

**IM 03-28-01**

**Application of Surge Dose<sup>®</sup> fast dissolution technology to axomadol**

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### EXECUTIVE SUMMARY

This report provides a review of axomadol as a candidate for the application of Imaginot's Surge Dose<sup>®</sup> drug delivery technology to increase the rates of dissolution and absorption for this synthetic centrally acting opioid analgesic. This is a hydroxylated derivative of tramadol, which was developed by Grünenthal GmbH in the 1970s for the management of moderate-to-severe pain with the benefit of reduced side effects relative to opioid analgesics. In February 2009, axomadol was licensed to Endo Pharmaceuticals for development and marketing in US and Canada while Grünenthal retains the rights for other markets. In June 2011, Endo announced that axomadol had failed primary endpoints in a Phase II randomized double blind 2-arm clinical trial in 236 patients comparing 100 and 300 mg axomadol daily in moderate-to-severe low back pain with placebo.

From a review of limited available information on axomadol and consideration of tramadol as a similar drug, it is possible that the poor efficacy seen in some clinical trials might be a function of variable absorption. It is possible that axomadol efficacy could be improved to achieve its full potential by formulation as a fast release, rapid absorbing drug rather than the slow release formulations that appear to have been used to date in order to achieve the convenience of twice daily dosage.

Surge Dose<sup>®</sup> provides improved clinical outcomes including faster onset of effective pain relief, faster achievement of peak analgesia and a higher probability of effective analgesia compared with conventional formulations. Surge Dose<sup>®</sup> 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<sup>®</sup> 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 or dissolving 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<sup>®</sup> technology was developed based on *in vivo* PK (pharmacokinetic) studies with paracetamol, a recognised marker for gastric emptying and to date has been validated with two non-steroidal anti-inflammatory agents (NSAIDs), lornoxicam and diclofenac. These studies demonstrated significantly faster and more

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consistent absorption for Surge Dose<sup>®</sup> formulations highlighting the slow and variable absorption from conventional tablets with higher  $C_{max}$  (peak plasma concentration) and shorter  $T_{max}$  (time to  $C_{max}$ ).

Surge Dose<sup>®</sup> **paracetamol** formulations achieved median  $T_{max}$  values of 17 and 25 min compared with 45 min for the fast release commercial tablet (Tylenol<sup>®</sup> Extra Strength Rapid Release Gels). With Surge Dose<sup>®</sup> more than 70 % subjects exceeded the minimum therapeutic level of 10 µg/mL in the first 15 min compared with only 20 % for the commercial tablet. For Tylenol<sup>®</sup>, 70 % of subjects experienced slow absorption with 16 % never reaching 10 µg/mL.

Based on these PK data, PK-PD (pharmacodynamic) modelling predicts that Surge Dose<sup>®</sup> 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<sup>®</sup> and confirmed by the lower NNT (Number Needed to Treat) of 2.8 predicted for Surge Dose<sup>®</sup> paracetamol compared with 4.2 for Tylenol<sup>®</sup>.

A film coated Surge Dose<sup>®</sup> **lornoxiam** 8 mg tablet resulted in absorption that was twice as fast as and more consistent than the commercial market leader. Surge Dose<sup>®</sup> mean and median  $T_{max}$  values were 0.51 and 0.50 h respectively. Individual subject  $T_{max}$  values for Surge Dose<sup>®</sup> ranged from 0.3 to 1 h with 75 % subjects achieving  $T_{max}$  within the first 0.5 h. The commercial tablet had a mean  $T_{max}$  of 1.06 h, median 0.83 h ranging from 0.5 to 2.3 h, with only 8 % subjects achieving  $T_{max}$  within the first 0.5 h. Surge Dose<sup>®</sup> 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.

A film coated Surge Dose<sup>®</sup> **diclofenac** sodium 50 mg tablet demonstrated absorption 4 – 5 times as fast as a dispersible tablet dissolved in water before administration which is promoted as fast acting (Voveran<sup>®</sup>-D, Novartis). Mean and median  $T_{max}$  values were similar for Surge Dose<sup>®</sup> tablets 19.5 min ( $\pm$  5.0) and 19.5 min (range 5 – 30 min). Voveran<sup>®</sup>-D showed much slower and more variable absorption with a median  $T_{max}$  of 1.5 h (range 15 min – 4 h). Surge Dose<sup>®</sup> 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<sup>®</sup>-D. Surge Dose<sup>®</sup>  $C_{max}$  values were comparable with those following IV or IM administration whereas those for Voveran<sup>®</sup>-D were lower than  $1,340 \pm 627$  ng/mL reported for standard tablets. With Surge Dose<sup>®</sup>, 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<sup>®</sup>-D subject (5 %) had  $T_{max}$  equal to or less than 20 min and 3

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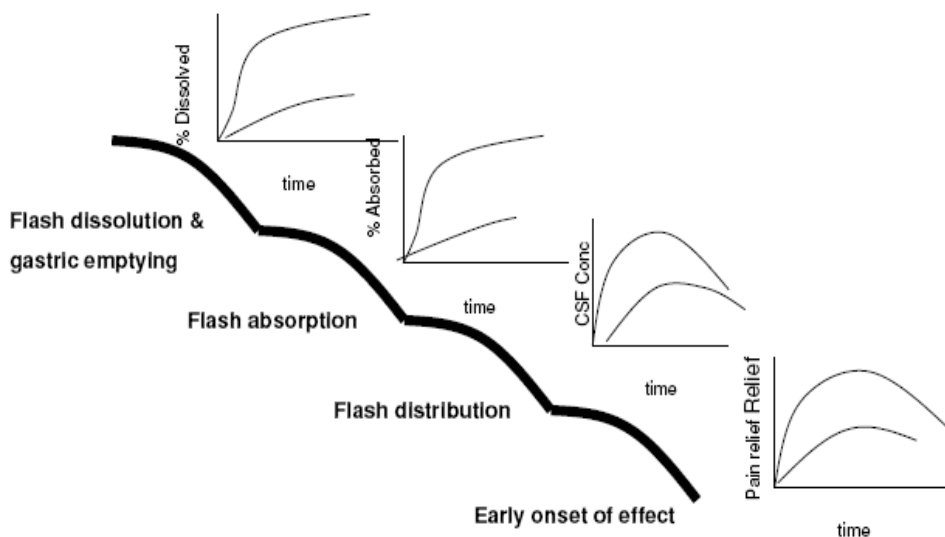
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(18 %) less than 30 min. With Voveran<sup>®</sup>-D, 70 % subjects had to wait at least 1 h to reach  $T_{max}$ , with 6 (30 %) waiting at least 2 h.

Increased and more consistent plasma levels will provide the driving force for distribution into tissues and the CNS which will translate to faster onset of action and increased efficacy. For those drugs where side effects can limit usage, this may allow use of lower doses to reduce side effects without compromising efficacy.

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 environment in relation to both pH and gastric motility typical of the wide range of physiological conditions 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<sup>®</sup> 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<sup>®</sup> 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

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- 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<sup>®</sup> 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<sup>®</sup> formulation is independent of gastric pH or gastric motility at the time of dose.

Axomadol is a basic drug, and so will demonstrate 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 potentially producing sub-therapeutic peak plasma concentrations when using low doses.

*In vitro* dissolution studies conducted on the physico-chemically related molecule tramadol, alone and in combination with paracetamol, demonstrate significantly improved dissolution for Surge Dose<sup>®</sup> formulations compared with existing tablets. *In vitro* dissolution for Surge Dose<sup>®</sup> tramadol exceeded 80 % in 3 min in typical fasted gastric conditions compared with less than 10 % in 30 min for a commercial tablet. Even under the most unfavourable *in vitro* test conditions, in the absence of stirring (0 rpm), Surge Dose<sup>®</sup> achieved 80 % dissolution in 3 min demonstrating the intrinsic activated dissolution of this formulation technology compared with negligible dissolution with conventional tablets.

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<sup>®</sup> 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

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commercial manufacture using direct compression and wet granulation processing and standard film coating techniques with additional drugs under development.

Based on the limited information available on axomadol, its physico-chemical properties and similarity to tramadol suggest that it is a suitable candidate for Surge Dose<sup>®</sup> formulation technology to increase its rate and extent of *in vivo* dissolution.

If the failure of axomadol in the clinical program is related to either slow and variable absorption or to high side effects as a result of using higher doses for a slow release twice daily product, then Surge Dose<sup>®</sup> could provide the ideal formulation technology to increase the rate of absorption and produce higher plasma levels with a smaller dose to achieve effective opioid receptor blockade in the CNS.

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## 1 Introduction

### 1.1 Surge Dose<sup>®</sup> drug delivery technology

The Surge Dose<sup>®</sup> formulation technology for fast dissolution and fast absorption of orally administered drugs has been developed by Imaginot Pty Ltd, a privately owned drug delivery company based in Queensland, Australia. Surge Dose<sup>®</sup> drug formulations provide faster and more consistent absorption resulting in faster and more reliable onset of action. Surge Dose<sup>®</sup> significantly reduces mean and median times to peak plasma drug concentration ( $T_{max}$ ) and reduces absorption variability as demonstrated for paracetamol (acetaminophen, APAP) and lornoxicam in pharmacokinetic (PK) studies in man. Based on PK-PD (pharmacodynamic) modelling, Surge Dose<sup>®</sup> paracetamol is predicted to achieve improved efficacy as the variable absorption of currently marketed tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy.

The Surge Dose<sup>®</sup> technology is well positioned to provide a clinical benefit 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 the gastric emptying cycle 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<sup>®</sup> 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<sup>®</sup> 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 gastrointestinal (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 highly variable.

### 1.2 IP status

The Surge Dose<sup>®</sup> technology is covered by three patent families filed in US, Canada, Europe, India, Japan and Australia:



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- i. PCT/AU 2006/001798 covering acidic and unionized, basic and amphoteric therapeutic agents claiming priority from three Australian provisionals, one on acids and unionized drugs filed on 28 Nov 2004, and two others on 13 May 2005. During examination the claims have been restricted to acidic and unionised drugs. The patent has been granted in Australia and is in examination in US under the PPH and in Japan.
- ii. PCT/AU 2005/00759 published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. This has been granted in Australia and Canada without limitation and is under examination elsewhere.
- iii. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations has been assigned to a third party in Australia (granted), Europe, India and Japan. The patent has been granted in US and Canada.

Patents are based on *in vitro* dissolution and *in vivo* PK results for paracetamol as a model drug and *in vitro* dissolution data for more than 30 other drugs described by chemical class as acidic, basic, amphoteric and unionized. Drugs other than those exemplified are covered by the broad claims in these patents.

### 1.3 Technical strategy

Formulation optimization is aimed at achieving total dissolution of the drug in available liquid in the stomach to provide a high concentration gradient for rapid absorption from the small intestine driving high plasma concentrations. Surge Dose<sup>®</sup> uses optimized levels and ratios of pH modulating agents and water uptake agents for each drug or drug combination to provide an activated dissolution system which will maximize the extent and rate of dissolution as demonstrated by *in vitro* testing.

The reaction between acidic and basic components produces effervescence which disrupts the boundary layers around the dissolving drug particles independent of the gastric pH, whilst controlling the pH to maximize solubility. This provides a higher concentration of drug in solution in the first few minutes after administration with the resultant drug solution draining from the stomach independent of the Migrating Motility Complex (MMC) and driving faster absorption. In contrast, traditional tablet formulations release drug into solution by passive diffusion across stagnant boundary layers around dissolving drug particles which provide a barrier to fast dissolution. Such slow dissolving tablets produce only low concentrations of dissolved drug and rely on MMC gastric emptying for drug absorption.

For ionized drugs, the pH modulating agents are optimized to favour the proportion of drug present in the more readily absorbed unionized form. At its pKa, 50 % of a drug will be

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present in its unionized form in equilibrium with 50 % in the ionized form. **Basic** drugs are present predominantly unionized at pH values above their pKa, whereas **acidic** drugs are present predominantly unionized below their pKa. **Amphoteric** drugs are zwitterions which have a net neutralisation of charge at their isoelectric point.

Surge Dose<sup>®</sup> formulations use approved GRAS excipients and conventional tablet manufacturing equipment using direct compression or wet compression. Use of this technology does not require any major capital outlay or present any regulatory hurdles through the use of unusual or new raw materials. Film coatings can be selected to have minimal impact on dissolution. For maximum stability and an acceptable shelf life of 2 years, low relative humidity (RH) manufacturing facilities around 20 % RH and unit packing in a suitable moisture-impervious laminate such as used for soluble effervescent tablets will be required. Small scale batches of a wide range of different drugs and a drug combination have been manufactured, and formulations of a basic drug and two acidic drugs have been successfully scaled-up for commercial manufacture.

Testing is conducted using a range of highly discriminating *in vitro* dissolution methods as a development rather than a QC tool. These use standard dissolution equipment with 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 is frequently used in pharmacopoeial test methods, 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*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.2, contains the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo*, and are the conditions used to characterise Surge Dose<sup>®</sup> formulations in the Imaginot patents
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, contains 3 mmoles of acid in a typical physiological volume based on 170 mL co-administered water with around 30 mL acidic gastric contents in the fasted state
- 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

#### 1.4 Commercialization

Imaginot is now seeking partners to commercialize its Surge Dose<sup>®</sup> technology. To date, deals involve a major international pharmaceutical company (confidential), a French drug

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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.

Surge Dose® formulations have been developed for a number of drugs 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.

## 2 Clinical premise for Surge Dose®

### 2.1 Key sources of physiological variability affecting drug absorption

#### 2.1.1 *Gastrointestinal (GI) motility*

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 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.

In the fasted state, subjects will be cycling through the three MMC phases with the 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

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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, reduced by Phase II or Phase III MMC activity to 12 and 5 min respectively<sup>1</sup>.

When a drug is administered to a fasted subject, they may be in any phase of the MMC. In late Phase II or Phase III, relatively fast absorption will occur as the total gastric contents are rapidly emptied into the small intestine. However, in Phase I or early Phase II, there will be slower absorption although there will be an initial fast absorption phase for any dissolved drug that passively drains from the stomach where the amount of dissolved drug will depend on its solubility and the dissolution characteristics of the dosage form. Initial absorption will be followed by a later absorption phase when the remaining gastric contents are emptied into the small intestine by Phase III MMC. This often results in double or multiple peaks in the plasma concentration – time profiles seen in many subjects particularly when there is sufficiently frequent sampling. These gastric emptying peaks occurring during the first two hours differ from later peaks due to entero-hepatic recycling.

Hence the underlying MMC will influence gastric emptying and drug absorption contributing to 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 absorb the drug slower than if they were in Phase II, with the fastest absorption occurring when the subject is in Phase III. It should be noted that 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 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 I MMC<sup>2</sup>.

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

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<sup>1</sup> 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

<sup>2</sup> 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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Surge Dose<sup>®</sup> formulations are designed to achieve ultra-fast activated dissolution of drug in co-administered liquid and stomach contents allowing the resultant solution to drain passively from the stomach independent of MMC.

#### 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.

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

#### 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<sup>3,4,5</sup>.

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 rats<sup>6</sup>.

***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:

- 
- <sup>3</sup> 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
  - <sup>4</sup> 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
  - <sup>5</sup> 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
  - <sup>6</sup> 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

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- iv. the rate at which the drug will dissolve from the dosage form into available fluids in the stomach including any co-administered liquid,
- v. the underlying GI motility or phase of the MMC which periodically empties the stomach contents into the small intestine, and
- vi. the rate of passive emptying of liquids, including dissolved drug, from the stomach into the small intestine which is independent of the MMC.

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<sup>®</sup> 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.

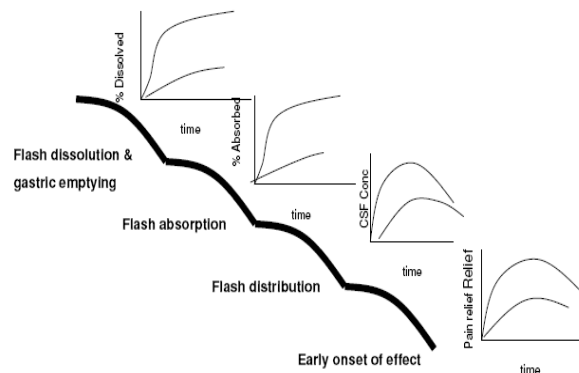
Surge Dose<sup>®</sup> is designed to maximize the extent of drug dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC as summarized below and in Figure 1:

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- 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
- 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<sup>®</sup> 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 subjects<sup>7</sup> demonstrated significantly faster absorption with two fast dissolving Surge Dose<sup>®</sup> paracetamol formulations that have subsequently been improved, compared with Tylenol<sup>®</sup> Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol<sup>®</sup>>:

- Median  $T_{max}$  values for the Surge Dose<sup>®</sup> formulations were 17 and 25 min compared with 45 min for Tylenol<sup>®</sup>

<sup>7</sup> Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane



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- Surge Dose<sup>®</sup> AUC<sub>0-30</sub> values indicated 3 times as much absorbed in the first 30 min compared with Tylenol<sup>®</sup>
- 64 and 76 % subjects receiving Surge Dose<sup>®</sup> tablets exceeded the reported minimum therapeutic level for paracetamol of 10 µg/mL in the first 15 min compared with only 20 % subjects receiving Tylenol<sup>®</sup>
- 16 % subjects taking Tylenol<sup>®</sup> never reached 10 µg/mL indicating sub-therapeutic dosing compared with only 4 % for Surge Dose<sup>®</sup> formulations

This study showed good *in vitro in vivo* correlations (IVIVC). Although paracetamol absorption was variable from one dose to another reflecting MMC activity, fast *in vitro* dissolution was associated with a higher frequency of fast absorption occasions and higher C<sub>max</sub> values. Slow absorption occasions were more frequent with Tylenol<sup>®</sup>, and were associated with lower C<sub>max</sub> 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<sup>®</sup> paracetamol tablets than Tylenol<sup>®</sup> tablets<sup>8</sup>. Improved clinical efficacy is predicted for Surge Dose<sup>®</sup> formulations as a result of fewer sub-therapeutic absorption profiles with 20% more patients achieving target end points than Tylenol<sup>®</sup>. This is reflected in the predicted lower NNT (Number Needed to Treat) of 2.8 for Surge Dose<sup>®</sup> compared with 4.2 for Tylenol<sup>®</sup>.

As paracetamol is a well-established marker for liquid gastric emptying, similar improved PK would be expected for other drugs where *in vitro* dissolution can be significantly improved with Surge Dose<sup>®</sup> formulations. 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 rate of absorption 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<sup>®</sup> to maximise *in vitro* drug dissolution compared with a conventional commercial tablet<sup>9</sup>. Surge Dose<sup>®</sup> tablets significantly reduced T<sub>max</sub> and resulted in

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<sup>8</sup> 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

<sup>9</sup> 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

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significantly higher  $C_{max}$  levels similar to parenteral administration<sup>10</sup>. Faster and more consistent absorption has the potential to improve efficacy. Absorption from Surge Dose<sup>®</sup> lornoxicam tablets was twice as fast as from the reference commercial product:

- Mean and median  $T_{max}$  values for Surge Dose<sup>®</sup> 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
- 75 % subjects on Surge Dose<sup>®</sup> lornoxicam achieved  $T_{max}$  within the first 0.5 h compared with only 8 % for the reference tablet
- Surge Dose<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> lornoxicam, respectively 3.9, 2.8 and 2.2 times higher than with the reference tablet

#### 2.3.3 Diclofenac

A film coated Surge Dose<sup>®</sup> diclofenac sodium 50 mg tablet with optimized levels of pHMA and WUA meeting the Surge Dose<sup>®</sup> in vitro dissolution specifications was compared with Voveran<sup>®</sup>-D (Novartis), a dispersible tablet dissolved in water before administration. This commercial product promoted as a fast absorbed product contained 46.5 mg diclofenac free acid equivalent to 50 mg diclofenac sodium.

Mean and median  $T_{max}$  values were similar for Surge Dose<sup>®</sup> 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<sup>®</sup>-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<sup>®</sup> produced significantly higher  $C_{max}$  values, reaching  $3,569 \pm 1,515$  ng/mL compared with  $1,042 \pm 518$  ng/mL for Voveran<sup>®</sup>-D. Surge Dose<sup>®</sup>  $C_{max}$  values were comparable with those obtained following

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of Lornoxicam Rapid Release 8 mg tablets comparing with Lornoxicam 8 mg tablets in healthy adult human subjects under fasting conditions. 11 Aug 2010

<sup>10</sup> 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

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IV<sup>11,12</sup> or IM<sup>13,14</sup> administration whereas those for Voveran<sup>®</sup>-D were lower than  $1,340 \pm 627$  ng/mL reported for standard tablets<sup>15</sup>.

With Surge Dose<sup>®</sup>, 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<sup>®</sup>-D subject (5 %) had  $T_{max}$  equal to or less than 20 min and 3 (18 %) less than 30 min. With Voveran<sup>®</sup>-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<sup>®</sup>-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 Axomadol

### 3.1 Patents

US 5,733,936 and USRE 37,355 (Grünenthal, priority 11 Jul 1995) covers the 6-dimethylaminomethyl-1-phenyl-cyclohexanes including axomadol as new centrally acting analgesics producing improved pain relief compared with tramadol and an improved spectrum of side effects relative to opioid analgesics. US 7,168,937 (Grünenthal, priority 04 Feb 2000) covers the stereo-selective synthesis involving enzymatic resolution of the racemates of aminomethyl-aryl-cyclohexanol derivatives including axomadol.

The use of axomadol for the treatment of arthrosis is covered by US 2008/0306161 and US 2010/0331424 (Grünenthal, priority 11 May 2007) which teaches the use of slow release formulations that are preferably taken twice daily. These contain 10 – 2,000 mg axomadol calculated as the free base in a unit dosage form of mass 100 – 1,000 mg. No specific

<sup>11</sup> 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

<sup>12</sup> 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

<sup>13</sup> 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

<sup>14</sup> 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

<sup>15</sup> 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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formulations are disclosed but US 2006/0121113 (WO/2005/009329) (Grünenthal, priority 24 Jul 2003) teaches the use of a hydroxypropyl methylcellulose matrix to produce a delayed release tablet releasing 3 – 35 % in 30 min, 5 – 50 % in 1 h, 10 – 75 % in 2 h, 15 – 82 % in 3 h, 30 – 97 % in 6 h, > 50 % in 12 h, > 70 % in 18 h and > 80 % in 24 h. It is assumed that these slow released formulations are used in the clinical studies on which the therapeutic claims in the patent are based.

US 2005/176790 (WO/2002/067916) covers less soluble salts of axomadol developed to provide slower absorption to support reduced dosing frequency. This describes the use of a lower solubility saccharinate salt. This is consistent with the strategy to achieve slow release and slow absorption for reduced frequency of dosing.

Other patent applications cover improved forms of axomadol and formulations but again the focus is on controlled slow release formulations:

- WO/2011/008298 (Nectid Inc) with a priority date of 30 Oct 2008 covers slow release formulations suitable for once or twice daily dosage, containing axomadol alone or with another therapeutic agent, such as paracetamol, an NSAID, opioid, antiepileptic monoamine reuptake inhibitor etc. This teaches the use of various coatings for the delayed release 'immediate release' axomadol tablets described in Table 18 [00161] which use hydroxypropyl methylcellulose as a binder to slow the release. These appear to be the formulations disclosed in US 2006/0121113. The coating slows the release further to 0 – 30 % at 1 h, 0 – 40 % at 2 h, 3 – 55 % at 4 h, 10 – 65 % at 8 h, 20 – 75 % at 12 h and 30 – 80 % at 16 h in 900 mL phosphate buffer pH 7.4 at 50 rpm. In 900 mL 0.1 N HCl at 75 % under which conditions this basic drug will have a higher solubility, the coating still slows release within the claims of 0 – 30 % in 2 h, 5 – 55 % in 4 h, > 50 % in 12 h and > 80 % in 24 h.
- WO/2009/067703 (Nectid Inc) with a priority date of 23 Nov 2007 covers the method of treatment with a slow release analgesic in combination with a second analgesic such as tramadol, GABA or a NSAID
- EP 1851190 (WO/2006/078239) (University of Florida, priority 18 Jan 2005) covers compositions and methods for inhibiting pain

Other patents US 2004/029878 (WO/2002/43714) and US 2004/242617 (WO/2002/024444) cover the use of axomadol alone and with a muscarine antagonist for the treatment of urinary incontinence.

Although axomadol is not specifically claimed in the Imaginot patents, an improved Surge Dose® formulation would be covered by the general claims for basic drugs in Imaginot patent

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### Application of Surge Dose® fast dissolution technology to axomadol

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WO/2005/0115345. The closely related tramadol is exemplified in the Surge Dose® patents both alone and in combination with paracetamol.

Additionally there is the opportunity for drug specific patents to be filed on optimized formulations identified during development.

#### 3.2 Regulatory status

Although tramadol was developed by Grünenthal GmbH in the 1970s as a synthetic analog of codeine to provide a centrally acting analgesic for moderate to severe pain with an improved safety profile, work has continued on other compounds to further reduce the problematic opioid side effects such as euphoria, respiratory depression and addiction. Axomadol is hydroxy-tramadol and so would have similar properties to tramadol which is a weak  $\mu$ -opioid receptor agonist, releases serotonin and inhibits re-uptake of norepinephrine, where the different mechanisms of action provides additive or synergistic analgesia with reduced adverse events as a result of less  $\mu$ -opioid receptor binding.

Grünenthal licensed the exclusive rights to develop and market axomadol in the US and Canada to Endo Pharmaceuticals in 2009. Grünenthal retains the rights for axomadol in other markets. The Phase II clinical development program covered evaluation of axomadol in moderate-to-severe chronic pain and diabetic peripheral neuropathic pain. Grünenthal received an up-front payment with further payments linked to clinical, regulatory and commercial milestones with Grünenthal manufacturing the final product and receiving a transfer price covering cost of goods and royalties on net sales in US and Canada.

In Jun 2011, Endo announced that in a Phase II study in low back pain, axomadol had missed undisclosed endpoint against placebo, and that the clinical data were being reanalysed.

Given that some patients experienced satisfactory pain relief, it is possible that lack of adequate efficacy overall is a function of the formulation strategy using a slow release drug delivery system instead of an immediate release product that produces high plasma concentrations to drive distribution and effect. Reformulation with Surge Dose® would require extensive clinical evaluation but may provide an opportunity to capitalise on the advantages offered by axomadol compared with other synthetic opioids drugs, allowing the use of low doses with associated lower levels of adverse events without compromising efficacy.

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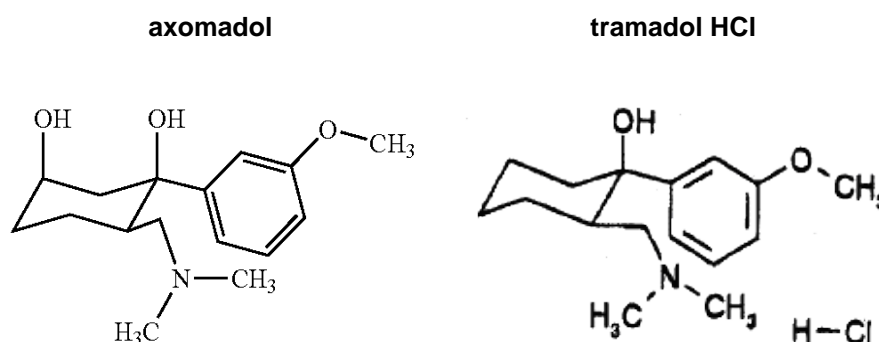
### Application of Surge Dose® fast dissolution technology to axomadol

#### 3.3 Physicochemical properties

##### 3.3.1 Structure

Axomadol is closely related to tramadol with the addition of a hydroxyl grouping on the cyclohexane ring. (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol has the chemical formula  $C_{16}H_{25}NO_3$  and a molecular weight of 279.37. Its chemical structure compared with tramadol is shown in Figure 2.

**Figure 2 Chemical structures of axomadol and tramadol hydrochloride**



##### 3.3.2 Solubility

Axomadol hydrochloride (HCl) has high aqueous solubility to the extent of 500 mg/mL which is higher than the lower solubility saccharinate at 71 mg/mL<sup>16</sup>. As a basic molecule, solubility of this drug would be higher under acidic conditions than at higher pH such as in the small intestine.

##### 3.3.3 Permeability

In the absence of any ionization or lipophilicity data on axomadol, it would be expected to be less lipophilic and more ionizable than tramadol based on the substitution of an additional hydroxyl group in the cyclohexane ring. Tramadol is slightly lipophilic with an octanol/aqueous partition coefficient at pH 7 of 1.35 and has a pKa at 9.41.

Axomadol would be expected to be readily absorbed through the intestinal mucosa and although the ionized form of the drug will predominate at around pH 5.0 – 7.0 in the small intestine, this will facilitate dissolution of any undissolved drug. The higher the concentration of drug in solution reaching the small intestine, the higher will be driving force for faster absorption. While the unionized form of the drug will be preferentially absorbed from the

<sup>16</sup> WO/2002/067916 Pharmaceutical salts. Grünenthal GmbH. Priority 28 Feb 2001 p43

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small intestine, the equilibrium between the ionized and unionized forms will drive continued absorption.

#### 3.3.4 *In vitro* dissolution

The FDA defines rapid dissolution as no less than 85 % dissolution in 30 minutes when tested in up to 900 mL 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer using either baskets at 100 rpm or paddles at 50 rpm.

However the formulation described in the patent literature for axomadol are all delayed release and even the 'Immediate release' axomadol 50 mg tablets disclosed in WO/2011/008298 are a slow release formulation<sup>17</sup>. When tested in 900 mL phosphate buffer 7.4 at 50 rpm, only 44 % had dissolved in 30 min, 73 % in 1 h and 96 % in 4 h.

It would be expected that axomadol dissolution from an immediate release tablet would be faster under acidic conditions than under alkaline conditions such as occur in the small intestine where absorption occurs. The dissolution profiles published for the formulations disclosed in the patent literature are very different to those that would be obtained with Surge Dose® formulations where target dissolution would be > 70 % in the first 3 minutes under both acidic and alkaline conditions.

#### 3.4 Pharmacokinetics (PK) and pharmacodynamics (PD)

Although no published PK data have been found for axomadol in man, the clinical program targeted analgesic efficacy with an improved profile of adverse events compared to other opiates, with tramadol as the benchmark for the reduced incidence of side effects.

The use of axomadol in arthrosis is based on the results from two placebo- controlled studies<sup>18</sup>. 44, 66 and 110 mg doses of axomadol calculated as the free base were compared with 100 mg tramadol twice daily in osteoarthritis of the knee or hip. Analgesia and side effects was dose dependent for axomadol with only the 110 mg dose demonstrating superior analgesia to placebo and having twice the level of side effects compared with the other treatment groups. The most common side effects were nausea, constipation, sweating, dizziness, vomiting, headache, dry mouth and drowsiness.

A second study in knee osteo-arthritis compared 100 and 150 mg axomadol as the free base with controlled release oxycodone 20 mg, both taken twice daily. Both doses of axomadol were equivalent to oxycodone and superior to placebo for the primary endpoint. Side effects

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<sup>17</sup> WO/2011/008298 Nectid Inc. Novel axomadol dosage forms Priority 16 Jul 2009 Table 18 [00161] Table 55 [00204]

<sup>18</sup> US 2008/0306161 Use of axomadol for treatment of arthrosis pain. Grünenthal



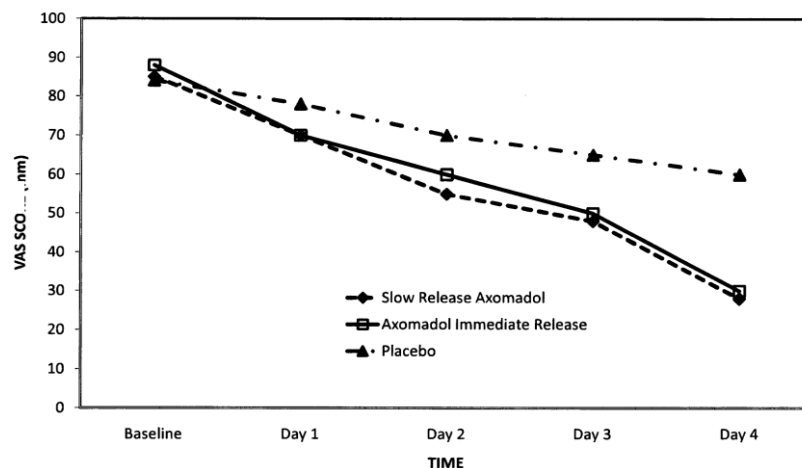
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for active treatments were greater than for placebo but axomadol was superior to oxycodone with 16.3 and 17.7 % side effects for the two doses compared with 31.5 % for oxycodone. Most common side effects were constipation, nausea, vomiting and dry mouth.

Compared with placebo, the time course for pain relief shown by reduction in a visual analog scale (VAS) of 100 was similar for both a delayed immediate release tablet and a slow release tablet taken twice daily as shown in Figure 3 showing increasing pain relief over the first 4 days<sup>19</sup>. These indicate that with these delayed release formulations, it takes at least 4 days to reach steady state plasma levels and efficacy.

**Figure 3 Time course of pain relief for delayed immediate and slow release axomadol tablets (from WO/2011/008298)**



## 4 Surge Dose<sup>®</sup> axomadol

### 4.1 Clinical considerations

If the failure of axomadol in clinical trials is related to lack of efficacy associated with slow and variable absorption, then Surge Dose<sup>®</sup> offers an opportunity for an improved immediate release tablet rather than the slow release formulations evaluated to date. Faster and more consistent absorption may offer the opportunity to use a lower dose without compromising efficacy to reduce the incidence and severity of any side effects.

On the limited information available, axomadol appears to be a suitable candidate for Imaginot's ultra-fast activated dissolution Surge Dose<sup>®</sup> technology:

<sup>19</sup> WO/2011/008298 Nectid Inc. Novel axomadol dosage forms Priority 16 Jul 2009



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- It is used to treat moderate - severe pain where fast and consistent onset of action is a clinical pre-requisite
- It is readily absorbed by passive diffusion across the intestinal mucosa and blood brain barrier into the CNS where high concentration of dissolved drug in the small intestine can provide the driving force for fast absorption and distribution to the central site of action

#### 4.2 Technical considerations

As the related compound tramadol is classified as BCS class I based on high solubility and high permeability<sup>20</sup>, axomadol would be expected to have a similar classification. Surge Dose<sup>®</sup> formulations significantly improve the *in vitro* dissolution of tramadol HCl compared with current IR tablets containing tramadol alone<sup>21</sup> and with paracetamol<sup>22</sup>.

Figure 4 shows rapid dissolution exceeding 90 % in the first 3 min for Surge Dose<sup>®</sup> tramadol tablets in 900 mL 0.0033 M HCl at 30 rpm compared with only 40 % dissolution after 10 min for the commercial product, Ultram<sup>®</sup>. Figure 5 shows that Surge Dose<sup>®</sup> tablets demonstrate ultra-fast activated dissolution exceeding 80 % within 3 min even in the absence of external stirring. These conditions simulate those that occur when there is gut stasis which frequently is associated with acute and chronic pain, and in the post-operative state.

**Figure 4 Dissolution profiles comparing Surge Dose<sup>®</sup> tramadol 30 mg with Ultram<sup>®</sup> in USP dissolution apparatus II in 900 mL 0.0033 M HCl at 30 rpm at 37 °C**

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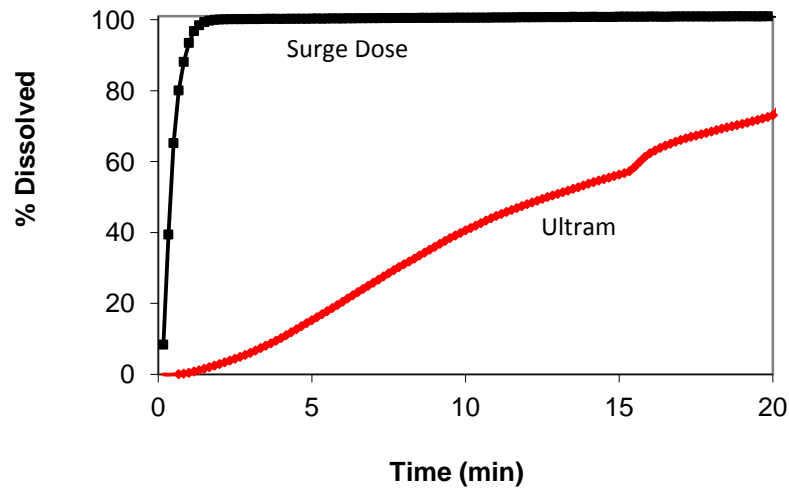
<sup>20</sup> Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain and Japan. *Mol Pharm* (2006) 3(6):631-643 SI1-SI25

<sup>21</sup> Imaginot Pty Ltd. DR 03-05-01 Effect of Surge Dose on tramadol HCl dissolution. 20 Dec 2005

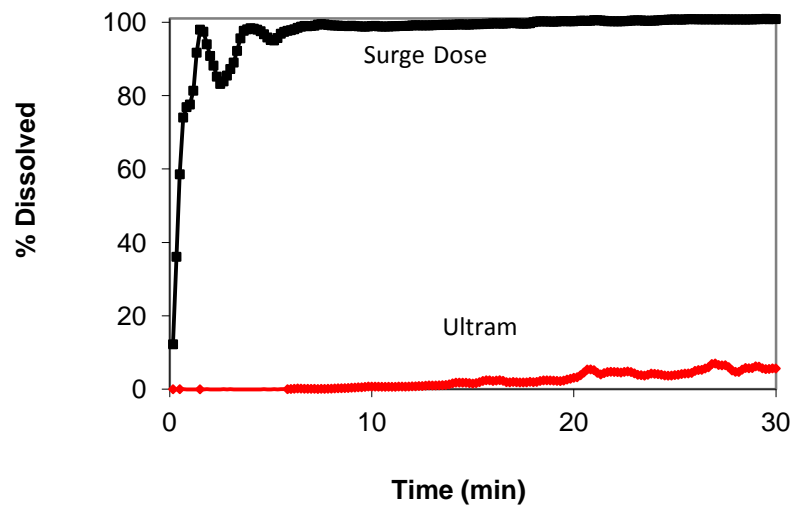
<sup>22</sup> Imaginot Pty Ltd. DR 02-01-01 Effect of Surge Dose on dissolution of a tramadol HCl / paracetamol combination tablet. 20 Dec 2005

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### Application of Surge Dose® fast dissolution technology to axomadol



**Figure 5** Dissolution profile for Surge Dose® tramadol 50 mg in USP dissolution apparatus II using 900 mL 0.0033 M HCl at 0 rpm at 37 °C

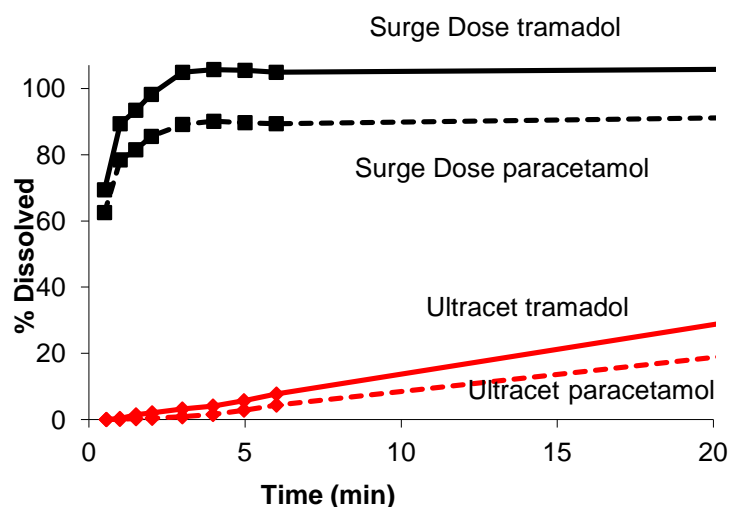


Surge Dose® also significantly increases the dissolution rate of both components when applied to a combination product of tramadol and paracetamol as shown in Figure 6. These dissolution profiles better reflect *in vivo* conditions using more discriminating conditions in 200 mL 0.0033 M HCl. The unoptimized Surge Dose® combination tablet exceeds 80 % dissolution for both drugs within 3 minutes compared with less than 5 % for Ultracet®.

**Figure 6** Dissolution profiles for Surge Dose® tramadol 37.5 mg with paracetamol 325 mg compared with Ultracet® in USP dissolution apparatus II using 200 mL 0.0033 M HCl at 30 rpm at 37 °C

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An optimized Surge Dose® axomadol formulation should achieve at least 70 % dissolution in the first 3 min in both stirred and unstirred conditions. This would translate to faster *in vivo* dissolution under both favorable and unfavorable GI conditions, resulting in faster delivery to the small intestine and subsequently faster absorption.

## 5 Conclusion

Based on the only information available being the physico-chemical properties of axomadol and its similarity to tramadol, axomadol would appear to be a suitable candidate for Surge Dose® to increase its rate and extent of *in vivo* dissolution.

If the failure in the clinical program is related to either slow and variable absorption or to high side effects as a result of using higher doses for a slow release twice daily product, then Surge Dose® could provide the ideal formulation technology to increase the rate of absorption and produce higher plasma levels with a smaller dose to achieve opioid receptor blockade in the CNS.

***Surge Dose® axomadol will maximise the rate of dissolution, even under unfavourable conditions, to ensure rapid delivery of dissolved drug to the small intestine to drive absorption and distribution in the CNS***

***Surge Dose® axomadol will reduce the variability in  $T_{max}$ , with more fast absorption profiles***

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*Surge Dose<sup>®</sup> axomadol will reduce the variability in  $C_{max}$  reducing the frequency of sub-therapeutic dosing to improve efficacy*

*Surge Dose<sup>®</sup> axomadol will provide faster absorption which may allow the use of lower doses with benefits of reduced adverse events*

*Surge Dose<sup>®</sup> axomadol can provide a true 'on demand' presentation without the delays associated with food consumption*

*Surge Dose<sup>®</sup> axomadol will provide faster onset of action and faster time to peak analgesia*