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Application of Surge Dose[®] fast dissolution technology to eszopiclone

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1 Executive Summary

Eszopiclone is a non-benzodiazepine (non-BZ) sedative hypnotic approved as an immediate release product for the effective treatment of transient and chronic insomnia in adults. In such indications, fast and consistent onset of action is an essential clinical requirement. This review presents the technical rationale for a fast dissolving Surge Dose[®] eszopiclone which is expected to provide advantages over the existing Lunesta[®] tablets as a result of faster and more consistent absorption reducing T_{max} values. Improved clinical outcomes would include reduction in the mean sleep latency with fewer patients experiencing delayed onset of action, and less next day sleepiness resulting from slow absorption and subsequent slower elimination.

Imaginot's patented Surge Dose[®] technology has been designed to minimise the time for *in vivo* dissolution under the wide range of physiological conditions found in the general population. These include less acidic and neutral pH, fed state and gut stasis, all of which slow *in vivo* dissolution and absorption. Based on *in vivo* pharmacokinetic (PK) studies with paracetamol tablets, faster *in vivo* dissolution leads to faster absorption with reduced inter- and intra-patient variability that for some drugs such as paracetamol can result in sub-therapeutic plasma concentrations. PK-PD (pharmacodynamic) modelling predicts that fast dissolving paracetamol tablets demonstrate higher clinical efficacy than conventional tablets.

Eszopiclone is a basic drug with a pKa of 6.7 which is covered by the broad platform claims in Imaginot's patents. No experimental work has been conducted on Surge Dose[®] eszopiclone, but work on zolpidem, another non-BZ hypnotic with similar physico-chemical properties, has shown that Surge Dose[®] significantly improves the *in vitro* dissolution rate exceeding 85 % dissolution in 3 minutes even under the most unfavourable test conditions. Similar ultrafast *in vitro* dissolution would be expected with optimised Surge Dose[®] eszopiclone tablets.

Eszopiclone is lipophilic and is well absorbed by passive diffusion across the intestinal mucosa showing good PK-PD correlation. It is generally described as fast acting with a time to peak plasma concentration (T_{max}) around 1 hour based on the median values from PK studies. However closer analysis of available data indicates that eszopiclone absorption is highly variable with individual T_{max} values ranging from 15 minutes to 3 hours. Longer mean T_{max} values in the region of 1.7 hours indicate that the distribution of T_{max} values is non-normal with a tail of subjects exhibiting delayed absorption. Slower absorption would be expected to be associated with slower onset of action which could be

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a major contributor to the variability in the clinical responses such as sleep latency (SL), a measure of the onset of action. This would also result in elimination over an extended period such that plasma concentrations of eszopiclone remain above the minimum level of 10 ng/mL reported for hypnotic effects until the next day. This may be responsible for the relatively high incidence of somnolence reported as an adverse event for eszopiclone, reported as up to 10 %, which in some cases results in patients discontinuing medication.

Typically, where delays in absorption occur as a result of slow and variable *in vivo* dissolution, this can be seen when comparing PK data on solutions and tablets. However available studies on eszopiclone solutions and tablets use infrequent sampling schedules with only four samples in the first two hours at 30 minute intervals, resulting in the same median T_{max} values of 1 hour quoted for both. As no mean values or ranges are available, it is not possible to estimate the impact of *in vivo* dissolution on eszopiclone absorption.

Nonetheless, rapid *in vivo* dissolution will deliver the eszopiclone in solution to the small intestine to drive fast passive absorption. Imaginot's Surge Dose[®] technology will maximise the solubility of this drug under a wide range of different conditions leading to faster and more complete *in vivo* dissolution, and hence faster and more consistent absorption. It would be expected that a fast dissolving Surge Dose[®] eszopiclone will produce more short T_{max} values in a study, thus reducing the mean T_{max} from around 1.7 hours towards 1 hour. With more frequent sampling in the first two hours, shorter mean and median T_{max} values would be expected for a Surge Dose[®] eszopiclone with a shorter median T_{max} in the region of 30 – 45 minutes.

Further formulation and process development work will be required to optimise Surge Dose[®] eszopiclone tablets to maximise the rate of dissolution. However formulations use GRAS excipients and no major issues would be expected in achieving product registration.

In the US, assuming the validity of current patents, eszopiclone will be effectively free from generic competition until patent expiry on 14 Feb 2014 or as late as 14 Aug 2014 if paediatric exclusivity is granted. There is already one generic with tentative approval for 1, 2 and 3 mg tablets (Lupin) and more would be expected. This review concludes that, subject to commercial considerations, there is a technically supportable opportunity to develop and register an improved Surge Dose[®] eszopiclone under the current Lunesta[®] brand, switching the market to the new formulation before patent expiry and potentially reducing the impact of generic competition.

2 Imaginot Pty Ltd and Surge Dose[®]

2.1 Surge Dose[®] activated ultra-rapid dissolution formulation technology

Imaginot is a privately owned, early stage drug delivery company based in Queensland, Australia. It has developed a ultra-rapid activated dissolution formulation technology suitable for a range of orally administered drugs covered by three patent families. This Surge Dose[®] technology has been exemplified *in vitro* and *in vivo* with paracetamol as a model drug and marker for liquid gastric emptying, and *in vitro* with more than 30 commonly used small molecule drugs classified by chemical class as acidic, basic, amphoteric and unionized. Surge Dose[®] formulations achieve ultra fast *in vitro* dissolution under both favourable and unfavourable test conditions reflecting the wide range of physiological conditions that occur in the general population.

Surge Dose[®] formulations are optimized for each drug with pH modulating agents (pHMA) and water uptake agents (WUA) to maximise any pH solubility effects and rate and extent of dissolution. Highly discriminating *in vitro* dissolution methods are used that have been developed as a development rather than a QC tool. These use standard dissolution equipment with different media at 37 °C, volumes and stirring speeds to simulate a wide range of *in vivo* conditions:

- 900 mL 0.05 M HCl at 30 rpm, pH 1.2, where the acidity is similar to that in the fasted stomach, but the volume and total amount of acid is much higher than would be found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH is 2.2, containing the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo* – which are the conditions used to characterise the performance of Surge Dose[®] formulations in the Imaginot patents, under which basic drugs will achieve at least 70 % dissolution in 180 seconds
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, containing 3 mmoles of acid in a volume to simulate the use of 170 mL co-administered water added to around 30 mL acidic gastric contents in the fasted state
- 200 mL 0.0033 M HCl at 30 rpm containing lower levels of acid in a typical physiological volume which simulates lower gastric acidity
- 900 mL 0.0033 M HCl at 0 rpm to simulate gut stasis such as occurs in migraine and the fed state where there is little gastric motility

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Surge Dose[®] formulations use GRAS ingredients and can be successfully manufactured by conventional tableting processes such as direct compression or wet granulation. For maximum stability, tablets must be manufactured under controlled low relative humidity conditions and should be unit packed in a suitable laminate.

A number of Surge Dose[®] formulations have now been developed which demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low humidity conditions. The first Surge Dose[®] product containing lornoxicam was launched in 2010 with a second product to be launched in 2012.

Imaginot is now seeking partners to commercialize its Surge Dose[®] technology. To date, deals involve a major international pharmaceutical company (confidential), a French drug delivery company (Ethypharm SA), India's largest pharmaceutical company (Abbott Healthcare Pvt Ltd) and Piramal Healthcare Ltd <Piramal>, an international drug delivery technology contract development and manufacturing company. Piramal can undertake formulation development, biostudies and contract manufacture of products based on the Surge Dose[®] technology for interested parties.

2.2 Proof of concept PK studies

2.2.1 Paracetamol

A proof of concept Phase I study in 25 fasted healthy subjects showed that the fast dissolving Surge Dose[®] paracetamol tablets achieved faster *in vivo* absorption than conventional slower dissolving commercial tablets, with good *in vitro in vivo* correlations (IVIVC)¹. Tablets with fast *in vitro* dissolution resulted in a higher frequency of fast absorption occasions where each fast absorption occasion was associated with a higher peak plasma concentration compared with slow absorption occasions. For some of the slow absorption profiles, it was notable that peak plasma concentrations of paracetamol failed to reach the documented 10 µg/mL minimum therapeutic plasma concentration for analgesia and antipyresis.

¹ Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

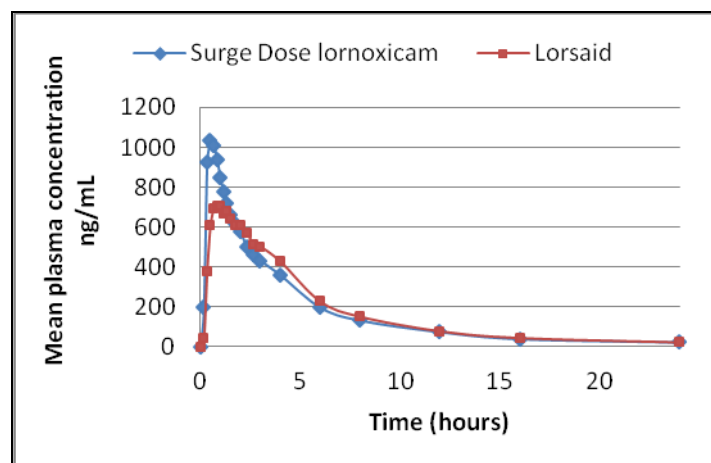
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Using PK-PD modelling to quantify pain relief following oral administration, more rapid onset and greater analgesia have been predicted for Surge Dose[®] paracetamol tablets compared with conventional tablets².

2.2.2 Lornoxicam

A film coated Surge Dose[®] lornoxicam 8 mg tablet was developed containing optimized levels of pHMA and WUA to meet the Surge Dose[®] in vitro dissolution specifications. A Phase I PK study in 24 fasted healthy subjects showed significantly faster absorption than Lorsaid[®] (Hetero Drugs Limited) as shown in Figure 1³. Compared with other generic lornoxicam tablets, Lorsaid[®] showed more extensive in vitro dissolution but did not meet the Surge Dose[®] specification.

Figure 1 Mean absorption profiles for 8 mg lornoxicam administered orally as a Surge Dose[®] tablet and Lorsaid[®]



- Mean and median T_{max} values for Surge Dose[®] lornoxicam were comparable at 0.51 and 0.50 h respectively, ranging from 0.3 to 1 h
- Median T_{max} for Lorsaid[®] was 0.83 h ranging from 0.5 to 2.3 h with a longer mean T_{max} of 1.06 h indicating a tail of subjects with slow absorption

² Green B, Chandler S, Macdonald G, Elliott G, Roberts MS, Quantifying pain relief following administration of a novel formulation of paracetamol (acetaminophen), *J. Clin. Pharmacol.* (2010) Online First doi 10.1177/0091270009359181

³ Wellquest Clinical Research. Report No CR-BE-267-LORN-2009. An open label, balanced, randomised, two-treatment, two-period, two-sequence, cross-over, single-dose bioequivalence study of Lornoxicam Rapid Release 8 mg tablets comparing with Lornoxicam 8 mg tablets in healthy adult human subjects under fasting conditions. 11 Aug 2010

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- 75 % subjects on Surge Dose[®] lornoxicam achieved T_{max} within the first 0.5 h compared with only 8 % for Lorsaid[®]
- Surge Dose[®] lornoxicam achieved C_{max} comparable with parenteral administration⁴, around 40 % higher than Lorsaid[®] with mean C_{max} 1,098 ng/mL (CV 18.71 %) compared with 788 ng/mL (CV 18.69 %)
- Although $AUC_{0-\infty}$ was the same for both Surge Dose[®] and Lorsaid[®] with values around 4,200 ng.h/mL, early exposure AUC values after 10, 20 and 30 min demonstrated significantly faster absorption with Surge Dose[®] lornoxicam, respectively 3.9, 2.8 and 2.2 times higher than Lorsaid[®]

2.2.3 Diclofenac

A film coated Surge Dose[®] diclofenac sodium 50 mg tablet was developed containing optimized levels of pHMA and WUA to meet the Surge Dose[®] in vitro dissolution specifications. This was compared with Voveran[®]-D (Novartis), a dispersible tablet dissolved in water before administration containing 46.5 mg diclofenac free acid equivalent to 50 mg diclofenac sodium. This Phase I PK study in 21 fasted healthy subjects demonstrated faster and more consistent absorption of diclofenac with significantly higher C_{max} for Surge Dose[®] as shown in Figure 2⁵.

Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (\pm 5.0) and 19.5 min (range 5 – 30 min). By comparison Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h). Surge Dose[®] tablets resulted in significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. C_{max} values for Surge Dose[®] were comparable with those obtained following IV^{6,7} or IM^{8,9} administration whereas as those for Voveran[®]-D were lower than reported for standard tablets of $1,340 \pm 627$ ng/mL¹⁰.

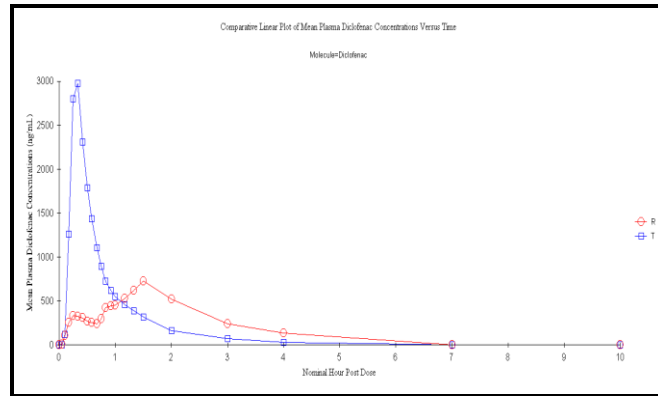
⁴ Radhofer-Welte S, Dittrich P, Simin M, Branebjerg PE. Comparative bioavailability of lornoxicam as single doses of quick release tablet, standard tablet and intramuscular injection – a randomized, open-label, crossover Phase I study in healthy volunteers. *Clin Drug Invest.* (2008) **28**(6): 345-51

⁵ Piramal Clinical Research. Report No CR-BE-324-DICL-2011 (draft) An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single-dose comparative pharmacokinetic study of Diclofenac Rapid Release tablets 50 mg sodium diclofenac comparing with Voveran D dispersible tablets 46.5 mg diclofenac free acid in healthy adult human subjects under fasting conditions. March 2012

⁶ Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* (2005) **59**(1):80-84

⁷ Willis JV, Kendall MJ, Flinn RM, Thornhill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur J Clin Pharmacol* (1979) **16**:405-10

Figure 2 Mean absorption profiles for 50 mg diclofenac sodium administered orally as a Surge Dose[®] tablet and a dispersible commercial tablet (Voveran[®]-D) dispersed in water before administration in 21 healthy fasted subjects



With Surge Dose[®], 76 % subjects had a T_{max} equal to or less than 20 min and 100 % reached T_{max} within 30 min. By comparison only one Voveran[®]-D subject (5 %) had T_{max} equal to or less than 20 min and 3 (18 %) less than 30 min. With Voveran[®]-D, 70 % subjects had to wait at least 1 h to reach T_{max} , with 6 (30 %) waiting at least 2 h.

Despite the marketing of the Voveran[®]-D dispersible tablets as providing faster pain relief, they showed slow absorption, low C_{max} and multiple peaks indicating that gastric emptying was absorption rate limiting. Although some dissolved drug emptied into the small intestine and was quickly available for absorption, a significant proportion of each dose was retained in the stomach until emptied during Phase III MMC (migrating motility complex).

3 Physiological basis for Surge Dose[®]

3.1 Utilise passive liquid gastric emptying for early absorption

Drug absorption following oral administration is influenced by:

- i. the rate at which the drug will dissolve from the dosage form into available fluids in the stomach including any co-administered fluids, and

- ⁸ Auler JO, Espada EB, Crivelli E, Quintavalle TBG, Kurata A, Stolf NAG, Issy AM, Paschoa OED, Danhof M, Breimer DD, Chamone DAF, Santos SRCJ. Diclofenac plasma protein binding: PK-PD modelling in cardiac patients submitted to cardiopulmonary bypass. *Braz J Med Biol Res* (1997) 30:369-74
- ⁹ Derendorf H, Mullersman G, Barth J, Gruner A, Mollmann H. Pharmacokinetics of diclofenac sodium after intramuscular administration in combination with triamcinolone acetate. *Eur J Clin Pharmacol* (1986) 31:363-5
- ¹⁰ Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arznei-Forsch/Drug Res* (2001) 51(11): 885 – 890

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- ii. the underlying gastrointestinal motility or MMC which periodically empties the stomach contents into the small intestine.

In the fasted state, subjects will be cycling through the three MMC phases which generally take 80 to 150 minutes:

- Phase I lasts 20 – 90 minutes, a quiescent period with little gastric motility
- Phase II lasts 10 – 135 minutes, with intermittent contractions increasing in strength
- Phase III, the most active phase also known as the housekeeper wave, lasts a short period (3 – 25 minutes) characterised by intense contractions emptying gastric contents into the small intestine

Independent of these MMC phases, liquids empty relatively quickly and exponentially from the stomach with a half life in the region of 20 minutes during Phase I, reduced by Phase II or Phase III MMC activity to 12 and 5 minutes respectively¹¹.

Therefore, when a drug is administered to a fasted subject, they may be in any of the three MMC phases. If the subject is in late Phase II or Phase III, then fast absorption will occur as the total gastric contents will be rapidly emptied into the small intestine. However, if they are in Phase I or early Phase II, there will be an initial fast absorption phase for any drug that has dissolved in the co-administered water and gastric contents which will passively drain into the small intestine. This will be followed by a later absorption phase when the remaining gastric contents are emptied into the small intestine by the Phase III MMC. This is often seen as double or multiple peaks in the plasma concentration – time profiles of some subjects particularly when there is sufficiently frequent sampling. These peaks during the first two hours post dose differ from later peaks attributable to entero-hepatic recycling.

Hence each subject's underlying MMC will influence gastric emptying and drug absorption accounting for some of the inter- and intra-subject variability seen in PK studies with orally administered solid dosage forms and solutions. For the same formulation, a subject in Phase I will produce a slower absorption profile than they would if they were in Phase II, with the fastest absorption occurring when the subject is in Phase III. The variability resulting from the underlying MMC is significant and can mask differences between formulations and other variables particularly in fasted PK studies. Delayed absorption and

¹¹ Oberle RL, Chen T-Z, Lloyd C, Barnett JL, Owyang C, Meyer J, Amidon GL. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroent* (1990) **99**:1275-1282

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reduced variability seen in fed studies result from the fact that the underlying MMC is interrupted by the ingestion of food which generally triggers Phase I¹².

Ideally for fast and consistent absorption following oral administration, a drug contained in a solid dosage form needs to dissolve rapidly and completely in the available gastric contents and any co-administered liquid. Surge Dose[®] formulations are designed to maximise the dissolution rate of the drug *in vivo* during the first few minutes post dose, so that the drug in solution drains into the small intestine initiating early absorption.

The higher the drug concentration, the greater will be the driving force for absorption across the intestinal mucosa resulting in rapid absorption and high peak plasma concentrations. In turn, higher plasma levels drive distribution into the effect compartment resulting in a faster onset of action. Conversely slow absorption is generally associated with lower plasma concentrations. Any remaining undissolved drug or drug solution retained in the gastric mucosal folds will remain in the stomach until emptied into the small intestine during Phase III MMC, initiating a second phase of absorption.

3.2 Optimize pH to maximise solubility for fast dissolution

pH will significantly change the solubility of many drugs and will also determine their degree of ionization. At its pKa, a drug is 50 % ionized and 50 % unionized where the unionized species is the more readily absorbed form compared with the poorly absorbed ionized form. Basic drugs such as eszopiclone have a higher pKa, in this case 6.7, and are more soluble in acidic conditions where the proportion of readily absorbed unionized species is lower. In contrast, acidic drugs which have low pKa values are more soluble in alkaline conditions where the proportion of unionized readily absorbed species is lower.

Hence when a basic drug is administered in the fasted state where gastric contents are acid, the drug will be more soluble and will dissolve faster than if the gastric contents are less acidic or neutral. Such conditions occur frequently in the general population in the fed or partial prandial state, as well in patients with achlorhydria, hypochlorhydria, impaired gastric function or on concurrent proton pump inhibitor or antacid medication.

Since there is intra- and inter-subject variability in gastric pH during the course of the day, Surge Dose[®] formulations are designed to provide an optimum pH in the environment of the dissolving drug particles to maximise solubility and ensure fast dissolution. This occurs independent of gastric conditions, ensuring that the drug is present in the small intestine in solution as the more readily absorbed unionized species.

¹² Rees WD, Go VL, Malagelada JR. Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. *Gut* (1979) **20**(Nov):963-970

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3.3 Provide activated dissolution

Traditional tablet formulations release drug into solution by passive diffusion of the drug across the stagnant boundary layers around the dissolving drug particles which provide a barrier to fast dissolution.

Surge Dose[®] formulations are customized with the right balance of drug, water uptake agents and pH modulating agents to provide activated dissolution with disruption of the boundary layers around the dissolving drug particles under a range of different conditions. This provides a higher concentration of drug in solution to drain from the stomach resulting in faster absorption.

Unlike Surge Dose[®] formulations with activated dissolution, a slow dissolving product produces only low concentrations of dissolved drug and relies more on MMC gastric emptying for the majority of drug absorption, although fast absorption can still occur if a fasted subject is in Phase III MMC.

4 Patent and regulatory considerations

4.1 Surge Dose[®]

Surge Dose[®] formulations containing basic drugs similar to eszopiclone are exemplified in Imaginot's patent application PCT/AU 2005/00759 covering basic and amphoteric actives claiming priority from 28 May 2004. Filed in Australia, US, Canada, Europe, India and Japan, this patent has to date been granted in Australia and Canada without limitation and is under examination elsewhere.

4.2 Eszopiclone patents

The US FDA Orange Book¹³ lists four patents on eszopiclone, all Continuations In Part (CIP) stemming from US 07/821,662 filed 16 Jan 1992:

- US 6,444,673 expiring 16 Jan 2012 and extended to 14 Feb 2014 for eszopiclone as the dextro-rotatory isomer of zopiclone, free of the levo-rotatory form
- US 6,319,926 expiring 16 Jan 2012 for methods of improving sleep quality and time using eszopiclone
- US 6,864,257 expiring 30 Aug 2012 for methods of inducing hypnotic, sedative and tranquillising effects using eszopiclone

¹³ FDA Orange Book, Lunesta[®], Sepracor
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021476&TA_BLE1=OB_Rx

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- US 7,381,724 expiring 16 Jan 2012 for methods of inducing hypnosis, sedation and tranquillisation using an isomeric mixture with a specified optical rotation

Other patents relating to eszopiclone formulations include:

- Sandoz Inc/Lek EP1 997 482 A1, US 2008/0299193 with a priority date 29 May 2007 claiming particles greater than 100 µm diameter on the basis that the drug's solubility is independent of particle size
- Dr Reddy's Labs Inc US 2009/0269409 A1 with a priority date 24 Apr 2008 claiming formulations with good stability containing microcrystalline cellulose, lactose anhydrous and mixtures thereof prepared at less than 15 % RH
- Dr Reddy's Labs Inc US 2007/0098788 A1 with priority date 28 Oct 2005 covering non-BZ drugs dispersed in a polymer for immediate and controlled release

4.3 US regulatory landscape

Sepracor's Lunesta[®] 1, 2 and 3 mg tablets, received FDA approval on 15 Dec 2004¹⁴.

NCE exclusivity expired 15 Dec 2009 and Lupin Ltd received tentative approval for 1, 2 and 3 mg tablets on 19 Mar 2010¹⁵. Generic eszopiclone marketing approvals are dependent on expiry of US 6,444,673 extended by 760 days to 14 Feb 2014. Sepracor is conducting paediatric studies that may result in a paediatric exclusivity to 14 Aug 2014.

For generic eszopiclone tablets, the FDA requires two single dose, two treatment, two period cross-over studies on a 3 mg dosage form, one in fasted and one in fed healthy subjects¹⁶. A biowaver will be allowed for 1mg and 2 mg strengths based on acceptable bioequivalence of the 3 mg formulation and acceptable *in vitro* dissolution using the FDA dissolution method for eszopiclone (USP apparatus II, 500 mL 0.1 N HCl, 50 rpm, sampling at 10, 20, 30 and 45 minutes)¹⁷.

¹⁴ NDA 021476 Lunesta tablets, Sepacor
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist

¹⁵ ANDA #091124 Eszopiclone tablets, Lupin Ltd
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>

¹⁶ Draft guidance on eszopiclone Jan 2008
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086253.pdf

¹⁷ FDA Dissolution methods data base – eszopiclone tablets 13 Sep 2007
http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1

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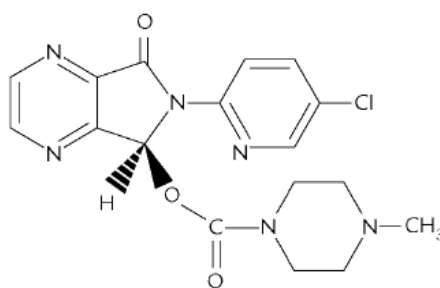
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5 Eszopiclone

5.1 Physicochemical properties

Eszopiclone is the active S-enantiomer of the racemic R,S-zopiclone, with a single (S) configuration chiral centre. It is a pyrrolopyrazine derivative of the cyclopyrrone class with the empirical formula $C_{17}H_{17}ClN_6O_3$ and a molecular weight 388.81. Its chemical structure which is unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, is shown in Figure 3¹⁸.

Figure 3 Chemical structure of eszopiclone (copied from Najib et al 2006)



5.1.1 Solubility

Eszopiclone is a basic compound with a pKa of 6.7. Its solubility is pH dependent as shown in Table 1¹⁹. These data confirm that the use of 500 mL 0.1 N HCl in the FDA dissolution method provides favourable conditions for dissolution of this very soluble drug which is used at a relatively low dosage.

Table 1 Effect of pH on eszopiclone solubility at room temperature (Garg et al 2009)

Solvent	Solubility (mg/mL)
0.1N Hydrochloric acid (pH 1.2)	39.11
0.01N HCl	4.18
Acetate buffer (pH 4.5)	11.62
Phosphate buffer (pH 6.8)	0.68
Phosphate buffer (pH 7.5)	0.33
Simulated gastric fluid (pH 1.2)	8.18
0.5% Sodium lauryl sulphate in water	1.83
Acid buffer (pH 1)*	23.02
Water	0.3

¹⁸ Najib J. Eszopiclone, a nonbenzodiazepine sedative-hypnotic agent for the treatment of transient and chronic insomnia. *Clin Therap* (2006) 28(4):491-516

¹⁹ Garg MK, Bord PP, Gupta PK. US 2009/0269409 Pharmaceutical compositions comprising eszopiclone. Dr Reddy's Labs Inc. Filed 23 Apr 2009

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Given that solubilities will be higher *in vivo* at 37 °C, a 6 mg dose of eszopiclone will readily dissolve in a relatively small volume across the physiological pH range even though the solubility decreases as the pH increases. At room temperature at pH 1.2, only 0.15 mL is required for complete dissolution, increasing to around 10 mL at pH 6.8. Only 20 mL water is required to dissolve 6 mg drug which meets the FDA BCS definition of a soluble drug since the maximum dose dissolves in less than 250ml water.

5.1.2 Permeability

In vitro Caco-2 studies indicate that eszopiclone has high absorptive and secretory permeability but its absorption is not affected by gastrointestinal transporter systems with secretory efflux similar to or less than absorptive transport.

Eszopiclone is lipophilic with an experimental log P of 0.8 compared with a predicted value of 0.97²⁰ which will favour intestinal absorption by passive diffusion. It readily crosses the blood brain barrier. With a pKa of 6.7, around 50 % of the drug will be present in the unionized form in the small intestine where the pH is around 6.5 – 7.5. The high proportion of unionized drug at a higher concentration produced by a fast dissolving product will provide a higher driving force for faster absorption.

5.2 Commercial products

Eszopiclone has been approved in US since Dec 2004 and in Europe (EMA) since May 2008, marketed by Sepracor as film coated tablets under the brand names Lunesta[®] ²¹ and Estorra[®]. The racemic mixture zopiclone first gained marketing approval in 1992, marketed by Rhone-Poulenc Rorer which became Aventis after the Hoechst Marion Roussel merger.

Eszopiclone, the active isomer was registered because it was believed to have the same pharmacological actions as the racemic mixture but to be effective at a lower dose, hence reducing the potential for side effects and toxicity. However although marketing authorisation was granted for Lunivia[®] by the European Medicines Agency, it was not granted New Active Substance status as the data submitted by Sepracor was deemed not to demonstrate a meaningful clinical difference between eszopiclone and zopiclone²².

²⁰ DrugBank <http://www.drugbank.ca/> Eszopiclone updated 23 Jun 2009

²¹ Sepracor Inc Lunesta[™] Prescribing Information NDA 21-476 Approved Labelling Text Dated December 15, 2004

²² European Medicines Agency. Withdrawal assessment report for Lunivia (eszopiclone) Procedure No EMA/H/C/000895
<http://www.ema.europa.eu/humandocs/PDFs/EPAR/lunivia/H-895-WAR.pdf>

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With one tentative approval already granted in the US for eszopiclone tablets, strong generic competition for the traditional tablet would be expected when patents expire in 2014. This creates the opportunity to launch an improved patented product, switching the market to the new product before 2014.

No information has been found on the development of other fast acting dosage forms such as ODTs or alternative routes of delivery.

Lunesta[®] tablets contain 1, 2 or 3 mg eszopiclone with calcium phosphate, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide and triacetin. The 1 mg and 3 mg tablets contain FD&C Blue #2.

5.3 Therapeutic use

Eszopiclone is a short-acting non-BZ sedative hypnotic which class includes zopiclone, zaleplon and zolpidem. It is the first sedative hypnotic approved for long-term use with others approved only for short-term treatment of insomnia over 6-8 weeks.

With a rapid onset of action and duration of effect lasting up to 6 hours, eszopiclone is efficacious and cost-effective in the treatment of transient and chronic insomnia, reducing sleep latency and improving sleep maintenance with less nocturnal awakening compared with placebo^{23,24, 25, 26}. It has lower abuse potential like other non-BZ hypnotics without the undesirable BZ side effects of rebound insomnia, dependency and tolerance.

Unlike BZs, nighttime administration of eszopiclone has been shown not to impair objective and subjective psychomotor skills the following day which is particularly important in the elderly²⁷. Morning sleepiness and daytime alertness scores are better after eszopiclone

²³ Morin AK, Willett K. The role of eszopiclone in the treatment of insomnia. *Adv Ther* (2009) 26(5):500-518

²⁴ Botteman MF, OzminkowskyRJ, Wang S, Pashos CL, Schaefer K, Foley DJ. Cost effectiveness of long-term treatment with eszopiclone in primary insomnia in adults. *CNS Drugs* (2007) 21(4):319-334

²⁵ Snedecor SJ, Botteman MF, Bojke C, Schaefer K, Barry N, Pickard AS. Cost effectiveness of eszopiclone for the treatment of adults with primary chronic insomnia. *Sleep* (2009) 32(6):817-824

²⁶ Hair PI, McCormack PL, Curran MP. Eszopiclone. A review of its use in the treatment of insomnia. *Drugs* (2008) 68(10):1415-1434

²⁷ Boyle J, Trick L, Johnsen S, Roach J, Rubens R. Next-day cognition, psychomotor function and driving related skills following nighttime administration of eszopiclone. *Hum Psychopharmacol Clin Exp* (2008) 23:385-397

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than placebo as a result of improved nocturnal sleep²⁸. However despite the lack of demonstrated effects on psychomotor performance the following day, reported treatment-emergent adverse events²⁹ and consumer reports³⁰ indicate that up to 10 % patients experience next day drowsiness, which in some cases is sufficiently severe to warrant discontinuation of treatment.

The recommended adult dose is 2 – 3 mg and for the elderly 1 – 2mg, taken immediately before bedtime since this drug is claimed to work very quickly. This avoids psychomotor side effects such as light-headedness, short-term memory loss, co-ordination problems and hallucinations. Since the effects of eszopiclone on sleep onset are reduced by food, it is recommended that the drug not be taken with or immediately after a meal.

Eszopiclone can also be used to improve compliance in continuous positive airway pressure (CPAP) therapy for patients with sleep apnoea as 50% of patients stop using CPAP within the first year, and most discontinue within the first month, usually because of discomfort, intolerance, or lack of perceived benefit³¹. Two weeks treatment with eszopiclone at the start of therapy led to increased CPAP adherence for the first six months compared with placebo.

5.4 Mode of action

The general class of BZ-receptor agonists (BZ-RAs) used for insomnia covers two groups of structurally unrelated drugs, BZs and non-BZs including eszopiclone. All potentiate gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS, by binding at different α subunits of the GABA_A receptor.

Non-selective BZ activity at these sites results in a wide range of pharmacological responses including sedative, anxiolytic, anti-convulsant, muscle relaxation and memory impairment. Non-BZs are more selective for the α_1 subunit of the GABA_A receptor and have a more specific hypnotic/sedative effect with fewer of the unwanted BZ effects.

²⁸ Rosenberg R, Caron J, Roth T, Amato D. An assessment of the safety and efficacy of eszopiclone in the treatment of transient insomnia in healthy adults. *Sleep Med* (2005) 6:15-22

²⁹ Zammit G. Comparative tolerability of newer agents for insomnia. *Drug Safety* (2009) 32(9):735-748

³⁰ Consumer Reports Best Buy Drugs. New sedative drugs used to treat insomnia. July 2008 <http://www.CRBBestBuyDrugs.org>

³¹ Lettieri CJ, Shah AA, Holley AB, Kelly WF, Chang AS. Short course of eszopiclone on continuous positive airway pressure adherence – a randomized study. *Ann Int Med* (2009) 151(10):696 - 702

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Zopiclone and its active isomer eszopiclone have been reported to bind with the α_1 and α_3 sub-units of the GABA_A receptor. With the active isomer eszopiclone having a 50 times greater affinity for this receptor than the R-isomer, and twice the binding affinity of the racemate zopiclone. However data submitted by Sepracor to differentiate the mechanism of action of eszopiclone from zopiclone, suggests that eszopiclone induces sleep by effects on the α_2 and α_3 subunits, whereas zopiclone produces predominantly α_1 subunit modulation³². This difference is thought to be responsible for the anxiolytic effects seen with eszopiclone in healthy subjects, which effects are not seen with zopiclone.

5.5 Pharmacokinetics (PK)

Eszopiclone is described as rapidly absorbed following oral administration in fasted subjects achieving peak plasma concentrations after approximately 1 hour (T_{max})³³. Eszopiclone exhibits linear pharmacokinetics for single doses between 1 and 7.5 with an elimination half life ($t_{1/2}$) around 6 hours (4 – 8 h). There is no evidence of drug accumulation with similar C_{max} levels following single and multiple dosing of 3 mg eszopiclone, 24.6 and 26.2 ng/mL respectively. When administered as 15 mg of the racemic mixture zopiclone, the PK appear to be stereo selective as shown in Figure 4 and Table 2 with preferential metabolism of the less active R(-) –zopiclone, resulting in higher plasma levels of the more active S(+) zopiclone^{34, 35}.

Figure 4 Mean (\pm SEM) plasma concentrations of racemic zopiclone and its two stereoisomers after 15 mg racemic zopiclone in 12 healthy subjects (Fernandez et al 1995)

³² European Medicines Agency. Withdrawal assessment report for Lunivia (eszopiclone) Procedure No EMEA/H/C/000895
<http://www.ema.europa.eu/humandocs/PDFs/EPAR/lunivia/H-895-WAR.pdf>

³³ Sepracor Inc Lunesta[™] Prescribing Information NDA 21-476 Approved Labelling Text Dated December 15, 2004

³⁴ Fernandez C, Maradeix V, Gimenez F, Thuiller A, Farinotti R. Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy adults. *Drug Metab Dispos* (1995) 21:1125-1128

³⁵ Fernandez C, Martin C, Gimenez F, Farinotti R. Clinical pharmacokinetics of zopiclone. *Clin Pharmacokinet* (1995) 29:431-441

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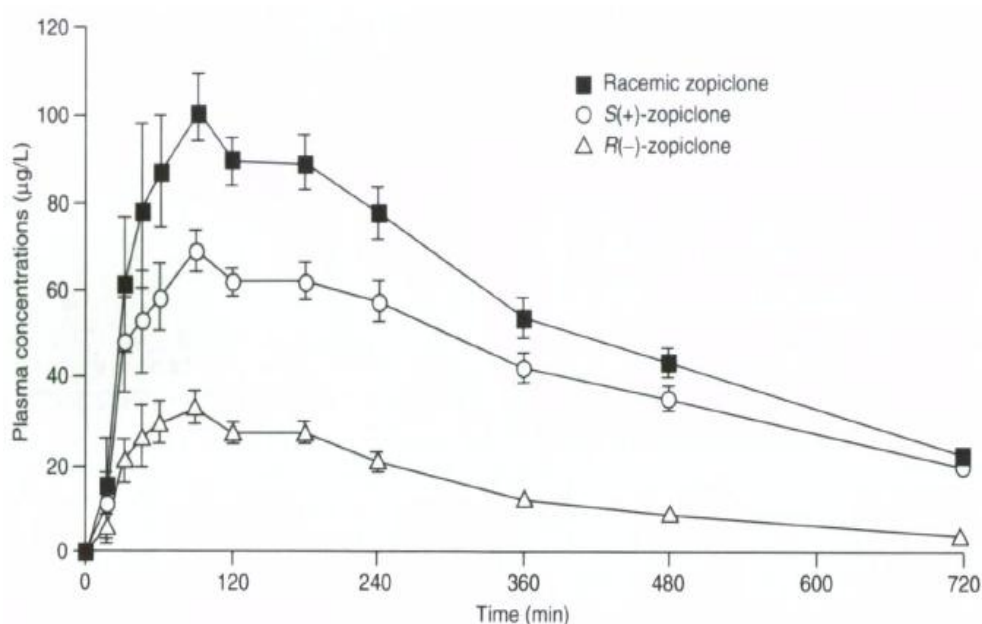


Table 2 PK parameters for zopiclone and its two stereoisomers S(+)-zopiclone and R(-)-zopiclone (Fernandez et al 1993)

	rac-ZOP	SD	(+)-ZOP	SD	(-)-ZOP	SD
$t_{1/2}$ el (min)	334.7	114.1	399.2	160.8	225.6	178.7
$t_{1/2}$ abs (min)	35.3	29.5	36.8	25.6	28.4	25.7
AUC (ng·ml ⁻¹ ·hr)	865.1	192.5	691.3	183.3	209.5	62.2
C_{max} (ng/ml)	131.3	33.6	87.3	18.9	44.0	16.1
T_{max} (min)	93.8	61.7	98.8	71.1	88.8	50.1
CL_{ss}/F (ml/min)	307.6	93.7	195.9	64.5	659.8	242.2
CL_r/F (ml/min)	11.7	8.4	10.6	7.7	12.7	11.6
V_d/F (l)	140.0	30.9	98.6	19.4	192.8	89.8
MRT* (min)	431.5	68.5	484.8	97.3	375.1	137.0

* MRT, mean residence time.

Given that the T_{max} for eszopiclone is generally stated as 1 hour and absorption of eszopiclone is described as fast, this table indicates a high degree of variability with a longer mean value in the region of 1.5 hours (SD 1 hour).

While no bioavailability data has been found for eszopiclone, the absolute bioavailability of racemic zopiclone is 75 – 80 % in healthy adults. With relatively weak plasma protein binding to the extent of 52 – 59 % and no selective uptake by erythrocytes, there are significant levels of dissolved free drug available for distribution. The volume of distribution (V_d) for eszopiclone is ~ 100 L with rapid distribution into tissues and the brain, greater than 0.9 L/kg corresponding to total body water indicating uptake by tissue membranes.

Eszopiclone undergoes extensive hepatic metabolism involving CYP 3A4 and 2E1 enzymes with oxidation and demethylation to (S)-zopiclone-N-oxide and (S)-N-desmethyl-

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zopiclone. Only the latter shows any significant binding to GABA_A receptors but this metabolite has lower potency than the parent drug. Less than 10 % eszopiclone is excreted in the urine unchanged. Based on the urinary excretion of zopiclone metabolites, it is expected that around 75 % eszopiclone will be excreted in the urine as metabolites. No stereo-conversion of eszopiclone to the less active R-form has been found in animals.

After a high fat meal, T_{max} is delayed by an hour to around 2 hours and C_{max} is decreased by around 21 % while the overall bioavailability (AUC) is unchanged. This effect of food is consistent with delayed gastric emptying as a result of food induced synchronisation of subjects into Phase I MMC.

No studies have been identified on the use of eszopiclone with drugs that increase gastric pH under which conditions its solubility will be reduced. PK data on the concurrent use of proton pump inhibitors and antacids would give an indication of the effect of gastric acidity on the rate of *in vivo* dissolution and absorption.

5.5.1 Formulation effects

The FDA approval package NDA 21-476 for Lunesta[®] ³⁶ contains data from a PK study comparing eszopiclone tablets with eszopiclone solution (volume and concentration unspecified) concluding that the tablets and solution have comparable bioavailability with median T_{max} values of 1.0 hour (p 23). Mean C_{max} values indicate a high degree of variability 29.57 ng/mL (SD 9.02) for the solution compared with 32.94 (SD 13.62) and 33.39 (SD 14.56) ng/mL for tablets.

The study on the effect of a high fat meal (pp 108) on eszopiclone absorption also used an oral solution but again without details on the volume and concentration. Median T_{max} values were 0.5 - 1.5 hours in the fasted state compared with 2 – 3 hours after food. In both cases, median values are reported without ranges, so that combined with the sparse sampling schedule, no differences between the PK of tablets and solutions are evident.

Based on experience with other drugs, it is likely that eszopiclone solutions demonstrate faster absorption with less variability than tablets despite the similar median T_{max} values. A Surge Dose[®] eszopiclone tablet would be expected to behave more like a solution than a tablet as a result of the faster *in vivo* dissolution.

³⁶ FDA CDER approval package for Lunesta[®] NDA application number 21-476 (eszopiclone) Clinical pharmacology and biopharmaceutics review

5.5.2 T_{max} variability

While the median T_{max} for eszopiclone is widely reported as 1 hour, ranging from 0.8 to 1.5 hours in the fasted state, to 2 – 3 hours in the fed state, there are few data available to assess the degree of variability in eszopiclone absorption. The ranges of T_{max} values in the NDA³⁷ have been redacted in the majority of data sets. Furthermore most studies reported use only five sampling times in the first 3 hours, at 0.5, 1, 1.5, 2 and 3 hours, so the PK protocols reported are not highly discriminating.

However, limited unredacted data sets were found which indicate a high degree of variability such as the example in Table 3, showing mean plasma concentrations and SD for the various sampling times. These results indicate high mean plasma concentrations at the first 0.5 hour sample, reaching some 60 – 80 % of the highest concentrations achieved, and similar mean plasma concentrations at 1, 1.5 and 2 hours. These data suggest that although eszopiclone is generally quickly absorbed with significant levels at 30 minutes post dose, there is a wide range of individual T_{max} values from 0.5 – 2 hours around the median value of 1 hour.

Table 3 Mean plasma concentrations (ng/mL) and nominal sampling times (hour) following the oral administration of 3 mg eszopiclone (ANDA #21-476 p 96)

Day	Time (hr)	N	Eszopiclone concentration (ng/ml)			
			Clinical Service Formulation		Intended-For-Market Formulation	
			Mean	SD	Mean	SD
1	Pre-dose	39	BLQ	-	BLQ	-
	0.5	39	28.45	15.51	26.32	11.66
	1	39	36.85	12.55	38.76	10.92
	1.5	39	36.36	11.72	36.40	10.38
	2	39	34.77	9.81	34.25	10.60
	3	39	29.71	8.64	30.54	8.68
	4	39	25.46	6.84	26.18	8.10
	6	39	19.40	4.75	18.85	5.91
	8	39	14.94	4.22	14.97	5.30
	12	39	8.91	3.40	8.45	3.18
	16	39	5.65	2.60	5.11	2.08
2	24	39	2.46	1.69	2.28	1.32

BLQ = Below limit of quantification

³⁷ FDA CDER approval package for NDA application number 21-476 (eszopiclone)
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This assessment is consistent with the results of a mass balance study using radio-labelled products that reported a range of T_{max} values from 15 min to 3 hours with a mean value of 1.7 hours (Figure 4). The high variability with a number of subjects demonstrating slow absorption would result in a faster median value in the region of 1 hour while the mean value is higher.

Figure 4 Range and mean of T_{max} values for a 7.5 mg dose of radio-labelled eszopiclone (NDA #21-476 section 6.3.3)

The concentrations of zopiclone in whole blood reached maximum from 15 min. to 3 hours. The peak concentration was 79.9 ± 21.2 ng - eq./ml.

The mean maximum concentration for plasma was 103.3 ± 24.0 ng - eq./ml.

The T_{max} varied from — , with a mean of 1.7 hours.

High T_{max} variability is confirmed by data reproduced in Table 4 which shows that T_{max} values range from 0.38 – 2.05 hours with a median value of 1 hour.

Table 4 Range and mean of T_{max} values for a 3 mg dose of eszopiclone administered alone and with 400 mg ketoconazole (NDA #21-476 p148)

Parameter	Mean \pm SD			
	N	Esopiclone	N	Esopiclone + Ketoconazole
Cmax (ng/ml)	17	39.84 \pm 8.60	18	56.81 \pm 14.63
AUC(0- τ) (hr*ng/ml)	17	260.95 \pm 64.05	18	588.23 \pm 196.03
AUC(0-last) (hr*ng/ml)	17	270.93 \pm 75.07	18	690.35 \pm 268.53
AUC(0- ∞) (hr*ng/ml)	17	286.45 \pm 79.47	18	724.69 \pm 293.83
t1/2 (hr)	17	7.21 \pm 1.25	18	9.44 \pm 2.12
tmax ^a (hr)	17	1.00 (0.38-2.05)	18	1.00 (0.50-2.00)
^a tmax is presented as median (range)				

This analysis of available T_{max} data for eszopiclone indicates a high degree of variability indicating that there is a population of people experiencing slow absorption and hence a slow onset of action for a drug where consistent fast onset of action is desirable. It is likely that the individual subject MMC and *in vivo* dissolution times contribute to this variability which effectively delays absorption in some subjects on some occasions. Surge Dose[®]

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eszopiclone will provide fast activated dissolution of the drug in the co-administered water and any gastric contents independent of pH, increasing the extent of dissolution in the stomach so that dissolved drug quickly reaches the small intestine to more consistently drive absorption.

5.5.3 Effect of food

The Prescribing Information on eszopiclone warns of reduced effects if taken with or after a high fat meal with T_{max} delayed by 1 hour and C_{max} values reduced by around 20 %. Data are provided in the NDA (p 23) for C_{max} and T_{max} but again T_{max} range values are redacted.

Given the circumstances under which eszopiclone would often be taken, namely after an evening meal, a Surge Dose[®] tablet that undergoes active dissolution in the presence of food will leverage the effects of differential and exponential drainage of liquids. This should achieve faster absorption in the fed state with lower and more consistent T_{max} values.

5.6 Pharmacodynamics (PD)

5.6.1 PK-PD correlation

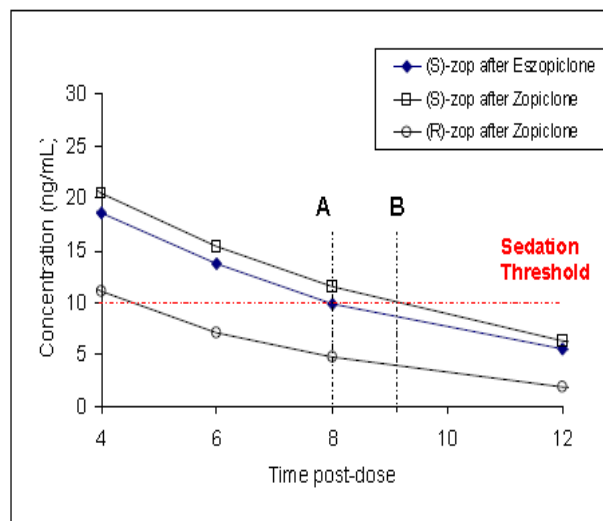
The PD profile of eszopiclone is consistent with its PK properties with onset of action usually within 30 minutes of dosing³⁸.

Minimum effective plasma concentrations for eszopiclone of around 10 ng/mL are reported for hypnotic effects with levels below this showing little change to EEG and cognitive impairment³⁹. As seen in Figure 5, it takes 8 hours for plasma levels to drop to 10 ng/mL following a 3 mg oral dose of eszopiclone because of the relatively long half life of this drug of 4 – 8 hours.

Figure 5 Mean eszopiclone levels after oral administration relative to minimum therapeutic levels for hypnosis

³⁸ Morin AK, Willett K. The role of eszopiclone in the treatment of insomnia. *Adv Ther* (2009) 26(5):500-518

³⁹ European Medicines Agency. Withdrawal assessment report for Lunivia (eszopiclone) Procedure No EMEA/H/C/000895 p 62
<http://www.ema.europa.eu/humandocs/PDFs/EPAR/lunivia/H-895-WAR.pdf>



*The values for eszopiclone tablet 3.5 mg in this figure are normalized to represent the equivalent administration of 3.75 mg eszopiclone. Actual values for the eszopiclone tablet were 7% lower.

PK data submitted in the NDA 21-476 such as that reproduced in Table 3 indicate that it can take even longer, 8 – 12 hours, for mean plasma concentrations to drop below the minimum therapeutic level of 10 ng/mL following a 3 mg dose. This suggests that many subjects will still have plasma levels higher than the minimum therapeutic level in the morning and so would be expected to still be showing some sedation particularly for higher doses and for any dose is taken late at night or in the early hours of the morning. Based on data available it is not surprising that next day sleepiness affects 10 % of patients.

5.6.2 Onset of action

The pharmacological effects of oral eszopiclone are dose dependent as seen in Table 5 for transient insomnia in healthy volunteers aged 25 – 50 years old in a sleep laboratory⁴⁰. Median time from dosing to the start of at least 10 minutes uninterrupted sleep ranged from 39.5 to 35 minutes with doses of 1, 2 and 3 mg compared with 42.4 minutes for placebo. Sleep latency (SL) was shorter for 2 and 3 mg eszopiclone taken 30 minutes before lights out compared with placebo ($p < 0.0001$).

Table 5 Median values for graphically estimated sleep parameters measured by polysomnography in a randomised double blind, placebo controlled multicentre trial (Rosenberg et al 2005 reproduced from Hair et al 2008)

⁴⁰ Rosenberg R, Caron J, Roth T et al. An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. *Sleep Med* (2005) 6(1):15-22

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Drug dose (mg) ^a [no. of volunteers]	SL ^b (min)	WASO ^c (min)	NA ^d	SE ^e (%)
ESZ 1 [47]	9.5	23 [*]	6	72 [*]
ESZ 2 [97]	6.5 ^{***}	26 [*]	5	71 [*]
ESZ 3 [98]	5.5 ^{***}	20 [*]	4 ^{**}	79 [*]
PL [98]	12.5	36	6	61

a. Results are shown for approved dosages only; ESZ or PL was administered 30 min before lights out.

b. Time from lights out to the start of 10 min of uninterrupted sleep; primary endpoint.

c. Total waking time after onset of persistent sleep.

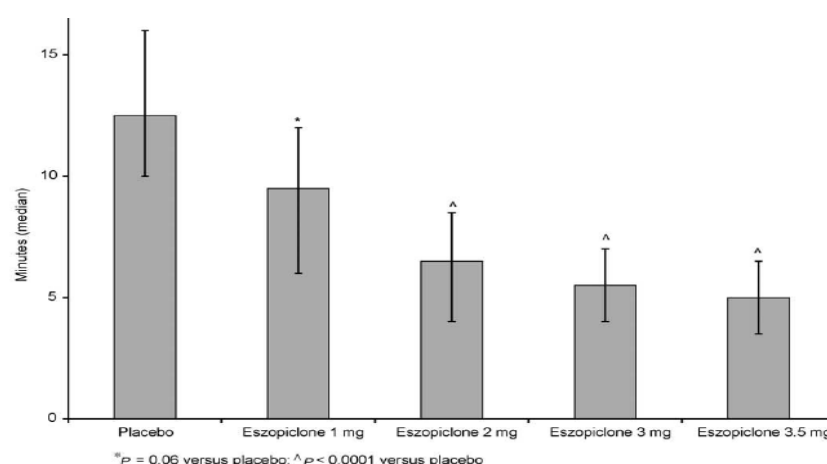
d. No. of wake periods of ≥ 1 min occurring after onset of persistent sleep.

e. Ratio of total sleep time to total time in bed, expressed as a percentage.

NA = no. of awakenings; SE = sleep efficiency; SL = sleep latency; WASO = wake time after sleep onset; ^{*} $p < 0.05$, ^{**} $p < 0.005$, ^{***} $p < 0.0001$ vs PL.

The histograms in Figure 6 highlight the variability in the time to onset of both placebo and the eszopiclone doses that could be related to the differences seen in T_{max} values and plasma concentrations.

Figure 6 Median values for graphically estimated sleep latency measured by polysomnography following oral administration of different doses eszopiclone 30 minutes before lights out (Rosenberg et al 2005)



Other studies report similar median SL by objective and subjective measures:

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- in menopausal insomnia, median SL measured by an interactive voice-response system, reduced to around 30 minutes compared with a baseline of 45 – 59 minutes and 60 minutes for placebo⁴¹
- slower median SL is reported for older patients, around 36 minutes⁴²
- in primary insomnia, SL values of around 20 minutes were reported in a 6 week study⁴³, with longer median values around 30 minutes over 6 months^{44,45}

5.6.3 PD variability

While studies do not always provide a direct measure of PD variability, comparison of mean and median values for SL do allow an assessment of the variability. Data from a number of phase III studies (Table 6) report mean onset of action from 18 – 54 minutes post dosing⁴⁶ with lower median values shown in parenthesis [] suggesting a non-normal distribution of results. Although the majority of subjects will have a SL less than the mean, some subjects appear to experience much slower onset of action which increases the mean.

Table 6 Mean and median [] values for sleep latency (SL) after oral eszopiclone (ESZ) against baseline (BL) and placebo (PL) in phase III randomized double blind multicentre studies with adult and elderly primary insomnia patients (Hair et al 2008)

-
- ⁴¹ Soares CN, Joffe H, Rubens R, Caron J, Roth T, Cohen L. Eszopiclone in patients with insomnia during perimenopause and early post-menopause. *Obstet Gynecol* (2006) 108:1402-10
- ⁴² McCall V. Diagnosis and management of insomnia in older people. *J Am Geriatr Soc* (2005) 53:S272-277
- ⁴³ Zammit GK, McNabb LI, Caron J, Amato JR, Wessel TC, Roth T. Efficacy and safety of eszopiclone across 6 weeks of treatment for primary insomnia. *Curr Med Res Opin* (2004) 20:1979-1991
- ⁴⁴ Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, Schaefer K, Roach J, Wallenstein G, Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life and work limitations. *Sleep* (2007) 30(8):959-968
- ⁴⁵ Krystal AD, Walsh JK, Laska E et al Sustained efficacy of eszopiclone over six months of nightly treatment: results of a randomised, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* (2003) 26:793-799
- ⁴⁶ Hair PI, McCormack PL, Curran MP. Eszopiclone. A review of its use in the treatment of insomnia. *Drugs* (2008) 68(10):1415-1434

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Study [duration of treatment]	Drug dose (mg/night)	No. of pts	SL (min) BL	result ^b
Adult pts (aged 21–65 y)				
Krystal et al. ^[25]	ESZ 3	593	91 [60]	47 [30] ^{†d}
[6 mo]	PL	195	96 [75]	63 [45] ^d
Walsh et al. ^[24]	ESZ 3	550	77 [67]	39 [27] ^{****}
[6 mo]	PL	280	83 [69]	59 [45] ^d
Zammit et al. ^[12]	ESZ 2	104	40 [30]	23 [15] ^{***}
[44 d]	ESZ 3	106	43 [30]	18 [13] ^{****}
	PL	99	38 [28]	33 [29] ^d
Elderly pts (aged 64–86 y)				
McCall et al. ^[27]	ESZ 2	136	53 [42]	19 [15] ^{****}
[2 wk]	PL	128	58 [47]	41 [33] ^d
Scharf et al. ^[26]	ESZ 1	72	88 [45]	54 [36] [*]
[2 wk]	ESZ 2	79	119 [35]	50 [36] ^{**d}
	PL	80	132 [60]	86 [52] ^d

When individual studies are reviewed, the high variability in SL results is more evident whether measured objectively or subjectively. Table 7 shows mean values for latency to persistent sleep measured by polysomnography of 33 minutes (SD 24.9) for 2 mg and 18 minutes (SD 15.7) for 3 mg eszopiclone respectively. Subjective reports indicate a slower onset, but with a higher degree of variability as seen in Table 8, with mean values of 48 minutes (SD 69.6) for 2 mg and 44 minutes (SD 68.8) for 3 mg eszopiclone respectively.

Table 7 Summary of polysomnography sleep efficacy results in primary insomnia over 6 weeks (Zammit et al 2004)

Measure		Baseline		Night 1		Night 15		Night 29		Double-blind average	
		Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
LPS (min)	PBO	38.4 (35.1)	27.5	35.2 (28.0)	28.6	34.0 (28.0)	27.0	30.2 (28.2)	20.5	33.0 (22.6)	29.0
	ESZ 2mg	39.5 (36.1)	30.0	21.4 (27.6)	11.8 [†]	21.9 (21.1)	15.5 [†]	24.0 (35.8)	12.9 [†]	23.0 (24.9)	15.0 [†]
	ESZ 3mg	42.8 (41.6)	30.1	17.5 (20.2)	12.3 [†]	19.5 (19.6)	13.8 [†]	18.1 (26.1)	11.5 [†]	18.0 (15.7)	13.1 [†]
Sleep efficiency (%)	PBO	81.3 (10.9)	83.7	83.8 (9.2)	85.7	83.4 (10.5)	86.0	82.9 (11.7)	86.5	83.5 (8.9)	85.7
	ESZ 2mg	81.2 (12.6)	84.2	89.3 (7.0)	90.3 [†]	85.0 (10.1)	87.5	86.2 (9.6)	88.9	86.5 (7.6)	88.1 [†]
	ESZ 3mg	81.3 (13.0)	85.2	90.3 (6.2)	92.0 [†]	87.4 (8.9)	88.5 [†]	88.4 (8.5)	90.8 [†]	88.8 (5.7)	90.1 [†]
WASO (min)	PBO	56.5 (41.7)	45.3	47.1 (37.3)	36.6	49.6 (42.1)	33.0	54.5 (47.5)	39.0	50.0 (34.5)	44.1
	ESZ 2mg	55.7 (51.3)	45.5	32.4 (24.0)	27.3 [†]	52.9 (41.3)	40.5	44.9 (34.7)	35.5	44.5 (29.4)	37.1
	ESZ 3mg	51.3 (44.7)	38.5	31.7 (24.7)	24.5 [†]	43.8 (39.1)	35.3	39.5 (34.0)	29.8 [†]	38.0 (26.7)	33.8 [†]
NAW	PBO	7.2 (4.6)	6.3	7.0 (4.3)	6.0	6.2 (3.8)	5.0	6.5 (4.5)	5.0	6.6 (3.5)	6.0
	ESZ 2mg	7.7 (4.3)	8.0	5.7 (3.4)	6.0 [*]	6.9 (3.8)	7.0	7.3 (4.0)	6.8	6.6 (3.1)	6.5
	ESZ 3mg	6.9 (3.7)	7.0	5.5 (3.4)	5.0 [*]	6.8 (3.9)	6.0	6.4 (3.6)	5.8	6.2 (3.1)	5.7

LPS: latency to persistent sleep; NAW: number of awakenings; WASO: wake time after sleep onset; ESZ: eszopiclone; PBO: placebo; SD: standard deviation
Double-blind average refers to the average of Nights 1, 15, and 29

*p < 0.05 vs placebo; †p < 0.01 vs placebo; **p < 0.001 vs placebo; all statistical tests were conducted using the ranked data

Table 8 Summary of patient reported sleep efficacy data in primary insomnia over 6 weeks (Zammitt et al 2004)

Subjective measure	Treatment†	Mean (SD)	Median	p value‡
Sleep latency (min)	PBO	58.4 (42.9)	46.0	–
	ESZ 2 mg	48.0 (69.6)	30.0	< 0.0001
	ESZ 3 mg	44.5 (68.8)	27.7	< 0.0001
Total sleep time (min)	PBO	363.8 (63.5)	366.0	–
	ESZ 2 mg	381.8 (63.8)	400.0	0.0207
	ESZ 3 mg	411.8 (124.0)	406.0	< 0.0001
Number of awakenings	PBO	3.2 (1.9)	3.0	–
	ESZ 2 mg	2.9 (1.7)	2.7	0.2956
	ESZ 3 mg	3.0 (2.2)	2.4	0.1720
WASO (min)	PBO	49.1 (36.1)	45.0	–
	ESZ 2 mg	53.4 (48.1)	37.1	0.6884
	ESZ 3 mg	41.2 (39.0)	30.2	0.0204
Quality of sleep§ (mm)	PBO	49.0 (18.1)	47.7	–
	ESZ 2 mg	54.4 (18.7)	54.5	0.0414
	ESZ 3 mg	55.4 (16.7)	56.6	0.0072
Depth of sleep¶ (mm)	PBO	50.5 (17.8)	51.7	–
	ESZ 2 mg	57.8 (19.0)	58.9	0.0052
	ESZ 3 mg	55.7 (15.7)	56.7	0.0457

WASO: wake time after sleep onset; ESZ: eszopiclone; PBO: placebo; SD: standard deviation

*Data calculated from the average of Nights 1, 15, 29, and 43+44

†PBO: n = 99; ESZ 2: n = 104; ESZ 3: n = 105

‡Versus placebo, all statistical tests were conducted using the ranked data

§On a 100 mm visual analog scale of 0 = poor and 100 = excellent

¶On a 100 mm visual analog scale of 0 = very light and 100 = very deep

Longer term studies over 12 months show similar highly variable SL results⁴⁷ with mean results ranging from 32.5 minutes (SD 30.0) to 44.9 minutes (SD 39.5) (Table 9). Again shorter median values ranging from 21.3 – 28.8 indicate that the results are not normally distributed and there is a tail of patients experiencing very slow onset of action increasing the mean but having little impact on the median value.

Table 9 Median SL data in primary insomnia over 12 months (Roth et al 2005)

Parameter	Time point	ESZ ESZ			PBO ESZ			P vs ESZ ESZ ^b
		Mean (SD)	Median	P vs OL baseline ^a	Mean (SD)	Median	P vs OL baseline ^a	
Sleep latency (min)	Pre study baseline	90.6 (79.6)	60.0		96.1 (94.7)	75.0		
	Month 6, OL baseline	47.0 (50.6)	30.0		63.1 (57.9)	45.0		
	Month 7	44.8 (51.5)	28.8	0.2638	35.1 (38.4)	21.3	≤0.0001	0.0625
	Month 8	40.8 (41.8)	27.5	0.0315	32.5 (30.0)	21.8	≤0.0001	0.0874
	Month 9	39.8 (39.3)	27.0	0.0262	36.6 (44.5)	21.7	≤0.0001	0.2904
	Month 10	42.5 (54.7)	27.3	0.0570	35.2 (34.2)	23.3	≤0.0001	0.3381
	Month 11	44.3 (52.8)	28.8	0.2371	38.4 (45.8)	22.5	≤0.0001	0.1335
	Month 12	45.9 (42.7)	27.5	0.0057	44.9 (39.5)	23.9	≤0.0001	0.4273

⁴⁷ Roth T. An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. *Sleep Med* (2005) 6():487-495

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5.6.4 Residual next day effects

Although objective measures on psychomotor effects the day after administration indicate that eszopiclone does not have significant residual effects, up to 10 % patients report sleepiness as an adverse effect of eszopiclone which in some cases results in discontinuation of treatment. Given the PK-PD relationship and the minimum therapeutic plasma levels of 10 ng/mL, as well as the high degree of variability in the PK, these side effects are not unexpected.

While the longer elimination half-life for eszopiclone of 4 – 8 hours, usually quoted as 6 hours, has the benefit of ensuring longer sleep maintenance, the disadvantage is the residual effects the following morning. Variability in absorption profiles and lack of certainty of achieving fast absorption means that some people on some occasions will be more prone to morning after sleepiness than others.

Fast absorption should result in lower levels of drug the following morning which in turn should reduce the incidence of residual drug effects and adverse event reports of sleepiness. If the drug is absorbed slowly, particularly when taken after food, then the peak is usually much broader with a later C_{max} . This means that elimination will occur over a longer period such that plasma levels are more likely to still be above 10 ng/mL even 8 – 12 hours after dosing causing sleepiness and other residual effects in the morning.

Therefore improvement in the certainty of achieving fast absorption is likely to provide a significant improvement in the efficacy and side effect profile for eszopiclone compared with the current tablets, with faster onset of action and less sleepiness the following morning.

6 Surge Dose[®] eszopiclone

6.1 Suitability as a Surge Dose[®] candidate

Based on a consideration of the available data on eszopiclone, it appears to be a suitable candidate for application of Imaginot's Surge Dose[®] technology:

- Eszopiclone is used for the treatment of acute and chronic insomnia where fast and consistent onset of action is desirable
- At the doses used eszopiclone has high solubility and should completely dissolve in the volumes of water used for swallowing a tablet
- Eszopiclone is a basic drug with a pKa of 6.7 so its solubility can be increased in acidic conditions which will in turn increase the rate of dissolution

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- Eszopiclone is lipophilic and is absorbed by passive diffusion across the intestinal mucosa and also the blood brain barrier without any evidence of active efflux mechanisms
- There is good PK-PD correlation with eszopiclone plasma levels directly related to its pharmacological effects with a minimum therapeutic plasma level of 10 mg/mL. The drug is also readily distributed into the CNS across the blood brain barrier to exert its central effect. Therefore it follows that faster absorption will result in faster onset of action once the minimum therapeutic levels have been reached.
- Despite the drug's apparent high solubility, there is evidence of high variability in both PK and PD that may be reduced by decreasing the time for *in vivo* dissolution.
- Although T_{max} values are generally quoted as 1 hour, there is significant variability with individual values ranging from 15 minutes to 3 hours and a longer mean value of 1.7 hours.
- While the median T_{max} values for solution and Lunesta[®] tablets are the same at 1 hour, the infrequent sampling interval, every 30 minutes over the first 2 hours, is insufficiently discriminating to pick up any formulation related differences.
- The relatively long elimination half-life for eszopiclone and the variability in absorption which produces some slow absorption profiles particularly after food, are likely to be contributing to the high frequency of residual sleepiness affecting up to 10 % patients using Lunesta[®] which maintains plasma levels above 10 mg/mL even 8 – 12 hours after dosing. .

This analysis suggests that, despite eszopiclone's high solubility, *in vivo* dissolution rates may be absorption rate limiting resulting in some patients who experience slow or delayed absorption and a corresponding delayed effect, and up to 10 % who experience next day sleepiness.

6.2 Potential for faster dissolution

6.2.1 Lunesta[®] dissolution

Sepracor agreed to adopt the *in vitro* dissolution method specified by the FDA to obtain a biowaver for approval of the 1 mg eszopiclone tablets on the basis of comparable dissolution data to the 2 and 3 mg tablets. Although the test conditions, acceptance

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criteria, individual results and ranges have been redacted in the NDA⁴⁸, the FDA has subsequently published a dissolution method for eszopiclone tablets specifying 500 mL 0.1 N HCl in USP apparatus II with paddles at 50 rpm taking samples at 10, 20, 30 and 45 minutes⁴⁹. This analysis assumes these are the conditions used for the dissolution data submitted to the FDA and summarised in Table 10.

Table 10 Summary dissolution data for eszopiclone tablets (FDA NDA review)

Strength	1 mg	2 mg	3 mg
No of batches	5	1	1
Minutes	Mean % dissolution (RSD %)		
5	74.1 (14.8) to 80.8 (11.7)	78.5 (8.8)	76.7 (10.0)
10	81.8 (8.7) to 88.8 (8.5)	86.2 (5.5)	84.1 (6.6)
20	88.2 (6.2) to 94.9 (5.5)	92.7 (3.5)	89.8 (4.4)
30	91.9 (3.8) to 98.0 (3.9)	96.3 (3.0)	92.6 (3.5)
45	94.3 (3.6) to 100.4 (3.6)	99.0 (2.6)	95.2 (2.8)

While all three tablet strengths demonstrate relatively fast dissolution under these test conditions, > 70 % in 5 minutes, these conditions favour fast dissolution and are not typical of the wide range found *in vivo*. As a basic molecule with greater solubility at low pH, eszopiclone is readily soluble in 0.1 N HCl. Hence in 500 mL 0.1 N HCl with a stirring speed of 50 rpm, fast dissolution would be expected. No data have been found using less vigorous conditions, such as reduced acidity, slower stirring speeds and reduced volumes which would be expected to result in slower dissolution.

6.2.2 Surge Dose[®] eszopiclone dissolution

While Imaginot has no dissolution data on a Surge Dose[®] eszopiclone formulation, it has demonstrated that the technology significantly increases the *in vitro* dissolution rate of zolpidem, another non-BZ drug. As shown in Table 11, based on the comparable physicochemical properties and PK-PD profiles of eszopiclone and zolpidem, similar faster dissolution would be expected with an optimised Surge Dose[®] eszopiclone tablet compared with Lunesta[®]. Since eszopiclone is less soluble in water than zolpidem, slower dissolution would be predicted with Lunesta[®] than Stilnox[®] even at the lower tablet strength.

⁴⁸ FDA CDER approval package for NDA application number 21-476 (eszopiclone)
Clinical pharmacology and biopharmaceutics review

⁴⁹ FDA Dissolution methods for eszopiclone tablets updated on 13 Sep 2007
http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1

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However both are basic drugs and will have higher solubility under acidic conditions such as in the fasted stomach, and lower solubility in the slightly alkaline intestinal conditions.

Table 11 Comparative data for zolpidem and eszopiclone

Parameter	Eszopiclone	Zolpidem
Dosage	6 mg	10 mg
Solubility in water	0.3 mg/mL	23 mg/mL
Volume water to dissolve dose	20 mL	2.3 mL
pKa	6.7	6.2
Median T _{max} fasted	1 h	1 – 1.5 h
Delay in median T _{max} by food	+ 1 h	+ 0.8 h

Lunesta[®] tablets exceed 70 % dissolution in 5 minutes⁵⁰ under favourable acidic test conditions where the drug has high solubility. However, slower dissolution would be expected under less favourable conditions such as used by Imaginot with less acidic media in which basic drugs such as zolpidem and eszopiclone have lower solubility. USP dissolution apparatus II is used but with different volumes, compositions of test media and stirring speeds to the FDA eszopiclone method to better simulate *in vivo* conditions.

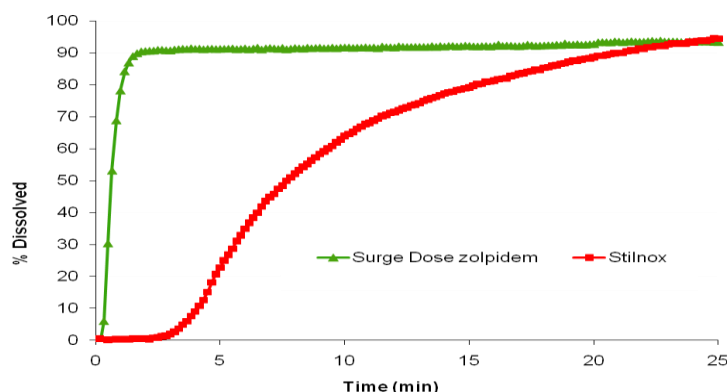
Figure 7 shows relatively slow dissolution for the commercial product, Stilnox[®] compared with Surge Dose[®] zolpidem in 900 mL 0.0033 M HCl which exceeded 90 % in 3 minutes. Here there is a limited amount of acid which will be neutralized by any alkaline tablet excipients thus increasing the pH under which conditions the drug will be less soluble.

Figure 7 Dissolution profiles for Surge Dose[®] zolpidem and Stilnox[®] tablets under different test conditions in USP dissolution apparatus II using 900 mL 0.0033 M HCl at 30 rpm at 37 °C

⁵⁰ FDA Dissolution methods for eszopiclone tablets updated on 13 Sep 2007
http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1

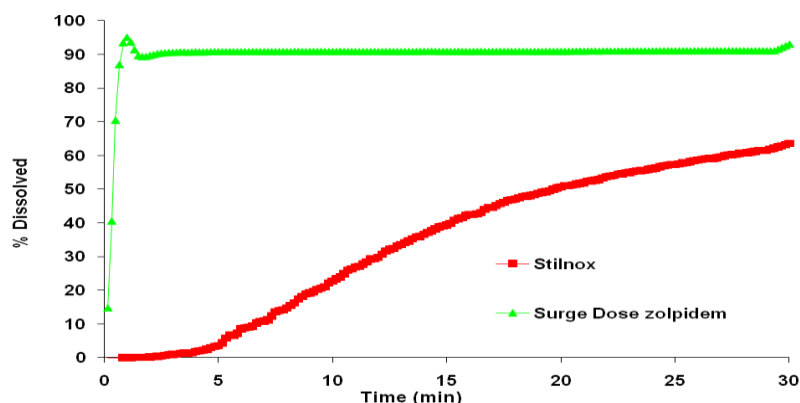
IM 03-20-01

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200 mL 0.015 M HCl more closely simulates *in vivo* conditions where a tablet is swallowed with around 150 mL water, which dilutes the limited gastric acid present in the fasted stomach. Comparative dissolution profiles are shown in Figure 8. The commercial tablet dissolves more slowly than in the higher volume, and again the Surge Dose[®] formulation exceeds 85 % dissolution in the first three minutes.

Figure 8 Dissolution profiles for Surge Dose[®] zolpidem and Stilnox[®] tablets under different test conditions in USP dissolution apparatus II using 200 mL 0.015 M HCl at 30 rpm at 37 °C



Dissolution profiles in Figure 9 and 10 provide an indication of the effect of food on *in vivo* dissolution which would affect drug absorption when a drug is taken after a meal. Figure 8 shows dissolution in the absence of stirring, typical of the low gastric motility in Phase I MMC which is generally triggered by food delaying gastric emptying.

Figure 9 Dissolution profiles for Surge Dose[®] zolpidem and Stilnox[®] tablets under different test conditions in USP dissolution apparatus II using 900 mL 0.0033 M HCl at 0 rpm at 37 °C

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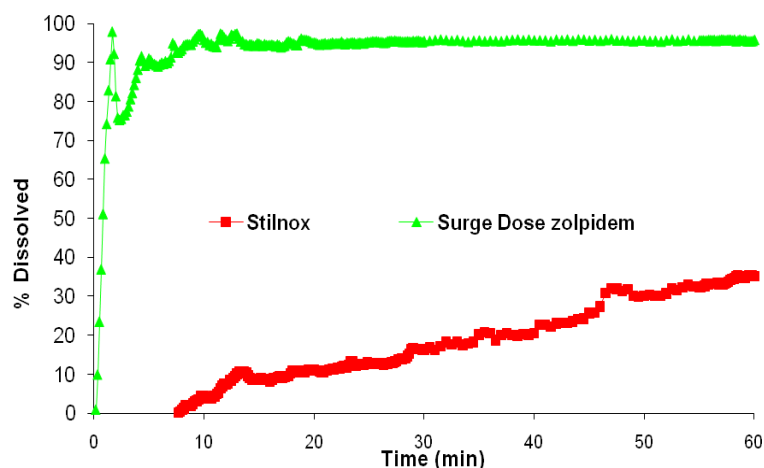
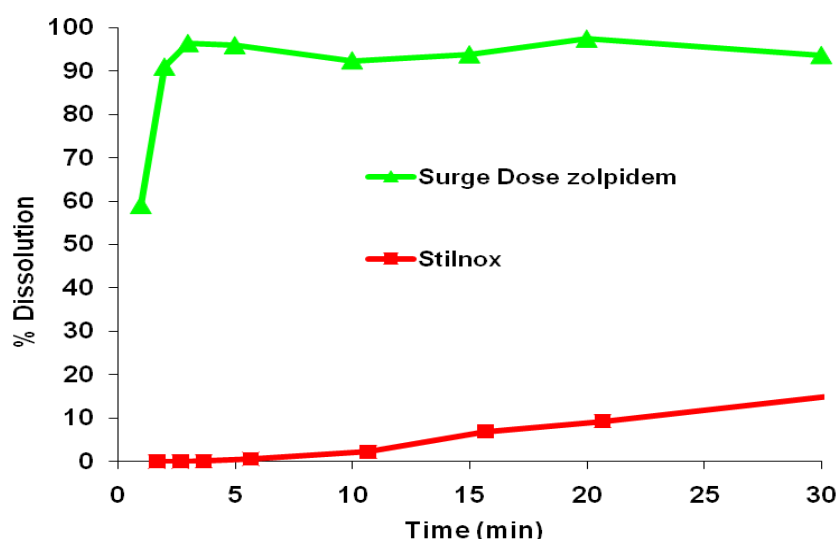


Figure 10 shows dissolution in 200 mL full cream milk where the viscosity and composition simulate fed gastric contents. In both cases Surge Dose[®] zolpidem shows very fast dissolution exceeding 85 % in 3 minutes whereas the commercial tablet Stilnox[®] shows much slower dissolution despite its relatively high solubility. Eszopiclone would be expected to show slower dissolution under these conditions as a result of its lower solubility.

Figure 10 Dissolution profiles for Surge Dose[®] zolpidem and Stilnox[®] tablets in USP dissolution apparatus II using 200 mL full cream milk at 30 rpm at 37 °C



Based on the comparative dissolution results for Surge Dose[®] zolpidem and Stilnox[®] tablets summarised in Table 12, it would be predicted that a Surge Dose[®] eszopiclone

Application of Surge Dose[®] fast dissolution technology to eszopiclone

would show similarly fast dissolution under these conditions, with Lunesta[®] demonstrating slower dissolution as a result of its lower solubility.

Table 12 Comparative dissolution data for Surge Dose[®] zolpidem tablets and Stilnox[®] tablets under different test conditions in USP dissolution apparatus II at 37 °C

<i>In vitro</i> test conditions	Surge Dose [®] zolpidem	Stilnox [®]
volume, medium, stirring speed, pH	% dissolved in 3 min	Time to 50 % dissolved or max
900 mL 0.05 M HCl, 30 rpm, pH 1.2	> 90 %	~ 6 min
900 mL 0.0033 M HCl, 30 rpm, pH 2.2	> 90 %	~ 7 min
900 mL 0.0033 M HCl, 0 rpm, pH 2.2	> 90 %	35 % in 60 min
200 mL 0.015 M HCl, 30 rpm, pH 1.7	> 90 %	~ 20 min
200 mL 0.0033 M HCl, 30 rpm, pH 2.2	~ 85 %	~ 26 min
200 mL water, 30 rpm, pH 6.2	> 90 %	~ 20 min
200 mL full cream milk, 30 rpm, pH 6.5	> 90 %	~ 15 % in 30 min

Surge Dose[®] eszopiclone with active fast dissolution independent of gastric conditions should lead to faster and more consistent absorption than the existing product in both fasted and fed states.

6.3 Improved clinical benefit

Based on the good PK-PD correlation and the high variability of T_{max} and onset of action for Lunesta[®] tablets, Surge Dose[®] eszopiclone would be expected to offer an improved PK and PD outcome, particularly for those patients that experience slow absorption with a corresponding slow onset of action, and for those that experience residual sleepiness the following day. The use of a more frequent sampling schedule in the first hour would be expected to better define the absorption peak for eszopiclone and to show significant differences between Surge Dose[®] eszopiclone and Lunesta[®]. It is also possible that the food delay in eszopiclone absorption may be reduced.

Optimised fast dissolving Surge Dose[®] eszopiclone tablets would be expected to demonstrate faster *in vivo* dissolution and faster *in vivo* absorption, resulting in faster onset of action across a wide range of different physiological pH compared with current Lunesta[®] tablets. Faster absorption would result in faster elimination thus reducing the potential for residual effects given the relatively long elimination half-life of 6 hours and the relatively high minimum therapeutic plasma levels of 10 ng/mL.

A fast dissolving Surge Dose[®] eszopiclone would be expected to produce more short T_{max} values in a study, thus reducing the mean T_{max} from around 1.7 hours towards 1 hour.

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With more frequent sampling in the first two hours, shorter mean and median T_{max} values would be expected for a Surge Dose[®] eszopiclone with a shorter median T_{max} in the region of 30 – 45 minutes. A reduction in the difference between the median and median results would be indicative of more consistent absorption with more consistent clinical outcomes.

6.4 Development requirements

Surge Dose[®] formulations use GRAS ingredients and conventional tablet manufacturing equipment, and so can be readily developed with existing plant and equipment, without any major capital outlay or regulatory hurdles presented by the use of unusual or new raw materials. Based on Surge Dose[®] formulations developed to date, normal tablet manufacturing equipment can be used and tablets prepared by direct compression or wet compression. Film coatings can be selected to have minimal impact on the dissolution rate. The one requirement is for low relative humidity manufacturing facilities with those used for the manufacture of soluble effervescent tablets being ideal, around 20 % RH. Additionally tablets should be individually strip packed in a suitable laminate to ensure adequate stability and an acceptable room temperature shelf life of 2 years.

Formulations are optimized in relation to the incorporation of pH modulating agents and water uptake agents to achieve fast and complete dissolution under a range of conditions that simulate those found *in vivo*. The use of an organic acid with low levels of an alkaline agent will provide a relatively low pH in the microenvironment around the dissolving drug particles with sufficient effervescence to provide micro-stirring for active dissolution. The resultant macro pH should ensure a higher proportion of the drug in the more readily absorbed unionized form.

7 Conclusions

Based on this review, eszopiclone is a suitable candidate for application of Imaginot's Surge Dose[®] technology where the addition of pH modulating agents and water uptake agents would be customised to optimise the dissolution rate of the drug. This should provide faster and more consistent absorption improving the efficacy for those patients where slow absorption results in a very slow onset of action.

Eszopiclone:

- is used as a hypnotic where fast and consistent onset of action is a clinical requirement and there is a high probability that the drug will be taken after food which delays absorption and hence onset of action

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- is a basic molecule with a pKa of 6.7 with lower solubility at higher pH, which means that dissolution *in vivo* will be slower under non-acid conditions
- is passively absorbed across the intestinal mucosa with no evidence of intestinal metabolism or efflux systems so that fast delivery of high drug concentrations into the small intestine will provide a driver for fast drug absorption
- shows good PK-PD correlation between plasma concentrations and effect with high plasma concentrations able to drive distribution across the blood brain barrier
- exhibits a high degree of variability around its median T_{max} quoted as 1 hour which may result from relatively slow *in vivo* dissolution of the current tablet formulation
- exhibits highly variable individual T_{max} values ranging from 15 minutes to 3 hours, with a mean T_{max} value of 1.7 hours which is longer than the median value indicative of a tail of subjects experiencing slow absorption
- shows variable PD effects consistent with PK variability, leading to sub-optimal clinical outcomes in many subjects

Based on this review, it is predicted that a fast dissolving Surge Dose[®] eszopiclone will reduce the contribution of variable *in vivo* dissolution to the PK and PD variability apparent with Lunesta[®] tablets. This will result in faster and more consistent absorption where the mean PK and PD measures will be closer to the median values, with fewer patients experiencing slow absorption and delayed efficacy and fewer adverse reports of residual sleepiness.

Given the current regulatory and patent landscape in the US, an improved faster absorbed Surge Dose[®] eszopiclone would provide an opportunity to reduce the impact of generic approvals by switching from the current Lunesta[®] tablets before patent expiry in 2014.