

IM 03-34-01

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

Imaginot Pty Ltd

ABN 34 089 023 352

Ground floor

100, Ipswich Rd

Woolloongabba

Qld 4102 Australia

Phone

+617 3392 3811

Contacts

Managing Director, Garth MacDonald

gmacdonald@imaginot.com.au

R&D Director, Geraldine Elliott

gelliott@imaginot.com.au

Reviewer Dr Geraldine Elliott, R & D Director Imaginot Pty Ltd

Issued 29 August 2011

Reissued 03 October 2012

IM 03-34-01

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

EXECUTIVE SUMMARY

Insomnia remains the most common sleep disorder affecting 20 – 30 % of the general population significantly impacting quality of life with impaired next-day functioning, increased risk of accidents, delayed recovery from illness, impaired immunological function, and increased risk of obesity and diabetes. As treatments based on γ -aminobutyric acid (GABA_A) receptor modulation such as zolpidem and zopiclone result in side effects including disruption of sleep architecture, insufficient sleep maintenance, next day “hangover”, withdrawal effects and abuse potential, there is a continuing need for effective fast acting hypnotics with an improved side effect profile.

The orexin signalling system in the lateral hypothalamus is now known to be involved in controlling the wake – sleep cycle, giving rise to a new class of drugs being evaluated for the treatment of primary insomnia. Almorexant (ACT-078573), a reversible, selective, dual orexin (OX₁ and OX₂) receptor antagonist was the first in class to be evaluated In Phase III clinical studies. However despite good efficacy and an improved side effect profile, development of almorexant was terminated in Jan 2011 based on tolerance concerns.

Several other drugs in this class continue in Phase II studies with suvorexant (MK-4305) the most advanced. This has a different chemical structure to almorexant and also a much faster elimination half life of around 3 hours compared with 13 – 24 hours which would be expected to provide a different PK (pharmacokinetic) - PD (pharmacodynamic) profile, possibly without the problems identified with almorexant.

The Surge Dose[®] ultra-fast activated dissolution technology has the potential to provide faster absorption producing higher plasma concentrations than conventional tablet formulations to drive rapid distribution into the CNS. Faster and more consistent absorption would reduce time to persistent sleep, and potentially improve efficacy. Given concerns about tolerance and tolerability, improved absorption of orexin receptor antagonists could allow overall reduced exposure to the drug by using a lower dosage with reduced side effects without compromising efficacy.

Improved clinical outcomes from faster and more consistent absorption would include:

- reduction in time to onset of persistent sleep,
- higher probability of reaching effective plasma concentrations leading to more patients reporting improved sleep maintenance
- reduction in probability of poor next day functioning

IM 03-34-01

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

Most published information is on almorexant with very few publications on other drugs in this category. Lead candidates in this class have been designed to provide good oral bioavailability with good permeability for passive absorption across the intestinal mucosa, and high lipid solubility to provide rapid penetration into the CNS for reaction with the OX receptors in the hypothalamus.

Almorexant has such a profile with good PK–PD correlation and a dose-dependent response in man. However despite this, there is evidence of dissolution rate limited and variable absorption with the almorexant tablets used in the clinical program. Surge Dose[®] fast dissolution drug delivery technology provides an ideal solution to such problems. Optimized tablet formulations provide rapid *in vivo* dissolution which leads to more consistent peak plasma concentrations (C_{max}) and faster times to C_{max} (T_{max}) compared with conventional formulations. Higher and more consistent plasma levels will drive distribution into the CNS which will translate to faster onset of action and increased efficacy. For drugs where side effects can limit usage, this may allow use of lower doses to reduce side effects without compromising efficacy.

Surge Dose[®] formulations provide a convenient, portable easy-to-swallow tablet that can be easily manufactured using conventional processing and GRAS excipients. By minimizing the *in vivo* dissolution time, Surge Dose[®] formulations provide fast absorption similar to that seen with solutions without the disadvantages associated with this dosage form including poor stability, need for taste masking, microbiological preservation, higher manufacturing and packaging costs as well as being bulkier and less convenient for the patient. Newer dosage forms such as liquid filled soft capsules, ODTs (orally disintegrating tablets) and absorption enhanced tablets do not deliver the desired fast and consistent onset of action with delays in release of drug and differences in solubility in different pH conditions in saliva, stomach and small intestine.

Imaginot's patented Surge Dose[®] technology was developed based on *in vivo* PK studies with paracetamol, a recognised marker for liquid gastric emptying and to date has been validated with two non-steroidal anti-inflammatory drugs (NSAIDs) lornoxicam and diclofenac. These studies demonstrated significantly faster and more consistent absorption for Surge Dose[®] formulations highlighting the slow and variable absorption from conventional products:

- Surge Dose[®] **paracetamol** formulations achieved median T_{max} values of 17 and 25 min compared with 45 min for the fast release commercial tablet (Tylenol[®] Extra Strength Rapid Release Gels). With Surge Dose[®] more than 70 % subjects

IM 03-34-01

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

exceeded the minimum therapeutic level of 10 µg/mL in the first 15 min compared with only 20 % for the commercial tablet. For Tylenol[®], 70 % of subjects experienced slow absorption with 16 % never reaching 10 µg/mL.

- Based on these data, PK-PD modelling predicts that Surge Dose[®] paracetamol will achieve a significantly faster onset of action and improved clinical efficacy with 20 % more patients achieving target end points than conventional tablets. This is consistent with fewer sub-therapeutic absorption profiles with Surge Dose[®] and confirmed by the lower NNT (Number Needed to Treat) of 2.8 predicted for Surge Dose[®] paracetamol compared with 4.2 for Tylenol[®].
- With optimized Surge Dose[®] **lornoxican** 8 mg tablets, absorption was twice as fast as and more consistent than the leading commercial tablet with comparable mean and median T_{max} values of 0.51 and 0.50 h respectively. Individual subject T_{max} values for Surge Dose[®] ranged from 0.3 to 1 h with 75 % subjects achieving T_{max} within the first 0.5 h. The commercial product had a mean T_{max} of 1.06 h, median 0.83 h ranging from 0.5 to 2.3 h, and only 8 % subjects achieving T_{max} within the first 0.5 h. Surge Dose[®] achieved 40 % higher mean C_{max} of 1098 ng/mL (CV 18.71 %) compared with only 788 ng/mL (CV 18.69 %) for the commercial tablet.
- With optimized Surge Dose[®] **diclofenac** sodium 50 mg tablets, absorption was 4 – 5 times as fast as a dispersible tablet dissolved in water before administration which is promoted for fast pain relief (Voveran[®]-D, Novartis). 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). 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[®] 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. Surge Dose[®] C_{max} values were comparable with those following IV or IM administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets. 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.

To achieve rapid absorption from a solid dosage formulation, ultra-fast activated dissolution *in vivo* is essential. Furthermore this must occur in the limited volume of available fluid in the stomach and the highly variable gastrointestinal (GI) conditions typical of the wide

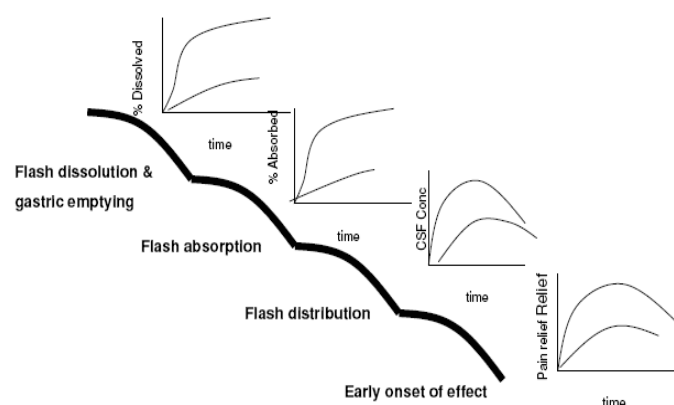
IM 03-34-01

Application of Surge Dose® fast dissolution technology to suvorexant

range found in the general population. **Gastric pH** can vary from highly acidic in the fasted state to neutral in the fed state or where there is concomitant use of drugs such as proton pump inhibitors or antacids. **Gastric motility** ranges from dormant to strong active contractions and propulsive waves of the underlying gastric emptying cycle known as the Migrating Motility Complex (MMC). Surge Dose® formulations are designed to minimise the time for *in vivo* dissolution independent of gastric pH or motility, maximising dissolution into co-administered water.

Ultra-fast active-dissolving Surge Dose® formulations produce the following cascade:

- The drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents
- The resultant solution empties rapidly and passively from the stomach in both fed and fasted states i.e. the drug empties as fast as if it had been taken as a solution
- The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption
- Fast absorption quickly saturates any protein binding sites and other saturable metabolic pathways leading to short T_{max} and high C_{max} with reduced intra- and inter-subject variability
- High plasma concentrations drive rapid distribution to the effect compartment resulting in rapid onset of action and rapid peak effect



Surge Dose® increases the probability of rapid absorption by controlling the pH of the dissolution reaction for maximum solubility and by creating a mechanism for active dissolution *in vivo*. Ultra-fast activated dissolution of drug from the Surge Dose® formulation is independent of gastric pH or gastric motility at the time of dose.

IM 03-34-01

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

Formulation optimization aims to achieve total dissolution of the drug in available liquid in the stomach to provide a high concentration gradient for rapid absorption from the small intestine producing higher plasma concentrations. Approved GRAS excipients are used and no major issues would be expected in achieving successful registration. Conventional tablet manufacturing equipment is suitable for Surge Dose[®] formulations using controlled low relative humidity (RH) conditions and unit packaging in moisture-impervious laminates for maximum stability. Small scale batches of a wide range of different drugs and a drug combination have been manufactured with accelerated stability indicating a shelf life of at least 2 years. To date formulations of three drugs have been successfully scaled-up for commercial manufacture using direct compression and wet granulation processing and standard film coating techniques with additional drugs under development.

Suvorexant and the other orexin receptor antagonists are basic drugs which are covered by the broad platform claims in Imaginot's patents. As a basic drug, suvorexant will demonstrate its maximum solubility under acidic conditions with solubility reducing as the pH increases. Hence while acidic gastric conditions in fasted subjects will favour dissolution, its dissolution rate in the general population is likely to be quite variable as gastric pH will vary significantly at the time of dosing. This will result in variable absorption with some slow absorption occasions possibly producing sub-therapeutic peak plasma concentrations particularly when using low doses.

Based on the limited published information on suvorexant, it is concluded that a Surge Dose[®] formulation would be likely to provide improved PK characteristics for use in the treatment of primary insomnia, and provide a patented formulation to add to existing patents on the drug per se.

Compared with conventional tablet formulations, Surge Dose[®] formulations would provide:

- More fast absorption profiles closer to the lower end of the individual subject T_{max} range
- Less effect of food in delaying absorption and onset of action
- More consistent absorption profiles with higher C_{max} levels that will exceed minimum effective levels for promotion of sleep within an acceptable time post-dose driving distribution into the CNS to bind with the OX receptors
- Higher and more consistent C_{max} may enable a reduction in dose to improve the side effect profile without compromising efficacy

IM 03-34-01

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

Table of Contents

1	INTRODUCTION	1
1.1	Technology overview	1
1.2	IP status	2
1.3	Commercialization.....	3
1.4	Insomnia	3
2	CLINICAL PREMISE FOR SURGE DOSE[®]	4
2.1	Physiological variability affecting drug absorption	4
2.1.1	Gastrointestinal (GI) motility	4
2.1.2	GI pH	7
2.2	Clinical rationale.....	8
2.3	Proof of concept.....	10
2.3.1	Paracetamol.....	10
2.3.2	Lornoxicam	11
2.3.3	Diclofenac	12
3	TECHNICAL REQUIREMENTS FOR SURGE DOSE[®]	13
4	OREXIN SIGNALLING SYSTEM	14
5	OREXIN RECEPTOR ANTAGONISTS (ORAS)	15
5.1	Players and lead candidates.....	15
5.2	Physicochemical properties	16
5.3	Suvorexant pharmacokinetics (PK) and pharmacodynamics (PD).....	17
6	POTENTIAL FOR SURGE DOSE[®] FORMULATIONS	18
7	CONCLUSIONS	19

IM 03-34-01

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

1 Introduction

1.1 Technology overview

The Surge Dose[®] formulation technology providing ultra-fast activated dissolution and fast absorption of oral drugs has been developed by Imaginot Pty Ltd <Imaginot>, a privately owned drug delivery company based in Queensland, Australia. Surge Dose[®] tablets are designed to provide superior performance even under unfavourable physiological conditions so that fast and consistent absorption and efficacy can be achieved independent of GI activity and pH. Surge Dose[®] maximizes the impact of pH dependent drug solubility to increase the rate of absorption, but is also effective for drugs where solubility is independent of pH. Although low RH and unit packaging are required, Surge Dose[®] tablets use conventional excipients and manufacturing processes.

Surge Dose[®] tablet formulations provide faster and more consistent drug absorption resulting in faster and more reliable onset of action. Mean and median T_{max} values are significantly reduced with Surge Dose[®] and there is less variability between subjects. This has been demonstrated in human PK studies on paracetamol (acetaminophen, APAP) and the acidic NSAIDs (non-steroidal anti-inflammatory drugs) lornoxicam and diclofenac. Based on PK-PD modelling, Surge Dose[®] paracetamol is predicted to achieve improved efficacy as variable absorption from conventional tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy.

Imaginot's Surge Dose[®] technology provides clinical benefits for drugs with:

- a clinical requirement for fast and reproducible onset of action when taken 'on demand' for acute episodic indications
- high passive absorption without significant intestinal metabolism or active efflux
- evidence of variable absorption associated with gastric emptying and/or *in vivo* dissolution seen when comparing absorption from aqueous drug solutions and solid dosage forms
- a direct temporal relationship between plasma concentrations and PD effects with no significant lag time

Surge Dose[®] maximizes the impact of pH dependent solubility to increase the rate of absorption, but is also effective for drugs where solubility is independent of pH. Surge Dose[®] formulations are designed to achieve ultra-fast activated dissolution even under unfavourable physiological conditions so that consistent absorption and efficacy can still be achieved independent of GI activity and pH. While this is important for drugs taken 'on demand' for acute episodic indications, it is equally important for drugs taken on a regular basis where GI conditions are variable.

IM 03-34-01

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

Surge Dose[®] formulations may also provide a clinical benefit for drugs taken on a regular basis, such as in the treatment of Parkinson's disease and other chronic indications, where GI conditions and resultant absorption can be highly variable.

Surge Dose[®] tablets provide a more convenient alternative to solutions and liquid formulations which are known to result in faster drug absorption than conventional solid dosage forms. Disadvantages of liquids and solutions include stability issues, the need for extensive flavouring for acceptable taste, preservation against microbial spoilage, reduced convenience for the patient unless doses are unit packed, the need for controlled storage and higher manufacturing and packaging costs.

In addition Surge Dose[®] tablets offer benefits over the new, heavily promoted second generation fast acting formulations such as liquid filled soft capsules, oral disintegrating tablets (ODTs) and absorption enhanced formulations. These do not always deliver the promised rapid onset of action required for drugs taken on demand for indications such as pain, migraine, allergy, nausea and erectile dysfunction.

Surge Dose[®] tablets are designed to act more like a solution or liquid formulation so that the drug will rapidly dissolve in the stomach contents after oral administration regardless of gastric pH and motility. This means that dissolved drug rapidly reach the small intestine and is available for absorption. Conventional formulations are associated with variable lag times resulting from *in vivo* capsule rupture, tablet disintegration, dispersion of capsule contents and drug dissolution which typically result in slower and more variable absorption.

1.2 IP status

Surge Dose[®] is covered by three patent families filed in US, Canada, Europe, India, Japan and Australia:

- i. PCT/AU 2006/001798 (WO/2007/059591) covering acidic and unionized actives claiming priority from 28 Nov 2004 which has been granted in Australia without limitation and is in examination in US under the PPH and Japan.
- ii. PCT/AU 2005/00759 (WO/2005/115345) covering basic and amphoteric actives claiming priority from 28 May 2004. Patents have been granted in Australia and Canada without limitation with examination progressing in US, Europe, India and Japan.
- iii. PCT/AU 2005/00758 (WO/2005/115344) covering paracetamol and combinations. The patent has been granted in Australia, Canada and US and has been assigned to a third party in Australia, Europe, India and Japan.

Patents are based on *in vitro* dissolution and *in vivo* PK results for paracetamol with *in vitro* dissolution data for more than 30 other drugs described by chemical class as acidic, basic, amphoteric and unionized. Drugs not exemplified are covered by broad platform claims.

IM 03-34-01

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

1.3 Commercialization

Imaginot is now seeking partners to commercialize its Surge Dose[®] technology. To date, three deals have been completed involving a major international pharmaceutical company (confidential), a French drug delivery company (Ethypharm SA) and India's largest pharmaceutical company (Abbot India). Imaginot has an agreement with Piramal Healthcare Ltd. in India for the contract development and manufacture of Surge Dose[®] formulations. Piramal can undertake formulation optimisation, scale, up, stability studies and Phase I studies comparing a SD formulation to an existing formulation to demonstrate the improved kinetics, at low cost for companies interested in exploring the use of the SD technology for their drugs.

Surge Dose[®] formulations demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low RH conditions. The first Surge Dose[®] product was launched in 2011 with the second planned for 2012. Other drugs are under development in optimized Surge Dose[®] formulations.

1.4 Insomnia

Insomnia is the most common sleep disorder affecting 20 – 30 % of the population significantly impacting quality of life with impaired next-day functioning, increased risk of accidents, impaired immunological function, and increased risk of obesity and diabetes^{1,2}. In the US, 25 % adults take sleep medications and the market for sleep drugs is estimated at US \$ 5 billion in 2010 with direct and indirect costs of insomnia exceeding US\$10 billion annually³. The most widely prescribed insomnia drugs are CNS depressants that enhance signalling of the inhibitory neurotransmitter γ - aminobutyric acid (GABA) but none provide the ideal efficacy profile with minimal side effects⁴.

Benzodiazepines developed in the 1960s bind to GABA_A receptors on postsynaptic neurons in the CNS to decrease sleep onset time. However side effects include daytime sleepiness, dizziness, impaired memory and risk of dependency. More recent selective benzodiazepine and non-benzodiazepine GABA_A modulators such as zolpidem, zopiclone and zaleplon have improved on

¹ Cox CD, Breslin MJ, Whitman DB, Schreier JD, McGaughey GB, Bogusky MJ, Roecker AJ, Mercer SP, Bednar RA, Lemaire W, Bruno JG, Reiss DR, Harrell CM, Murphy KL, Garson SL, Doran SM, Prueksaritanont T, Anderson WB, Tang C, Roller S, Cabalu TD, Cui D, Hartman GD, Young SD, Koblan KS, Winrow CJ, Renger JJ, Coleman PJ. Discovery of the dual orexin receptor antagonist [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the treatment of insomnia. *J Med Chem* (2010) 53:5320-32

² Malherbe P, Borroni E, Wettstein J, Knoflach F. Biochemical and Electrophysiological Characterization of Almorexant, a Dual Orexin 1 Receptor (OX₁)/Orexin 2 Receptor (OX₂) Antagonist: Comparison with Selective OX₁ and OX₂ Antagonists. *Mol Pharmacol*. (2009) 76:618-631

³ Nishino S. The hypocretin/orexin receptor: therapeutic prospective in sleep disorders. *Expert Opinion Investig Drugs*. (2007) 16(11): 1785-1797

⁴ Sullivan SS & Guilleminault. Emerging drugs for insomnia: new frontiers for old and new targets. *Expert Opin Emerging Drugs* (2009) 14(3):411-22

IM 03-34-01

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

some of these issues but concerns still remain about their overall safety and efficacy. Ramelton, a melatonin receptor antagonist approved by the FDA in 2005, was the first hypnotic with a novel mechanism of action but questions remain about its efficacy relative to the GABA_A modulators.

Hence there has been a continuing need for effective fast acting hypnotics with an improved side effect profile where the discovery of the orexin (OX) signaling system has provided a new class of OX receptor antagonists being evaluated as an improved means of effectively treating insomnia with minimal adverse events^{5,6}. Proof of concept has been established with almorexant the first of the dual orexin receptor antagonists (DORA) but the clinical program was terminated in Jan 2011 based on tolerance concerns. Almorexant has been evaluated as a good candidate for the Surge Dose[®] ultra-fast activated dissolution technology where faster *in vivo* dissolution than conventional tablet formulations would be likely to lead to faster absorption producing higher plasma concentrations to drive distribution into the CNS⁷.

Faster and more consistent absorption would reduce time to persistent sleep, and potentially improve efficacy. Given concerns about tolerance and tolerability, improved absorption could allow overall reduced exposure to the drug by using a lower dosage with reduced side effects without compromising efficacy. This report considers available data to see if the Surge Dose[®] technology might provide a clinical benefit with suvorexant (MK-4305), which is now the most advanced of the DORAs in Phase III clinical evaluation.

Merck has at least 17 patent applications on a wide range of different compounds as orexin receptor antagonists including suvorexant. Although suvorexant is not exemplified or named in the Surge Dose[®] patents it would be covered by the broad claims for basic drugs. Additionally there is the opportunity for drug specific patents to be filed on optimized formulations identified during development.

2 Clinical premise for Surge Dose[®]

2.1 Physiological variability affecting drug absorption

2.1.1 Gastrointestinal (GI) motility

The underlying MMC (migrating motor complex) influences gastric emptying contributing to the inter- and intra-subject variability seen in PK studies with solid dosage forms and solutions administered

⁵ Neubauer D. Almorexant, a dual orexin receptor antagonist for the treatment of insomnia. *Curr Opin Investig Drugs*. (2010) **11**(1):101-110

⁶ Hoever P, de Hass S, Winkler J, Schoemaker, RC, Chiossi E, van Gerven J, Dingemanse J. Orexin Receptor Antagonism, a New Sleep-Promoting Paradigm: An Ascending Single-Dose Study With Almorexant. *Clin Pharm Ther*. (2010) **87**(5):593-600

⁷ IM 03-27-01 Application of Surge Dose to almorexant. Imaginot Pty Ltd. Reissued 23 Jul 2011

IM 03-34-01

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

orally. MMC effects are significant and can mask differences between formulations and other variables particularly in fasted PK studies.

In the fasted state, subjects will be cycling through the three MMC phases with the total cycle time generally being from 80 to 150 min:

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

Independent of these MMC phases, liquids empty relatively quickly and exponentially from the stomach with a half life in the region of 20 min during Phase I, reducing to 12 and 5 min respectively in Phase II and Phase III⁸.

Delayed absorption and reduced variability seen in fed studies result from interruption of the underlying MMC by food triggering Phase I MMC⁹.

When a drug is administered to a fasted subject, they may be in any phase of the MMC. Thus for the same formulation, a subject in Phase I will absorb the drug slower than if they are in Phase II, with the fastest absorption occurring when the subject is in Phase III. This means that even a slow dissolving product can result in fast absorption occasions as well as slow absorption occasions.

However the frequency of fast absorption occasions will be less for a slow dissolving product than for a fast dissolving product.

Well documented gastric emptying effects are responsible for the double or multiple absorption peaks often seen in individual subject PK profiles particularly with frequent sampling¹⁰. Multiple gastric emptying peaks in the first two hours differ from later peaks due to entero-hepatic recycling. They are associated with longer T_{max} values and are reported for many drugs including the NSAID diclofenac^{11, 12, 13, 14, 15, 16, 17, 18, 19, 20}.

⁸ 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

⁹ Rees WD, Go VL, Malagelada JR. Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. *Gut* (1979) **20**(Nov):963-970

¹⁰ Metsugi Y, Miyaji Y, Ogawara K, Higaki K, Kimura T. Appearance of double peaks in plasma concentration-time profile after oral administration depends on gastric emptying profile and weight function. *Pharm Res* (2008) **25**(4):886-95

¹¹ Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Szelenyi I, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* (2005) **59**:80-84

¹² Mummaneni V, Amidon GI, Dressman JB. Gastric pH influences the appearance of double peaks in the plasma concentration-time profiles of cimetidine after oral-administration in dogs *Pharm Res* (1995) **12**(5):780-786

IM 03-34-01

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

In late Phase II or Phase III, fast absorption occurs as gastric contents rapidly empty into the small intestine resulting in a short T_{max} . In Phase I or early Phase II, there is slower absorption with a longer T_{max} . However in Phase I or II, there will be fast absorption of any dissolved drug that drains passively from the stomach. This is followed by a later absorption phase when remaining gastric contents containing any dissolved drug retained in the mucosal folds, any tablet fragments and undissolved drug particles, are emptied by Phase III MMC. The amount of dissolved drug in the initial absorption phase and the relative sizes of these peaks will depend on its solubility and the dissolution characteristics of the dosage form.

GI motility is influenced by other factors, and where slowing occurs, this will have an impact on gastric emptying and subsequent drug absorption. Certain conditions will reduce GI activity such as diabetes mellitus and also migraine where drug efficacy can be delayed by gut stasis. Opiates generally reduce GI activity which will slow absorption and hence slow onset of action.

Surge Dose[®] formulations are designed to achieve ultra-fast activated drug dissolution in co-administered liquid and stomach contents allowing dissolved drug to drain passively from the stomach independent of MMC activity

- ¹³ Yin OQ, Tomlinson B, Chow AH, Chow MS. A modified two-portion absorption model to describe double-peak absorption profiles of ranitidine. *Clin Pharmacokinet* (2003) **42**(2):179-92
- ¹⁴ Takamatsu N, Welage LS, Hayashi Y, Yamamoto R, Barnett JL, Shah VP, Lesko LJ, Ramachandran C, Amidon GL. Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility. [erratum appears in *Eur J Pharm Biopharm* (2002) 54(2):255]. *Eur J Pharm Biopharm* (2002) **53**(1):37-47
- ¹⁵ Marathe PH, Sandefer EP, Kollia GE, Greene DS, Barbhuiya RH, Lipper RA, Page RC, Doll WJ, Ryo UY, Digenis GA. In vivo evaluation of the absorption and gastrointestinal transit of avitriptan in fed and fasted subjects using gamma scintigraphy. *J Pharmacokinet Biopharm* (1998) **26**(1):1-20
- ¹⁶ Langguth P, Lee KM, Spahn-Langguth H, Amidon GL. Variable gastric emptying and discontinuities in drug absorption profiles: dependence of rates and extent of cimetidine absorption on motility phase and pH. *Biopharm Drug Dispos* (1994) **15**(9):719-46
- ¹⁷ Charman WN, Rogge MC, Boddy AW, Barr WH, Berger BM. Absorption of danazol after administration to different sites of the gastrointestinal tract and the relationship to single- and double-peak phenomena in the plasma profiles. *J Clin Pharmacol* (1993) **33**(12):1207-13
- ¹⁸ Suttle AB, Pollack GM, Brouwer KL. Use of a pharmacokinetic model incorporating discontinuous gastrointestinal absorption to examine the occurrence of double peaks in oral concentration-time profiles. *Pharm Res* (1992) **9**(3):350-6
- ¹⁹ Oberle RL, Amidon GL. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J Pharmacokinet Biopharm* (1987) **15**(5):529-44
- ²⁰ Lunell E, Andersson KE, Borga O, Fagerstrom PO, Johannesson N, Kjellin G, Persson CG, Sjolund K. Absorption of enprofylline from the gastrointestinal tract in healthy subjects. *Eur J Clin Pharmacol* (1984) **27**(3):329-33

IM 03-34-01

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

2.1.2 GI pH

2.1.2.1 Stomach

Although gastric contents are acidic in the fasted healthy state, there is significant variability in inter- and intra-subject gastric pH. Gastric pH typically varies between 1 and 7 during the course of the day in the general population depending on age, presence of food, concomitant medication and pathophysiology:

- A significant proportion of the population has low gastric acidity such as those with achlorhydria where gastric pH does not drop below pH 4, and hypochlorhydria which affects up to 50 % of the population increasing with age or pathology such as diabetes mellitus and autoimmune conditions
- Patients taking drugs such as antacids and proton pump inhibitors will also experience less acidic gastric pH most of the time
- Food increases gastric pH and patients using 'on demand' medication will very often be in the post-prandial or partial prandial state where gastric pH will be higher

Many drugs exhibit pH dependent solubility and the proportion present as the more readily absorbed unionized species will depend on the pKa of the drug. Higher solubility favours faster dissolution:

- Acidic drugs with a low pKa are more soluble and will dissolve faster at high pH but the proportion of the readily absorbed unionized species is lower.
- Basic drugs with a high pKa are more soluble and dissolve faster in acidic conditions but the proportion of readily absorbed unionized species will be lower.

When formulating for fast absorption, both solubility and degree of ionization must be considered. However for drugs with a high permeability coefficient, the effects of increased solubility more than compensate for the ionization effects.

Consequently gastric pH will significantly affect the rate of dissolution of an orally administered drug depending on its physicochemical properties. Increased drug solubility is associated with an increased dissolution rate in any co-administered water before it empties from the stomach. Conversely reduced solubility will slow the rate of dissolution, with less drug dissolved and available for absorption when emptied into the small intestine.

This highlights the importance of optimizing drug formulations to ensure adequate solubility and fast dissolution under a wide range of physiological conditions.

IM 03-34-01

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

2.1.2.2 Small intestine

Conditions in the small intestine which is the primary site for absorption of most drugs, differ to those in the stomach, with a more consistent higher pH and high secretion rates of relatively alkaline intestinal fluids. Under such conditions, poorly soluble drugs which are weak bases and are more soluble under acidic conditions in the stomach may precipitate out. This will slow absorption and may be responsible for long T_{\max} values seen for drugs which are weak bases. This problem is well recognized and *in vitro* methods have been developed to predict the impact of such behaviour on drug absorption^{21,22,23}.

Where a basic drug has not already completely dissolved in the stomach, the alkaline secretions will reduce solubility and hence delay dissolution and slow absorption. There is also the potential for precipitation of the less soluble form on the surface of undissolved drug which will further slow dissolution and absorption. This is demonstrated for the antifungal agent itraconazole, where use of hydroxypropyl methylcellulose as a precipitation inhibitor improved its oral bioavailability by some 60 % in rats²⁴.

Surge Dose[®] formulations are designed to maximize solubility by controlling the pH in the micro-environment of the dissolving drug particles, ensuring fast dissolution into available liquids in the stomach independent of gastric pH, and maximising the amount of drug in solution delivered into the small intestine for fast absorption

2.2 Clinical rationale

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 liquid,
- ii. the underlying GI motility or phase of the MMC which periodically empties the stomach contents into the small intestine, and
- iii. the rate of passive emptying of liquids, including dissolved drug, from the stomach into the small intestine which is independent of the MMC.

²¹ Kostewicz ES, Brauns U, Becker R, Dressman JB. Forecasting the oral absorption behaviour of poorly soluble weak bases using solubility and dissolution studies in biorelevant media Pharm Res (2002) 19:345-9

²² Kostewicz ES, Wunderlich M, Brauns U, Becker R, Bock T, Dressman JB. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. JPP (2004) 56:43-51

²³ Gu C-H, Rao D, Gandhi RB, Hilden J, Raghavan K. Using a novel multicompartiment dissolution system to predict the effect of gastric pH on the oral absorption of weak bases with poor intrinsic solubility. J Pharm Sci (2005) 94(1):199-208

²⁴ Van Speybroeck M, Mols R, Mellaerts R, Thi TD, Martens JA, van Humbeeck J, Annaert P, van den Mooter G, Augustijns P. Combined use of ordered mesoporous silica and precipitation inhibitors for improved oral bioavailability of the poorly soluble weak base itraconazole. Eur J Pharm Biopharm (2010) 75:354-65

IM 03-34-01

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

While the physiological conditions of the patient cannot be changed by the dosage form, strategic formulation design can improve the probability of rapid absorption by modifying the pH of the dissolution reaction and creating a mechanism for activated dissolution *in vivo*. Surge Dose[®] formulations are designed to achieve ultra fast dissolution under the wide range of favourable and unfavourable conditions that occurs in the general population. This is important for drugs taken 'on demand' for immediate effect where delayed absorption often results from prevailing physiological conditions.

Where speed and consistency of *in vivo* dissolution directly impact the clinical outcome, faster *in vitro* dissolution profiles relative to currently marketed products can offer significantly improved patient outcomes and associated compliance.

Dissolved drug will reach the small intestine quickly independent of gastric motility. The higher the drug concentration, the greater will be the driving force across the intestinal mucosa for rapid absorption and high peak plasma concentrations (C_{max}). Total dissolution of the drug from a solid dosage form into the co-administered liquid and gastric contents provides the maximum concentration to drive absorption and distribution to effect compartments by passive diffusion resulting in faster onset of action and improved efficacy.

Conversely, slow dissolution generally leads to slow absorption associated with lower and sometimes sub-therapeutic plasma concentrations. Where there is slow drug dissolution, gastric emptying will be the major factor in transferring drug into the small intestine where dissolution and absorption occur. This means that early absorption can occur with slow dissolving formulations on some occasions if Phase III MMC occurs soon after ingestion. There may be some initial dissolution which results in absorption from the resultant solution, but drug concentrations will be low and absorption slow as a result of the low driving force. Such variability is evident in many PK studies reporting individual subject data and may explain the lack of efficacy demonstrated by some patients.

Surge Dose[®] is designed to maximize the extent of drug dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC as summarized below and in Figure 1:

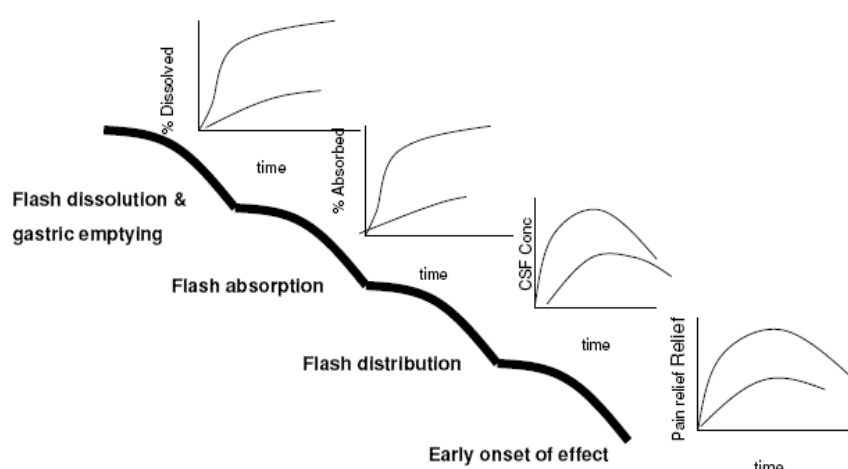
- i. Drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents
- ii. Resultant solution empties rapidly and passively from the stomach in fed and fasted states independent of the MMC i.e. empties as fast as when taken as a solution
- iii. The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption

IM 03-34-01

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

- iv. Fast absorption quickly saturates any protein binding sites and saturable metabolic and transport processes leading to earlier achievement of therapeutic plasma concentrations with short T_{max} and high C_{max} as well as reduced intra- and inter-subject variability
- v. High plasma concentrations drive rapid distribution to effect compartments resulting in rapid onset of action and rapid peak effect

Figure 1 Surge Dose[®] cascade resulting in faster onset of action



2.3 Proof of concept

2.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects²⁵ demonstrated significantly faster absorption with two fast dissolving Surge Dose[®] paracetamol formulations that have subsequently been improved, compared with Tylenol[®] Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol[®]>:

- Median T_{max} values for the Surge Dose[®] formulations were 17 and 25 min compared with 45 min for Tylenol[®]
- Surge Dose[®] AUC_{0-30} values indicated 3 times as much absorbed in the first 30 min compared with Tylenol[®]
- 64 and 76 % subjects receiving Surge Dose[®] tablets exceeded the reported minimum therapeutic level for paracetamol of 10 $\mu\text{g/mL}$ in the first 15 min compared with only 20 % subjects receiving Tylenol[®]

²⁵ Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

IM 03-34-01

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

- 16 % subjects taking Tylenol[®] never reached 10 µg/mL indicating sub-therapeutic dosing compared with only 4 % for Surge Dose[®] formulations

This study showed good *in vitro in vivo* correlations (IVIVC). Although paracetamol absorption was variable reflecting MMC activity, fast *in vitro* dissolution was associated with a higher frequency of fast absorption occasions and higher C_{max} values. Slow absorption occasions were more frequent with Tylenol[®], and were associated with lower C_{max} values sometimes failing to reach reported minimum therapeutic plasma levels. PK-PD modelling to quantify pain relief following oral administration predicted more rapid onset and greater analgesia with Surge Dose[®] paracetamol tablets than Tylenol[®] tablets²⁶. Improved clinical efficacy is predicted for Surge Dose[®] formulations as a result of fewer sub-therapeutic absorption profiles with 20% more patients achieving target end points than Tylenol[®]. This is reflected in the predicted lower NNT (Number Needed to Treat) of 2.8 for Surge Dose[®] compared with 4.2 for Tylenol[®].

As paracetamol is a well-established marker for gastric emptying, similar improved PK would be expected for other drugs where *in vitro* dissolution can be significantly improved with Surge Dose[®]. Increasing the probability of rapid absorption will lead to an increased probability of reaching therapeutic plasma levels quickly with a faster onset of action. Where sub-therapeutic plasma levels can occur as a result of slow absorption, increasing the absorption rate can lead to increased clinical efficacy through a higher frequency of doses exceeding minimum therapeutic plasma concentrations.

2.3.2 Lornoxicam

A PK study in 24 fasted subjects with the NSAID lornoxicam has also demonstrated the benefits of Surge Dose[®] used to maximise *in vitro* drug dissolution compared with a conventional tablet²⁷. Surge Dose[®] lornoxicam showed significantly reduced T_{max} and resulted in significantly higher C_{max} similar to parenteral administration²⁸. Faster and more consistent absorption has the potential to improve efficacy. Absorption from Surge Dose[®] lornoxicam tablets was twice as fast as from the reference commercial product:

- 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 the reference tablet was 0.83 h ranging from 0.5 to 2.3 h with a longer mean T_{max} of 1.06 h indicating more subjects with slow absorption

²⁶ 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

²⁷ 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

²⁸ 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

IM 03-34-01

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

- 75 % subjects on Surge Dose[®] lornoxicam achieved T_{\max} within the first 0.5 h compared with only 8 % for the reference tablet
- Surge Dose[®] lornoxicam achieved peak plasma concentrations comparable with parenteral administration, around 40 % higher than the reference tablet with mean C_{\max} 1098 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 reference lornoxicam tablets 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 with the reference tablet

2.3.3 Diclofenac

An optimized film coated Surge Dose[®] diclofenac sodium 50 mg tablet 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. Despite the marketing of the Voveran[®]-D dispersible tablets for fast pain relief, this dispersed product 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.

Surge Dose[®] provided 4- 5 times faster absorption of diclofenac than from a dispersible tablet:

- 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) indicating fewer slow absorption profiles with a high T_{\max} . Voveran[®]-D showed much slower and more variable absorption with a median T_{\max} of 1.5 h (range 15 min – 4 h) indicating a tail of slow absorption profiles.
- Surge Dose[®] produced significantly higher C_{\max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. Surge Dose[®] C_{\max} values were comparable with those obtained following IV^{29,30} or IM^{31,32} administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets³³.

²⁹ 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

³⁰ 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

³¹ 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

³² 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

³³ 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

IM 03-34-01

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

- 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.

3 Technical requirements for Surge Dose[®]

Formulation optimization aims to maximize drug dissolution in available liquid in the stomach to provide a high concentration gradient to drive absorption. Optimized levels and ratios of pH modulating agents (pHMA) and water uptake agents (WUA) provide a pH-controlled activated dissolution system to maximize the extent and rate of *in vitro* drug dissolution, exceeding 70 % dissolution in 3 minutes even using *in vitro* methods that simulate adverse *in vivo* conditions.

The reaction between acidic and basic components produces effervescence which disrupts the boundary layers around dissolving drug particles independent of the gastric pH, whilst controlling pH to maximize solubility. This provides a higher concentration of dissolved drug in the first few minutes after administration with the drug solution draining from the stomach independent of the MMC. In contrast, traditional tablets release drug into solution slowly by passive diffusion across stagnant boundary layers around dissolving drug particles which are a barrier to fast dissolution. Such slow dissolving tablets produce low concentrations of dissolved drug so that absorption is more dependent on MMC gastric emptying.

For ionized drugs, pHMA are optimized to favour the proportion of drug in the more readily absorbed unionized form. At its pKa, 50 % of a drug will be present in its unionized form in equilibrium with 50 % in the ionized form. **Basic** drugs are predominantly unionized at pH values above their pKa, whereas **acidic** drugs are predominantly unionized below their pKa. **Amphoteric** drugs are zwitterions with a net neutral charge at their isoelectric point.

Surge Dose[®] formulations use GRAS excipients and traditional manufacturing equipment for direct compression or wet granulation. Low RH manufacturing facilities around 10 - 20 % RH and unit packing in a suitable moisture-impervious laminate such as used for effervescent tablets provide maximum stability and an acceptable shelf life of 2 years. No major capital investment is required and use of conventional ingredients should not present any regulatory hurdles. Film coatings can be selected to have minimal impact on dissolution. Small scale Surge Dose[®] batches of several drugs have been manufactured, with successful scale-up to commercial batches undertaken.

A range of highly discriminating *in vitro* dissolution methods is used as a development rather than a QC tool, with standard equipment such as USP dissolution apparatus II with paddles, different media at 37 °C, different volumes and different stirring speeds to simulate *in vivo* conditions:

- 900 mL 0.05 M HCl at 30 rpm where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*

IM 03-34-01

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

- 900 mL 0.0033 M HCl at 30 rpm, pH 2.3, used to characterise Surge Dose[®] formulations contains the finite amount of acid (3 mmoles) estimated to be present in the fasted state
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, contains 3 mmoles of acid in a typical physiological volume based on co-administered water with 30 mL fasted acidic gastric contents
- 200 mL 0.0033 M HCl at 30 rpm simulates a typical physiological volume with lower gastric acidity as occurs in many subjects in the general population
- 900 mL 0.0033 M HCl at 0 rpm simulates gut stasis such as occurs in migraine and the fed state where there is little gastric motility

4 Orexin signalling system

Originally recognized as regulators of feeding behaviour³⁴, the OX neuropeptide system is now known to play an important role in maintaining wakefulness³⁵. They also have roles in co-ordination of emotion, energy homeostasis, reward and arousal. These orexins are also called hypocretins reflecting their location in the lateral hypothalamus. The OX signalling system involves two excitatory neuropeptides OXA and OXB, with two receptors OX₁R and OX₂R which have partially overlapping distribution throughout the CNS. OXA and OXB have different affinity for these two receptors. OX₁R binds OXA with greater affinity than OXB, while OX₂R has similar affinity for both.

OX levels vary throughout the day, with OX neurons being most active during the day during waking hours and showing very little activity during the normal sleep period. CSF levels peak at the end of the active phase and reduction in orexinergic tone is important for normal initiation and maintenance of sleep in man and other species. Narcolepsy, a neurological sleep disorder characterized by abnormal transitions between wake and REM (rapid eye movement) sleep, cataplexy (loss of muscle control) and excessive daytime sleepiness, is associated with genetic mutations or dysfunction of the OX signalling pathways.

Antagonists of this system promote sleep, providing a new mechanism of action to be investigated for the treatment of insomnia. The mechanism differs from the overall CNS activation through potentiation of inhibitory neurotransmission using GABA_A modulators such as zolpidem, zopiclone and zaleplon leading to the expectation that this class of drugs will provide an improved efficacy-side effect profile. There is no evidence of classic narcolepsy symptoms on repeat dosage suggesting that intermittent antagonism does not cause chronic loss of the OX signalling system.

³⁴ Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JRS, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu W-S, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. Orexins and Orexin Receptors: A Family of Hypothalamic Neuropeptides and G Protein-Coupled Receptors that Regulate Feeding Behavior. *Cell* (1998) 92: 573–85

³⁵ Sakurai T, Mieda M, Tsujino N. The orexin system: roles in sleep/wake regulation. *Ann N Y Acad Sci* (2010) 1200:149-61

IM 03-34-01

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

Animals provide a relevant model for studies on this system with some canine genetic lines such as in the Doberman pinscher exhibiting classic cataleptic phenotypes. Mutations are associated with severe disruption of OX₂R with loss of wakefulness. Antagonism of both receptors in rodents, dogs and man induces sleep and increases sleep maintenance, with the effects evident in healthy volunteers as well as patients with severe primary insomnia. Hence the mechanism of action is thought to be inhibition of the endogenous OX arousal system rather than corrective inhibition of an overactive OX function.

This means that OXR antagonists may be useful for the treatment of a wider range of arousal related disorders than just insomnia. Specifically the OX signalling system is involved in reward pathway modulation, with OX released from the extensive hypothalamic neurons acting on the brain nuclei associated with reward and behavioural response to drugs of addiction. OX neurones are activated by cocaine and OX reinstate extinguished cocaine seeking behaviours in rodents. OXR antagonists attenuate the drug abuse potential in nicotine reinstatement, cocaine sensitization, morphine relapse, alcohol seeking, amphetamine self-administration, effects related to OX₁R modulation of dopamine levels³⁶. Hence the potential use of this class of drugs to reduce drug relapse and treat addictions.

5 Orexin receptor antagonists (ORAs)

5.1 Players and lead candidates

Major players with patents on OXR antagonists are Actelion, Merck, Hoffman-La Roche, GSK, Sanofi, Biovitrum and Concert Pharmaceuticals and patented OXR antagonists have a diverse range of different structures albeit with some common features³⁷.

To date three dual OX receptor antagonists (DORAs) have been characterised and evaluated in the clinic. Almorexant [ACT-078573] (Actelion/GSK) was the first in class to show efficacy in proof of concept studies in man with improved sleep efficacy and no significant next-day effects. However in 2011, despite good efficacy with doses up to 400 mg, the clinical program was terminated as a result of tolerance concerns arising from the longer term Phase III studies. The second DORA, SB-649868 (GSK) which showed dose proportional sleep promotion in noise induced insomnia at 10 and 30 mg without carry over drowsiness was halted as a result of pre-clinical toxicities. However both induced a natural sleep architecture with increased time in both REM and non-REM sleep not seen with GABA_A modulators such as zolpidem which reduces these important sleep stages essential for memory consolidation and restorative properties. This leaves suvorexant (MK-4305) (Merck) as the most advanced DORA under clinical development.

³⁶ Winrow CJ, Gotter AL, Cox CD, Doran SM, Tannenbaum PL, Breslin MJ, Garson SL, Fox SV, Harrell CM, Stevens J, Reiss DR, Cui D, Coleman PJ, Renger JJ. Promotion of sleep by suvorexant – a novel dual orexin receptor antagonist. *J Neurogenetics* (2011) 25(1-2):52-61

³⁷ Coleman PJ, Renger JJ. Orexin receptor antagonists: a review of promising compounds patented since 2006. *Expert Opin Ther Patents* (2010) 20(3):307-24

IM 03-34-01

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

A placebo-controlled long term safety study in patients with primary insomnia taking the drug or placebo at night for up to 14 months is due for completion in Aug 2011³⁸. Primary outcome measures are the proportion of patients experiencing narcolepsy like effects, complex sleep-related behaviours, falls and suicidal ideation and behaviours. Secondary outcomes measures are changes in the subjective total sleep time and time to onset of sleep after the first month of treatment.

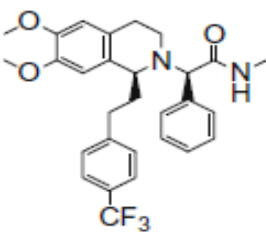
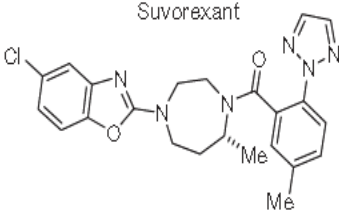
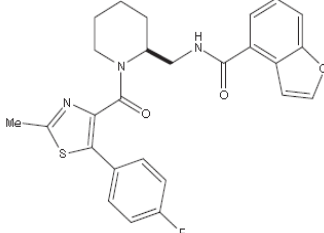
A placebo-controlled safety and efficacy study of four doses, 20 and 40 mg in patients less than 65 years old and 15 and 30 mg in patients older than 65 years old, was due for completion in Dec 2011³⁹. Primary outcome measures after 1 and 3 months comparing suvorexant with placebo are changes from baseline in subjective total sleep time, wake time after persistent sleep onset, subjective time to sleep onset and latency to onset of persistent sleep. Secondary outcome measures are based on results at different times including night 1, 1 week, 1 and 3 months.

J&J has pursued selective OX_R antagonists with JNJ-10397049, a selective OX₂R antagonists producing similar sleep induction to almorexant at lower receptor occupancy, whereas the selective OX₁R antagonist SB-408124 had no sleep effects at all in the rat. When both were administered together there was an attenuated sleep effect but the improvement in non-REM sleep latency and non-REM sleep duration was lost. As OX₂R antagonism does not stimulate dopamine release in the brain, selective OX₂R antagonists may have an advantage over DORAs such as almorexant.

5.2 Physicochemical properties

As seen from Figure 2, a diverse range of chemical structures are active antagonists of the OX receptors resulting in central activity to improve primary insomnia.

Figure 2 Chemical structure of lead DORAs (from Cox et al 2010)

Almorexant	Suvorexant (MK-4305)	SB-649868
		

³⁸ NCT01021813 A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Long Term Safety Study of MK4305 in Patients With Primary Insomnia
<http://www.clinicaltrials.gov/ct2/show/study/NCT01021813>

³⁹ NCT01097616 A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of MK4305 in Patients With Primary Insomnia- Study A
<http://www.clinicaltrials.gov/ct2/show/results/NCT01097616>

IM 03-34-01

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

All contain nitrogen atoms and are likely to exhibit basic characteristics, such that they will be more soluble under acidic conditions and less soluble in the alkaline conditions of the small intestine.

Suvorexant is a semicrystalline solid with good thermal and pH dependent stability and modest aqueous solubility. Key physicochemical properties of suvorexant are summarized in Table 1.

Table 1 Properties of suvorexant (from Cox et al 2010)

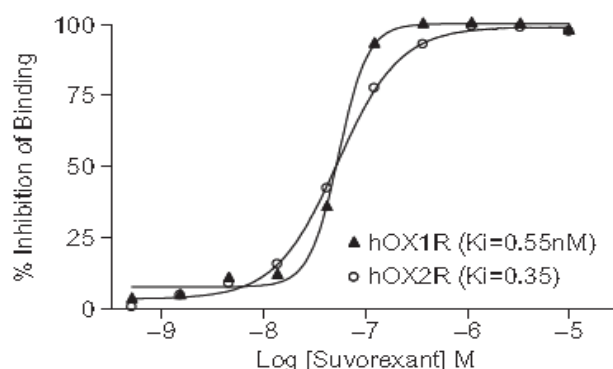
Property	Suvorexant	Implications
Passive permeability	37×10^{-6} cm/s	Passive intestinal absorption
B-A/A-B ratio	0.8	Not a Pgp efflux substrate
Log P	3.6	High lipophilicity with good CNS penetration
Brain – plasma ratio (rat)	~ 1	No concentration gradient between CNS & plasma
OX ₂ R selectivity	>10,000	Clean ancillary profile

5.3 Suvorexant pharmacokinetics (PK) and pharmacodynamics (PD)

Suvorexant is the result of a rational synthetic development program to improve the PK properties of earlier lead compounds targeting good oral absorption with low hepatic metabolism and good CNS penetration⁴⁰. Suvorexant is 99 % bound by plasma proteins.

Suvorexant has similar affinity for human OX₁R and OX₂R and also in rat, dog and monkey. It blocks OXA stimulated calcium response *in vitro* demonstrating equivalent potency for both receptors with IC₅₀ for OX₁R = 50 nM and OX₂R = 55 nM. Suvorexant occupancy of the receptors is dose related as shown in Figure 3.

Figure 3 Inhibition of radio-ligand binding by suvorexant (from Winrow et al 2011)



⁴⁰ Cox CD, Breslin MJ, Whitman DB, Schreier JD, McGaughey GB, Bogusky MJ, Roecker AJ, Mercer SP, Bednar RA, Lemaire W, Bruno JG, Reiss DR, Harrell CM, Murphy KL, Garson SL, Doran SM, Prueksaritanont T, Anderson WB, Tang C, Roller S, Cabalu TD, Cui D, Hartman GD, Young SD, Koblan KS, Winrow CJ, Renger JJ, Coleman PJ. Discovery of the dual orexin receptor antagonist [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the treatment of insomnia. *J Med Chem* (2010) 53:5320-32

IM 03-34-01

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

Metabolism is by oxidation and subsequent glucuronidation with the relatively short half life of up to 3 hours (0.6 – 3.3 h) being conducive to reduced carry over next day effects. This is much shorter than the terminal elimination half-life of 13 - 24 h for almorexant which is also metabolized by N-oxidation.

No human PK or PD data have been found, but the effects of suvorexant on sleep/wake patterns in laboratory rats, dogs and monkeys have been published⁴¹. T_{max} values of 30 minutes in rats and dogs are consistent with fast absorption and fast onset of action.

- In rats, suvorexant reduced wake activity and promoted sleep with 20 % oral bioavailability, clearance of 4.4 mL/min/kg and a terminal half life of 0.6 h. Non-REM and REM sleep durations were increased for 2 – 7 h after dosing reducing sleep latency by 24 – 41 %.
- In dogs, suvorexant had a higher oral bioavailability of 56 % with a longer terminal half life of 3.3 h and clearance of 4.0 mL/min/kg. EEG studies showed a clear dose-response relationship with reduced wake activity, increased non-REM and REM sleep duration, and reduced sleep latency by 35 – 63 %.
- In monkeys, oral bioavailability was lower at 9 % with intermediate terminal half life of 1.2 h and moderate clearance of 9.9 mL/min/kg. Again wake activity and sleep latency were reduced and times of non-REM and REM sleep increased.

6 Potential for Surge Dose[®] formulations

Suvorexant has been designed to be readily absorbed from the small intestine with high lipid solubility which allows it to readily cross the blood-brain barrier for rapid uptake at the OX receptors. Almorexant shows rapid association and dissociation at the OX₁ receptor with $t_{1/2}$ of 4.95 min whereas dissociation at the OX₂ receptor is much slower with $t_{1/2}$ of 104.6 min⁴².

In the absence of any human data on suvorexant, it would be expected to be a suitable candidate for Imaginot's Surge Dose[®] technology to significantly increase its rate and extent of *in vivo* dissolution relative to conventional tablet formulations:

- Suvorexant is targeted for use in primary insomnia where fast and consistent onset of action is a clinical pre-requisite and there is a need for an improved adverse effects profile compared with GABA_A modulators
- Suvorexant is rapidly absorbed by passive diffusion across the intestinal mucosa so faster Surge Dose[®] dissolution *in vivo* means dissolved drug reaches the small intestine more quickly for earlier absorption

⁴¹ Winrow CJ, Gotter AL, Cox CD, Doran SM, Tannenbaum PL, Breslin MJ, Garson SL, Fox SV, Harrell CM, Stevens J, Reiss DR, Cui D, Coleman PJ, Renger JJ. Promotion of sleep by suvorexant – a novel dual orexin receptor antagonist. *J Neurogenetics* (2011) 25(1-2):52-61

⁴² Neubauer D. Almorexant, a dual orexin receptor antagonist for the treatment of insomnia. *Curr Opin Investig Drugs*. (2010) 11(1):101-110

IM 03-34-01

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

- Suvorexant readily crosses the blood brain barrier and exerts its effect centrally, so faster and more consistent absorption from a Surge Dose[®] tablet will result in higher plasma C_{max} values that will more quickly and more consistently reach minimum therapeutic levels (estimated around 25 ng/mL) in plasma and the CNS
- Good PK-PD correlation and a linear relationship between dose and effect means that faster absorption will lead to faster onset of action
- Although suvorexant is described as modestly water soluble and is being evaluated at doses of 15 – 40 mg, activated pH-controlled Surge Dose[®] dissolution will provide faster dissolution than conventional tablet formulations under the same conditions regardless of the ratio of dose to solubility
- If suvorexant absorption is dependent on gastric emptying, then a Surge Dose[®] formulation will reduce the delays of food delays on absorption due to delayed gastric emptying triggered by food
- Depending on the extent of adverse events observed with suvorexant, more consistent absorption with Surge Dose[®] may allow use of a lower dose with an improved adverse event profile without compromising efficacy

7 Conclusions

Based on limited published information available on suvorexant, it is concluded that a Surge Dose[®] formulation would be likely to provide improved PK characteristics for use in the treatment of primary insomnia, and provide a patented formulation to add to existing patents on the drug per se.

Compared with conventional tablet formulations, Surge Dose[®] formulations would provide:

- More fast absorption profiles closer to the lower end of the individual subject T_{max} range
- Less effect of food in delaying absorption and onset of action
- More consistent absorption profiles with higher C_{max} levels that will exceed minimum effective levels for promotion of sleep within an acceptable time post-dose driving distribution into the CNS to bind with the OX receptors
- Higher and more consistent C_{max} may enable a reduction in dose to improve the side effect profile without compromising efficacy