that the

expressions "mucoadhesion" and "bioadhesion" may often be used interchangeably. In this respect, the presence of a mucoadhesion promoting agent helps facilitate the partial or complete adhesion of sublingual tablets comprising active ingredient to the mucosal membrane under the tongue.

5

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

Examples of suitable mucoadhesion promoting agents include cellulose derivatives such as modified cellulose gum and, more particularly, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose and sodium carboxymethyl cellulose (NaCMC); starch derivatives such as modified starch, sodium starch glycolate and, more particularly, moderately cross-linked starch; acrylic polymers such as carbomer and its derivatives (Polycarbophil, Carbopol®, etc.); polyvinylpyrrolidone; polyethylene oxide (PEO); chitosan (poly-(D-glucosamine)); natural polymers such as gelatin, sodium alginate, pectin; scleroglucan; xanthan gum; guar gum; poly co-(methylvinyl ether/maleic anhydride); and crosscarmellose (e.g. crosscarmellose sodium). Such polymers may be crosslinked. Combinations of two or more bio/mucoadhesive polymers can also be used.

Suitable commercial sources for representative bio/mucoadhesive polymers include: Carbopol® acrylic copolymer (BF Goodrich Chemical Co, Cleveland, OH, USA); HPMC (Dow Chemical Co., Midland, MI, USA); NEC (Natrosol; Hercules Inc., Wilmington, DE. USA); HPC (Klucel®; Dow Chemical Co., Midland, MI, USA); NaCMC (Hercules Inc. Wilmington, DE. USA); PEO (Aldrich Chemicals, USA); sodium alginate (Edward Mandell Co., Inc., Carmel, NY, USA); pectin (BF Goodrich Chemical Co., Cleveland, OH, USA); crosslinked

polyvinylpyrrolidone (Kollidon CL®, BASF, Germany, Polyplasdone XL®, Polyplasdone XL-10® and Polyplasdone INF-10®, ISP Corp., US); Ac-Di-Sol® (modified cellulose gum with a high swellability; FMC Corp., USA); Actigum (Mero-Rousselot-Satia, Baupte, France); Satiaxana (Sanofi BioIndustries, Paris, France); Gantrez® (ISP, Milan, Italy); chitosan (Sigma, St Louis, MS, USA); and sodium starch glycolate (Primojel®, DMV International BV, Netherlands, Vivastar®, J. Rettenmaier & Söhne GmbH & Co., Germany, Explotab®, Roquette America, US).

10 However, preferred mucoadhesion promoting agents that may be employed in sublingual tablet formulations described herein include sodium carboxymethylcellulose.

Suitable forms of sodium carboxymethylcellulose include internally crosslinked sodium carboxymethylcellulose, such as croscarmellose sodium NF (e.g. Ac-Di-Sol® (FMC Corp., USA)).

Suitably, the amount of mucoadhesion promoting agent that is present in a tablet formulation may be in the range 0.1 to 25%, such as 0.5 to 15% and preferably 1 20 to 10% by weight based upon the total weight of the formulation. A preferred range is from 2 to 8%, such as from about 3.5 to about 6.5% (e.g. about 5%) by weight.

Tablet formulations described herein may comprise one or more binder and/or 25 disintegrating agent or "disintegrant". A binder may be defined as any material that is capable of acting as a bond formation enhancer, facilitating the compression of the powder mass into coherent compacts.

A disintegrant may be defined as any material that is capable of accelerating to a 30 measurable degree the disintegration/dispersion of a tablet formulation, and in particular carrier particles, as defined herein. This may be achieved, for example, by the material being capable of swelling and/or expanding when placed in contact

with water and/or mucous (e.g. saliva), thus causing the tablet formulations/carrier particles to disintegrate when so wetted.

Suitable disintegrants include cross-linked polyvinylpyrrolidone, carboxymethyl starch and natural starch, and suitable binders include cellulose gum and, particularly, microcrystalline cellulose.

Preferred forms of microcrystalline cellulose include silicified microcrystalline cellulose (a mixture of microcrystalline cellulose and a small amount of colloidal silicon dioxide), such as ProSolv[®] (JRS Pharma, Germany).

If present, binders and/or disintegrating agents are preferably employed in an amount of between 0.5 and 10% by weight based upon the total weight of the formulation. A preferred range is from 1 to 8% (e.g. 5%), such as from about 2.0 to about 3.0% (e.g. about 2.25%) by weight.

It should be noted that sodium carboxymethylcellulose may function in tablet formulations described herein both as mucoadhesion promoting agent and as a disintegrating agent.

Preferably, carrier particles for use in tablet formulations described herein are of a size that is between about 50 and about 750 μm , and preferably between about 100 and about 600 μm , such as between about 150 μm and about 400 μm (e.g. about 200 μm). Suitable carrier particle materials include carbohydrates, e.g. sugar, mannitol and lactose; pharmaceutically-acceptable inorganic salts, such as sodium chloride, calcium phosphate, dicalcium phosphate hydrate, dicalcium phosphate dehydrate, tricalcium phosphate, calcium carbonate, and barium sulfate; polymers, such as microcrystalline cellulose, cellulose and crosslinked polyvinylpyrrolidone; or mixtures thereof. It is preferred that the carrier particle material comprises a pharmaceutically-acceptable substance that is adequately soluble in water (e.g. exhibits a solubility of greater than 0.01 g/mL at room temperature and atmospheric pressure). Preferred materials thus include sugar

alcohols and/or sugars, such as mannitol and lactose, or pharmaceutically-acceptable inorganic salts, such as sodium chloride.

Preferred carrier particle materials include mannitol, such as granulated mannitol
5 (Pearlitol 400 DC; Roquette, France) and spray-dried mannitol (Parreck M200; Merck, Germany).

Carrier particles preferably comprise an amount of between 50 and 95% by weight based upon the total weight of the formulation. A preferred range is from 60 to
10 90%, such as from 65 to 85% (e.g. between about 70 and about 85%) by weight.

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

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

Tablet formulations may be prepared by standard techniques, using standard equipment known to the skilled person.

5 Active ingredient and other essential constituents mentioned hereinbefore may be combined with conventional pharmaceutical additives and/or excipients used in the art for such preparations, and thereafter preferably directly compressed/compacted into tablets. (See, for example, *Pharmaceutical Dosage Forms: Tablets. Volume 1*, 2nd Edition, Lieberman *et al* (eds.), Marcel Dekker,
10 New York and Basel (1989) p. 354-356 and the documents cited therein.)

Suitable further additives and/or excipients may thus comprise:

- 15 (a) surfactants or wetting agents, which may enhance that hydration of the active ingredient and carrier particles, resulting in faster initiation of both mucoadhesion and dissolution. If present, the surfactant should be provided in finely dispersed form and mixed intimately with the active ingredients. Examples of suitable surfactants include sodium lauryl sulphate, polysorbates, bile acid salts and mixtures thereof. If present, the surfactant may comprise between 0.3 and 5% by weight based upon the
20 total weight of the tablet formulation, and preferably between 0.5 and 3% by weight;
- (b) lubricants (such as sodium stearyl fumarate or, preferably, magnesium stearate). When a lubricant is employed it should be used in very small amounts (e.g. up to about 3%, and preferably up to 2%, by weight based
25 upon the total weight of the tablet formulation);
- (c) flavourings (e.g. lemon, menthol or, preferably, peppermint powder), sweeteners (e.g. neohesperidin) and dyestuffs; and/or
- (d) other ingredients, such as carrier agents, preservatives and gliding agents.

30 The various ingredients may be dry mixed together in several ways for a sufficient time in order to produce a mixture. This results in discrete particles of drug and other relevant excipients, in particular the mucoadhesion promoting agent, being presented on, and/or adhered to, the surfaces of the carrier particles. Standard

mixing equipment may be used in this regard. The mixing time period is likely to vary according to the equipment used.

Suitable compacting equipment includes standard tableting machines, such as the
5 Kilian SP300 or the Korsch EK0.

Irrespective of the foregoing, the tablet formulation should be essentially free (e.g. less than 20% by weight based on the total weight of the formulation) of water. It will be evident to the skilled person that "premature" hydration will dramatically
10 decrease the mucoadhesion promoting properties of a tablet formulation and may result in premature dissolution of the active ingredient.

Suitable final sublingual tablet weights are in the range 30 to 400 mg, such as 50 to 200 mg, for example 60 to 180 mg, more preferably between about 70 and
15 about 160 mg. Suitable final tablet diameters are in the range 4 to 10 mm, for example 5 to 9 mm, and more preferably about 6 to about 8 mm. A preferred tablet weight is about 80 mg and a preferred tablet diameter is about 6 mm.

Wherever the word "about" is employed herein in the context of concentrations
20 (e.g. of drug in plasma), timescales (e.g. *in vitro* drug release and measured/measurable drug plasma concentrations), dimensions (e.g. particle and tablet sizes), surface coverage (e.g. of carrier particles by active ingredient), and amounts (e.g. absolute doses of active ingredient and relative amounts of individual constituents), it will be appreciated that such variables are approximate
25 and as such may vary by $\pm 10\%$, e.g. $\pm 5\%$, from the numbers specified herein.

The tablet formulations described herein may be administered sublingually by way of appropriate dosing means known to the skilled person. A sublingual tablet may be placed under the tongue, and the active ingredients absorbed through the
30 surrounding mucous membrane.

The formulations according to the present invention are useful in the treatment of insomnia and particularly transient insomnia. According to a further aspect of the

invention there is provided a method of treatment of insomnia which method comprises administration of a formulation according to the invention to a person suffering from, or susceptible to, such a condition.

- 5 For the avoidance of doubt, by “treatment” we include the therapeutic treatment, as well as the symptomatic treatment, the prophylaxis, or the diagnosis, of a condition.

The formulations according to the present invention are easy and inexpensive to
10 manufacture, and consistently enable the rapid uptake of the active ingredient through the mucosa, such as the oral mucosa. This enables “on demand” sleep, which is achievable before retiring, following an interruption of sleep, or in other situations when rapid sleep induction is desired. Most usefully, formulations according to the present invention are capable of providing this effect, whilst at
15 the same time reducing or preventing inconveniently rapid onset of sleep in, for example, patients that are particularly sensitive to the relevant drug.

Furthermore, formulations according to the present invention are capable of maintaining a drug-induced sleep throughout the night, whilst at the same time
20 preventing or reducing the post-sleep residual effects mentioned hereinbefore.

Finally, the present invention enables these surprising effects to be achieved in a highly consistent manner, in which inter- and intra-individual variations are significantly reduced or eliminated, providing the physician and end user with a
25 dosage form that is capable of providing far more reliable sleep, both in terms of induction and duration.

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

Formulations according to the present invention may also have the advantage that they may be more efficacious than, be less toxic than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile than, and/or have other useful pharmacological, physical, or chemical properties over, pharmaceutical formulations known in the prior art, whether for use in the treatment of insomnia or otherwise.

The invention is illustrated by way of the following examples with reference to Figure 1, which shows a comparison of plasma concentrations of zolpidem produced by way of two sublingual tablet formulations according to the present invention *versus* a commercially-available peroral formulation.

Example 1

Preparation of Sublingual Tablets

Sublingual tablets comprising 5 mg and 10 mg of zolpidem hemitartrate were prepared as follows.

Zolpidem hemitartrate (Boehringer Ingelheim, Germany) was firstly ground for 20 minutes in a ball mill.

The active ingredient was then accurately weighed out, along with the other excipients (see below), in appropriate proportions that would enable the production of tablets with the absolute amounts of various ingredients mentioned below.

Pre-weighed quantities of zolpidem hemitartrate and mannitol (Parateck M200; Merck, Germany) were then mixed in a Turbula mixer for 96 hours. Then, pre-weighed quantities of silicified microcrystalline cellulose (ProSolv[®]; JRS Pharma, Germany), sodium carboxymethylcellulose (Croscarmellose Sodium NF; Ac-Di-Sol[®]; FMC Corp., USA), Neohesperidin DC (Exquim, Spain) and peppermint powder (Firmenich, Germany) were added and mixing was continued for 30

minutes. Finally, a pre-weighed quantity of magnesium stearate (Peter Greven, Netherlands) was added and mixing continued for another 2 minutes.

The powder mixture was then compacted using a single punch press (Korsch EK0) with 6 mm flat bevel edged punches, to produce tablets of a total weight of 80 mg.

The absolute amounts of individual ingredients are as presented in the table below.

In-process controls were employed (tablet weight, crushing strength, friability and disintegration time), with test samples being withdrawn throughout the tableting process. Tablets were packaged and labelled for use in Example 2.

| | 5 mg Tablet | 10 mg Tablet |
|---------------------------------------|-------------|--------------|
| Ingredient | Amount (mg) | Amount (mg) |
| zolpidem hemitartrate | 5.00 | 10.00 |
| mannitol | 65.00 | 60.00 |
| silicified microcrystalline cellulose | 1.80 | 1.80 |
| sodium carboxymethylcellulose | 4.00 | 4.00 |
| neohesperidin | 0.20 | 0.20 |
| peppermint powder | 3.00 | 3.00 |
| magnesium stearate | 1.00 | 1.00 |
| Total tablet weight | 80.00 | 80.00 |

15

Example 2

Clinical Study

An open randomized three-period crossover single-centre study was devised to evaluate the pharmacokinetic profile of the sublingual zolpidem 5 mg and 10 mg tablets prepared by way of Example 1 above, as compared to a peroral zolpidem formulation (Stilnoct[®] 10 mg; Sanofi-Synthélabo, France).

The trial was a pharmacokinetic study in healthy male and female volunteers to test for dose proportionality as between the two sublingual tablet formulations. The pharmacokinetic profiles were evaluated, focussing on bioavailability and time and rate of absorption. The study also included a subjective assessment of efficacy, i.e. the subjects' perceived degree of sedation.

18 healthy subjects aged between 18 and 40 were used in this study. Signed informed consents were obtained in all cases.

10

Each of the three formulations were given to each of the 18 volunteers, in a random order, at three visits to the study centre (hereinafter "Visits 1, 2 and 3"). Visits 1 and 2 were followed by a wash-out period of at least 2 days.

15 At a pre-study visit, the subjects underwent a full clinical examination to assess medical history, undertake a physical examination, with routine screens for haematology, clinical chemistry, drugs and alcohol. This pre-study visit was conducted no more than 14 days prior to Visit 1.

20 Blood samples for determination of the concentration of zolpidem in plasma were collected on 14 occasions on each study day. Samples were collected immediately before administration and at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480 and 600 minute intervals thereafter. Tolerability and safety parameters were followed during the study day. Subject-rated sedation scores by visual analogue
25 scales were assessed during each study day.

A safety follow-up visit, which included a physical examination, with routine screens for haematology and clinical chemistry was performed no more than 10 days after Visit 3.

30

Any of the following was regarded as a criterion for exclusion from the study:

1. the subject was overweight (i.e. with a body mass index of greater than 30);
2. the subject was a smoker;

3. if the subject had drunk alcohol within the previous 24 hours;
4. if the subject showed any evidence of drug abuse;
5. if the subject had used a prescription medication within the previous 14 days;
6. if, in the investigator's judgement, the subject exhibited clinically significant abnormalities at the screening examination or in the laboratory test results;
- 5 and
7. if the subject was female and was either pregnant, breast feeding or was of childbearing potential and was not using adequate birth control.

10 Subjects were free to discontinue their participation in the study at any time. A subject could be withdrawn from the study at any time at the discretion of the investigator. Subjects were to be discontinued from the study in event of, for example:

1. unacceptable adverse events;
- 15 2. non-compliance with the study protocol; or
3. failure to attend study visits.

However, all subjects completed the study in accordance with the protocol and none of the subjects were replaced.

20 Each subject received three single doses of each of the three formulations. The study nurse made sure that the formulations were administered correctly, with the sublingual tablets administered deeply under the tongue with the subject remaining in a supine position for at least ten minutes. The oral tablet was swallowed.

25 Confirmed eligible subjects were assigned a subject number in a strictly consecutive order. Each subject number was randomised to one of six possible treatment sequences (3 x 2 x 1) according to a computer generated randomisation list provided by the study statistician. Three subjects were thus assigned to each

30 treatment sequence.

In order to allow time for 10 hours of blood plasma sampling, administration of the study drug formulation took place at approximately 0800 hours on the morning of each visit.

- 5 The subjects fasted overnight before each visit. Upon arrival at the clinic, the subjects had a standard breakfast, after which study drug was administered. Standard meals were served during the study day, with lunch at 1200 hours and dinner at 1700 hours. Subjects had their meals after taking blood samples at 240 minutes and 480 minutes, and never directly before blood sampling.

10

Blood samples (7mL) were collected in heparinised Vacutainer[®] tubes. The samples were kept on ice and then centrifuged for 10 minutes at 2000 x g. The plasma was transferred into labelled plastic tubes and stored at -20°C prior to analysis. The frozen plasma samples were transported to Quintiles, Uppsala,
15 Sweden, where the zolpidem concentration in the samples was measured.

20

Pharmacokinetic variables were derived from the zolpidem plasma concentration time curve. The primary pharmacokinetic variable was AUC_{0-t} , i.e. the area under the zolpidem plasma concentration time curve from 0 minutes to 600 minutes after
administration of study drug.

To further evaluate the pharmacokinetic profile of the sublingual zolpidem formulations, the following secondary pharmacokinetic variables were derived from the plasma concentration time curve:

- 25 (a) the area under the curve from 0 minutes extrapolated to infinity ($AUC_{0-\infty}$);
(b) maximum plasma concentration (C_{max});
(c) time for maximum plasma concentration (t_{max});
(d) half-life of the active substance ($t_{1/2}$);
(e) first measurable plasma concentration (C_{first}); and
30 (f) time to first measurable plasma concentration (t_{first}).

The primary efficacy variable was subject-rated sedation as measured on a VAS. The VAS consisted of a 100 mm non-graded scale between the extremes

“completely awake” and “practically asleep”. The subjects were to fill in the sedation scales immediately before administration of study drug and at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, 540, 570 and 600 minutes afterwards. If the subject fell asleep, the study nurse made a note
5 of this in the case report form.

Safety variables included adverse events reported and laboratory assessments.

The recording of adverse events was made on each study visit and on the post-
10 study visit. Patients were also free to report adverse events between visits. Adverse events were to be registered by the reporting of spontaneously mentioned symptoms and by open questioning. The investigator and the medical/laboratory staff were also instructed to record any adverse event that they observed during the investigation.

15 Plasma concentrations of zolpidem were determined by using HPLC with fluorescence detection. This analytical procedure is capable of measuring concentrations of zolpidem in human plasma within the range 1.0 to 400 ng/mL. Zolpidem and an internal standard Trazodone were purified from human heparin
20 plasma by solid phase extraction using Bond Elute C₁₈ cartridges, rinsed with water and eluted with methanol. The eluate was injected onto a reversed phase C₁₈ LC column (150 x 4.6 mm, 5µm) with a mobile phase composed of acetonitrile:50 mM potassium phosphate buffer at pH 6.0 (4:6, v/v) and determined by fluorescence detection (excitation at 254 nm and emission at 400
25 nm).

The study was performed in accordance with Good Clinical Practise (GCP) and Good Laboratory Practise (GLP). In order to ensure the use of standard terminology, and the collection of accurate, consistent, complete and reliable data,
30 the study was preceded by a training session for the investigator and study nurses.

The study was regularly monitored by external monitors appointed by the study sponsor. Complete source data verification of all parameters was performed and

the case report forms were thereafter collected from the study site. Data was checked for accuracy by proof-reading, entered into a database, validated and analysed by the sponsor. All corrections and additions were signed and dated by the investigator.

5

Log AUC and log dose adjusted AUC were analysed using the SAS statistical program PROC GLM (SAS Institute Inc., Cary, NC, USA) with subject, treatment and period as class variables. Differences between treatments were given as 90% confidence intervals. Equivalence, and dose proportionality, respectively, were considered proven if the 90% confidence interval for the difference between treatments/doses did not exceed $\pm 20\%$ (or the ratio was within 0.80 and 1.25).

The quality of the determination of zolpidem concentration was satisfactory and within the quality control (QC) acceptance criteria of $\pm 15\%$. The lower limit of quantification was 1.00 ng/ml for zolpidem in human plasma. The mean accuracy of the assay as determined from the analysis of QC samples was within $\pm 10.0\%$.

15

Results

Pharmacokinetic data for all subjects are given as mean values in Table 1.

25

30

Table 1

Non-compartmental pharmacokinetic parameters (mean and SD) of zolpidem following sublingual and oral administration (n=18).

| PK Parameter | 5 mg sublingual | 10 mg sublingual | Stilnoct [®] |
|-----------------------------------|------------------------|-------------------------|-------------------------|
| AUC _{0-t} (min•ng/ml) | 14913.8 (SD 6714.2) | 30855.5 (SD 14446.7) | 26879.1 (SD 14605.3) |
| AUC _{0-∞} (min•ng/ml) | 16064.3 (SD 7770.4) | 33466.2 (SD 16682.5) | 30093.7 (SD 18976.9) |
| C _{first} (ng/ml) | 5.2 (SD 2.8) | 8.7 (SD 5.8) | 10.8 (SD 11.5) |
| t _{first} (min) | 6.4 (SD 2.3) | 6.4 (SD 2.3) | 47.5 (SD 34.6) |
| C _{max} (ng/ml) | 50.0 (SD 20.8) | 98.8 (SD 32.7) | 90.6 (SD 35.1) |
| t _{max} (min) | 92.5 (SD 42.8) | 122.5 (SD 58.3) | 176.7 (SD 79.6) |
| t _{1/2} (h) | 2.57 (SD 0.79) | 2.56 (SD 0.82) | 2.58 (SD 1.04) |

5

These results demonstrate bioequivalence between the 10 mg sublingual tablet and Stilnoct[®] (10 mg) for AUC_{0-t}. Dose proportionality between sublingual zolpidem 5 mg and 10 mg tablets for dose adjusted AUC_{0-t} was established.

- 10 Most surprisingly, the time to the first measurable plasma concentration (t_{first}) and the time to the maximum plasma concentration (t_{max}) are significantly shorter for the 10 mg sublingual tablet, as compared to Stilnoct[®] (p<0.0001 and 0.0165, respectively). See also Figure 1 in this regard. The difference in the slope of the absorption curves i.e. absorption rate, is not statistically significant (p=0.478).
- 15 Mean absorption rates are given in Table 2.

Table 2

Absorption rate (slope of absorption phase of concentration-time curve) by treatment, mean (SD) (n=18).

| 5 mg sublingual | 10 mg sublingual | Stilnoct® (10 mg) |
|--------------------|--------------------|--------------------|
| 0.0344 (0.0108) | 0.0359 (0.0135) | 0.0315 (0.0206) |

5

The elimination half-life ($t_{1/2}$) of zolpidem was similar for the two sublingual tablets (2.57 and 2.56 hours, respectively), indicating that the elimination kinetics are linear. There was also no statistically significant difference in $t_{1/2}$ between the two sublingual tablets and Stilnoct® (2.58 hours). Elimination rates are given in

10 Table 3.

Table 3

Elimination rate (slope of elimination phase of concentration-time curve) by treatment, mean (SD) (n=18).

15

| 5 mg sublingual | 10 mg sublingual | Stilnoct® (10 mg) |
|---------------------|---------------------|---------------------|
| -0.0050 (0.0014) | -0.0052 (0.0021) | -0.0052 (0.0019) |

Subject-rated sedation VAS scores were assessed and compared between treatments. No significant differences in efficacy between treatments was found. However, after adjustment for period baseline VAS values (change from baseline) there was a statistically significant difference in mean VAS change from baseline between the sublingual 10 mg tablet and Stilnoct® in favour of the former (p=0.0062).

The number of subjects asleep was observed during ten hours following administration of the study drug. With the sublingual 10 mg tablet, more subjects were asleep at 90 minutes than for Stilnoct®.

To further assess and compare sleep after the different study drug administrations, the following values were calculated:

- (a) first time of sleep (i.e. sleep latency; mean per treatment);
- 5 (b) total number of sleep episodes (i.e. the total number of 30 minute episodes any subject was asleep per treatment; there were 377 episodes altogether); and
- (c) total sleeping time (mean per treatment).

10 Table 4

Additional sleep variables (n=18)

| Sleep variable | 5 mg sublingual | 10 mg sublingual | Stilnoct [®] 10 mg |
|--|-------------------|--------------------|-----------------------------|
| First time of sleep (mean min) | 100.6 (39.6) | 85.0 (31.3) | 95.6 (38.3) |
| Total number of sleep episodes (n/377 and %) | 81/377 (21.5%) | 101/377 (26.8%) | 101/377 (26.8%) |
| Total sleep time (mean min) | 135.0 (70.7) | 168.3 (74.3) | 168.3 (98.8) |

For the sublingual 10 mg tablet and Stilnoct[®], the total sleeping time as well as the
 15 number of sleeping episodes were similar, indicating that subjects slept equally long and deeply after administration of the two study drugs. The first time of sleep, however, occurred earlier for the sublingual 10 mg tablet, indicating that the onset of hypnotic effect is earlier for sublingual zolpidem compared to the oral administration (see Table 4).

20

In terms of safety, there were no unexpected or serious adverse events for any of the study medications.

Conclusions

This study shows that sublingual zolpidem (10 mg) tablets are bioequivalent to a peroral zolpidem formulation (Stilnoct®; 10 mg), with regard to AUC_{0-t} , AUC_{0-inf} and C_{max} . The pharmacokinetic analysis further shows that the extent of absorption and bioavailability of zolpidem was linear throughout the studied dose interval. In addition, the initial absorption rate of sublingual zolpidem is unaffected by the dose, which indicates that the same time to onset of effect can be expected for both doses.

10

There were no statistically significant differences between doses for dose adjusted AUC and C_{max} , and dose proportionality of sublingual zolpidem 5 mg and 10 mg was established. The linear increase of the AUC with increased dose provides strong evidence for a similar extent of absorption of zolpidem after sublingual administration of the studied doses in these subjects.

15

Dose proportionality of sublingual zolpidem (5 mg and 10 mg tablets) was established, with t_{first} and t_{max} being significantly shorter for sublingual zolpidem. This demonstrated that an earlier absorption into the blood stream is achieved compared to oral administration. There is no statistically significant difference in the rate of absorption for sublingual zolpidem and Stilnoct® 10 mg, assessed from the slope of the absorption phase of the plasma time-concentration curves.

20

The lower inter- and intra-individual variability in the pharmacokinetic parameters of sublingual zolpidem *versus* oral zolpidem in healthy volunteers, suggest that the *in vivo* performance of the sublingual tablet is better.

25

There was a greater number of subjects falling asleep earlier after administration with sublingual 10 mg tablets, compared to the other study treatments. The mean total sleeping time, as well as the number of sleeping episodes was similar after treatment with sublingual 10 mg tablets and Stilnoct®.

30

These results indicate that formulations according to the present invention may be capable of providing, in a consistent fashion, sleep on demand in insomnia patients.

Claims

1. A pharmaceutical formulation suitable for transmucosal administration comprising a short acting hypnotic drug, which formulation provides a measurable
5 plasma concentration of drug within 10 minutes of administration.
2. A formulation as claimed in Claim 1, wherein, when measured in a standard *in vitro* paddle apparatus according to the United States Pharmacopoeia, using a phosphate buffer at pH 6.8 (USP) as dissolution medium, at least 50% of
10 the drug that is initially present in the formulation is released within 5 minutes.
3. A formulation as claimed in Claim 2, wherein the drug is released within 3 minutes.
- 15 4. A transmucosal formulation comprising a short acting hypnotic drug.
5. A formulation as claimed in Claim 4, which is suitable for providing sleep on demand.
- 20 6. A formulation as claimed in any one of the preceding claims, wherein the formulation provides for a time difference between:
(a) the first measurable; and
(b) the maximum measured
plasma concentration of drug following administration of the formulation, which
25 time difference is within the range of about 80 minutes to about 160 minutes.
7. A formulation as claimed in any one of the preceding claims, wherein the formulation provides for a plasma concentration of drug that is capable of maintaining sleep at least about 6 hours after administration.
- 30 8. A formulation as claimed in any one of the preceding claims, wherein the formulation provides for a plasma concentration of drug that does not result in

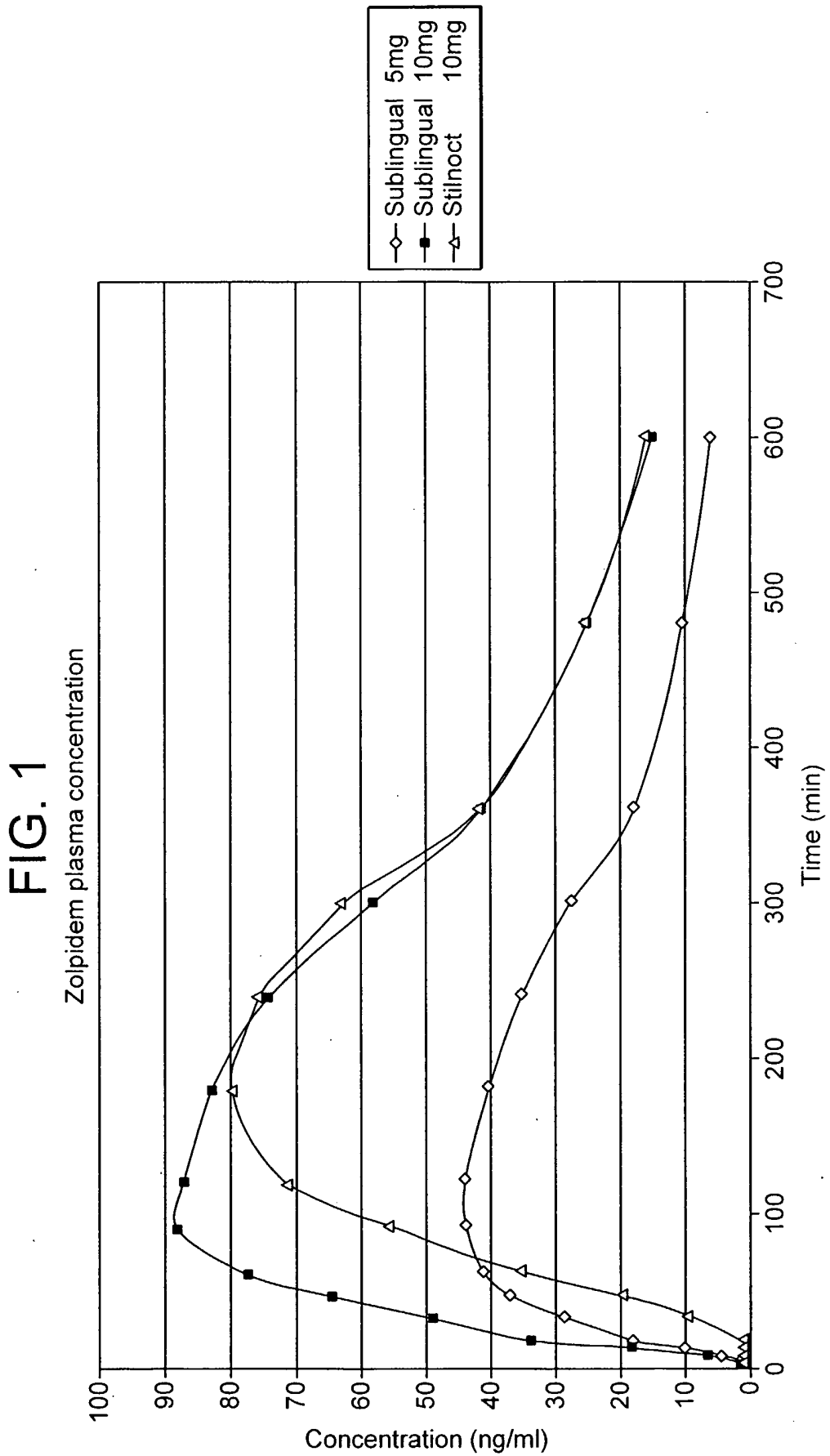
decreased alertness and/or impairment of psychomotor function in a patient following sleep at least about 7 hours after administration.

9. A formulation as claimed in any one of the preceding claims, which is
5 suitable for administration across the oral mucosa.
10. A formulation as claimed in Claim 9, which is a sublingual tablet.
11. A formulation as claimed in Claim 10, which comprises particles of:
10 (a) the short acting hypnotic drug; and
(b) a mucoadhesion promoting agent,
which particles of components (a) and (b) are each presented, at least in part, upon
the surfaces of larger carrier particles.
12. A formulation as claimed in any one of the preceding claims, wherein the
15 drug is zolpidem or a pharmaceutically acceptable salt thereof.
13. A formulation as claimed in Claim 12 wherein the salt is zolpidem
hemitartrate.
20
14. A formulation as claimed in any one of the preceding claims, wherein the
drug is in the form of microparticles.
15. A formulation as claimed in Claim 14, wherein the microparticles have a
25 weight based mean diameter of between about 1 and about 10 μm .
16. A formulation as claimed in any one of the preceding claims, wherein the
amount of drug is in the range of about 5% to about 15% by weight.
17. A formulation as claimed in any one of the preceding claims, wherein the
30 dose of drug per tablet is in the range of about 5 mg to about 12 mg.

18. A formulation as claimed in any one of Claims 11 to 17, wherein the mucoadhesion promoting agent is sodium carboxymethylcellulose.
19. A formulation as claimed in Claim 18, wherein the sodium
5 carboxymethylcellulose is internally crosslinked sodium carboxymethylcellulose (croscarmellose sodium).
20. A formulation as claimed in any one of Claims 11 to 19, wherein the amount of mucoadhesion promoting agent that is present is in the range of about
10 3.5% to about 6.5% by weight.
21. A formulation as claimed in any one of Claims 11 to 20 which further comprises and binder or disintegrating agent.
- 15 22. A formulation as claimed in Claim 21, wherein the binder is microcrystalline cellulose.
23. A formulation as claimed in Claim 22, wherein the microcrystalline cellulose is silicified microcrystalline cellulose.
20
24. A formulation as claimed in any one of Claims 11 to 23, wherein the amount of binder/disintegrating agent is in the range of about 2.0% to about 3.0% by weight.
- 25 25. A formulation as claimed in any one of Claims 11 to 24, wherein the size of the carrier particles is in the range of about 150 to about 400 μm .
26. A formulation as claimed in any one of Claims 11 to 25, wherein the carrier particles comprise mannitol.
30
27. A formulation as claimed in Claim 26, wherein the mannitol is spray-dried mannitol.

28. A formulation as claimed in any one of Claims 11 to 27, wherein the carrier particles are present in an amount of between about 70% and about 85% by weight.
- 5 29. A formulation as claimed in any one of Claims 11 to 28, wherein the relative sizes and amounts of the particles of active ingredient and the carrier particles that are employed are sufficient to ensure that the carrier particles may be at least about 90% covered by the active ingredient.
- 10 30. A formulation as claimed in Claim 29, wherein the coverage is between about 130% and about 180%.
31. A formulation as claimed in any one of Claims 11 to 30, which further comprises a lubricant.
- 15 32. A formulation as claimed in Claim 31, wherein the lubricant is magnesium stearate.
33. A formulation as claimed in any one of Claims 10 to 32 wherein the tablet weight is about 80 mg and the tablet diameter is about 6 mm.
- 20 34. A process for the preparation of a formulation as claimed in any one of Claims 11 to 33, which comprises dry mixing the ingredients together to produce a mixture, followed by directly compressing or compacting the resultant mixture into tablet form.
- 25 35. A process as claimed in Claim 34 wherein:
- (i) the drug is first mixed with the carrier particles;
 - (ii) the mucoadhesion promoting agent, and any other optional additives or ingredients (such as a binder or a disintegrating agent), are then added to the mixture with continued mixing;
 - (iii) a lubricant is then added to the mixture with continued mixing; and
 - (iv) compaction is then carried out in a single punch press.
- 30

36. A formulation obtainable by a process according to Claim 34 or Claim 35.
37. Use of formulation as defined in any one of Claims 1 to 33 or 36 for the
5 manufacture of a medicament for the treatment of insomnia.
38. A use as claimed in Claim 37 wherein the insomnia is transient insomnia.
39. A method of treatment of insomnia which method comprises
10 administration of a formulation as defined in any one of Claims 1 to 33 or 36 to a
patient suffering from, or susceptible to, such a condition.
40. A method as claimed in Claim 39 wherein the insomnia is transient
insomnia.
15
41. A method of providing sleep on demand, which method comprises
administration of a formulation as defined in any one of Claims 1 to 33 or 36 to a
patient in need of such sleep.
- 20 42. A method of reducing the level of inter- and/or intra-patient variability in
sleep induction and/or maintenance in one or more patients receiving a short
acting hypnotic drug, which method comprises administration of a formulation as
defined in any one of Claims 1 to 33 or 36 to said one or more patients.



INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2005/004147

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P25/20 A61K9/00 A61K31/44

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

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

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | EP 1 260 216 A (PEIRCE MANAGEMENT, LLC) 27 November 2002 (2002-11-27) page 11, line 40 - page 12, line 6; claims 1-3,26; example 2 page 2, lines 5,6,49-51 | 1-42 |
| X | WO 00/33835 A (SANOFI-SYNTHELABO; ALAUX, GERARD; LEWIS, GARETH; ANDRE, FREDERIC) 15 June 2000 (2000-06-15) cited in the application page 1, last paragraph - page 2, paragraph 2; figures; examples page 4, line 35 - page 5, line 35; example 2 figure 5 | 1-42 |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 March 2006

Date of mailing of the international search report

16/03/2006

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2005/004147

(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|--|
| X | WO 00/16750 A (DIABACT AB; PETTERSSON, ANDERS; NYSTROEM, CHRISTER) 30 March 2000 (2000-03-30) cited in the application page 9, line 13; claims 1-7,11-15,17,19 ----- | 1-42 |
| X | WO 03/059349 A (BIOVAIL LABORATORIES INC; O'TOOLE, EDEL; FOGARTY, SIOBHAN) 24 July 2003 (2003-07-24) cited in the application claims; figures; examples page 28, lines 15-20 ----- | 1-42 |
| X | WO 01/30391 A (FARMARC NEDERLAND BV; PENKLER, LAWRENCE, JOHN) 3 May 2001 (2001-05-03) page 1, paragraph 2 page 3, paragraph 2; claim 1 ----- | 1-9 |
| X | DATABASE WPI Section Ch, Week 200368 Derwent Publications Ltd., London, GB; Class B05, AN 2003-713684 XP002325581 & CN 1 418 631 A (WANG D) 21 May 2003 (2003-05-21) abstract ----- | 1-10, 36-42 |
| X | DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 December 2001 (2001-12-04), YUAN, SHIJUN ET AL: "Freeze dried Zaleplon instant oral composition" XP002325587 retrieved from STN Database accession no. 2001:871521 abstract & CN 1 290 525 CN (WANQUAN SUNLIGHT MEDICINE SCIENCE AND TECHNOLOGY CO., LTD., PEOP. REP.) 11 April 2001 (2001-04-11) ----- | 1-11,17, 25,26, 36-42 |
| P,X | WO 2004/091585 A (SYNTHON B.V; PLATTEEUW, JOHANNES, JAN; VAN DEN HEUVEL, DENNIE, JOHAN,) 28 October 2004 (2004-10-28) example 20 ----- | 1-14, 16-19, 21,22, 30,33, 35-42 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004147

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 39-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

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