

**DR 06-04-01**

**Application of Surge Dose<sup>®</sup> technology to temazepam**

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20 December 2008

Date

05 October 2012

Reissued

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### 1 Executive Summary

Imaginot developed its ultra-rapid activated, pH-controlled dissolution Surge Dose<sup>®</sup> formulation technology based on in vitro dissolution testing and in vivo evaluation of fast dissolving paracetamol tablet formulations in fasted subjects, where fast in vitro dissolution is associated with fast in vivo absorption. Paracetamol is a well recognised marker of gastric emptying and the in vivo results demonstrated the effect of the different phases of gastrointestinal (GI) motor activity known as the Migrating Motility Complex (MMC) on the pharmacokinetic (PK) profile. The results from Imaginot's proof of concept clinical trial in 25 fasted subjects showed good in vitro in vivo correlations (IVIVC).

Imaginot has evaluated the potential for application of its Surge Dose<sup>®</sup> technology to temazepam, a short-acting benzodiazepine hypnotic, widely used for insomnia and premedication before surgical procedures. Based on a review of the physicochemical, PK and pharmacodynamic (PD) properties of this drug and some preliminary in vitro dissolution data, Imaginot believes that optimised Surge Dose<sup>®</sup> temazepam tablets are likely to result in faster in vivo absorption and faster onset of action than standard formulations. Such formulations would be expected to demonstrate reduced intra-subject variability.

In general, slow dissolution leads to slow gastric emptying, with a corresponding low driving force across the intestinal mucosa, resulting in slow absorption and lower peak plasma concentrations ( $C_{max}$ ). Imaginot has demonstrated that slow absorption for paracetamol can lead to a high proportion of low  $C_{max}$  values below the minimum therapeutic plasma concentration of 10 mcg/mL. Sub-therapeutic plasma levels will reduce efficacy and can lead to repeat dosing or use of a higher dose which may be associated with an increase in side effects. More consistent fast absorption with Surge Dose<sup>®</sup> formulations allows the use of minimum doses for fast onset of action without compromising efficacy. PK-PD modelling based on the PK results with paracetamol predict improved efficacy for Surge Dose<sup>®</sup> formulations compared with regular formulations.

Application of the Surge Dose<sup>®</sup> formulation technology to more than 30 drugs has demonstrated that the rate and extent of in vitro dissolution can be significantly increased compared with standard tablet formulations and even solubilised soft gelatin capsules. The improved absorption kinetics seen with paracetamol have been demonstrated in vivo for two nonsteroidal anti-inflammatory drugs, lornoxicam and diclofenac. Film coated optimised Surge Dose<sup>®</sup> tablets achieved faster and more consistent absorption compared with a regular lornoxicam tablet and a dispersible diclofenac tablet.  $C_{max}$  values were higher comparable with injectable administration and times to  $C_{max}$  ( $T_{max}$ ) were significantly reduced

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with mean and median values in the range 20 – 30 minutes compared to 1 – 1.5 hours for the commercial products which for some subjects was 2 – 4 hours.

Reformulating a drug that is readily absorbed across the intestinal mucosa to ensure rapid dissolution in vivo is likely to lead to:

- (i) rapid absorption and more rapid onset of peak effect
- (ii) a reduction in slow absorption occasions, which lead to low, possibly sub-therapeutic plasma concentrations

Temazepam is an amphoteric drug with reasonable solubility such that a dose will be soluble in typical volumes of co-administered water, which is readily absorbed across the intestinal mucosa, and where there is close correlation between its PK and the PD. There is also evidence that the drug is absorbed more quickly than from tablets when in the pre-solubilised form such as an aqueous solution or a propylene glycol solution filled soft gelatin capsule. In addition the pharmacological effects of temazepam are such that its performance impairment and sedative effects can be measured non-invasively in healthy subjects by a variety of test methods.

Such observations highlight the potential of temazepam as a candidate for the Surge Dose<sup>®</sup> technology where the dissolution rate can be enhanced by control of the pH around the dissolving particles and micro-stirring. Faster in vivo dissolution, regardless of the gastric acidity, will lead to a consistent and increased rate of absorption with the benefit of faster onset of action and improved therapeutic outcomes for a higher proportion of patients.

A preliminary screening of reformulated 10 mg temazepam tablets applying Surge Dose<sup>®</sup> technology shows that the rate of in vitro dissolution can be significantly increased where the composition of the pHMA contains sodium bicarbonate with an organic acid. Such a formulation containing 20 mg sodium bicarbonate with 10 mg anhydrous citric acid achieves around 60 % dissolution after 3 minutes in 900 mL 0.0033 M hydrochloric acid (HCl) in a USP dissolution apparatus II at 30 rpm and 37 °C, compared with negligible dissolution even after 20 minutes from a standard tablet. Even in the absence of stirring (0 rpm), the experimental Surge Dose<sup>®</sup> formulation achieved 50 % dissolution in the first 5 minutes demonstrating the synergy between the inherent micro-stirring in the formulation and pH control in the vicinity of the dissolving drug particles. The Surge Dose<sup>®</sup> formulation exemplified in this study provides a suitable starting point for formulation optimisation to maximise the in vitro dissolution rate.

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Based on these results, it appears that optimized Surge Dose<sup>®</sup> formulations of temazepam can be developed that will demonstrate significantly faster in vitro dissolution under a variety of conditions. In turn, such formulations are likely to result in faster in vivo dissolution and faster in vivo absorption resulting in a faster onset of action than conventional solid dosage forms, and could be at least as fast as liquid filled soft gelatin capsules. Based on available comparative data for capsules and a solution, it would be expected that Surge Dose tablets would behave more like a solution with mean  $T_{max}$  values around 30 minutes compared to around 1 hour for solid dosage forms including tablets and soft gelatin capsules.

## 2 Introduction

### 2.1 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  $T_{max}$  and reduces absorption variability as demonstrated for paracetamol (acetaminophen, APAP), diclofenac and lornoxicam in PK studies in man. Based on PK-PD 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

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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.

#### 2.2 IP status

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

- 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 granted in US and Canada. This patent has been assigned to a third party in Australia (granted), Europe, India and Japan.

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.

#### 2.3 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 (pHMA) and water uptake agents (WUA) 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

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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 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

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- 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

#### 2.4 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 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<sup>®</sup> technology for interested parties.

Surge Dose<sup>®</sup> 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<sup>®</sup> product containing lornoxicam was launched in 2010 with a second product to be launched in 2012.

### 3 Clinical premise for Surge Dose<sup>®</sup>

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

##### 3.1.1 Gastrointestinal (GI) motility

Drug absorption following oral administration is influenced by:

- the rate at which the drug will dissolve from the dosage form into available fluids in the stomach including any co-administered liquid,
- the underlying GI motility or MMC which periodically empties the stomach contents into the small intestine, and
- 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



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- 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, 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 Reisinger-Gonik-Malaga-Jacob-Ric-Simble on the gastric emptying of liquids. *Gastroenterology* (1990) 97:131-136.  
<sup>2</sup> Reisinger-Gonik-Malaga-Jacob-Ric-Simble on the gastric emptying of liquids. *Gastroenterology* (1990) 97:131-136.

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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.

#### 3.1.2 Gastric pH

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.

### 3.1.3 Intestinal pH

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<sup>®</sup> 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***

### 3.2 Clinical rationale

Drug absorption following oral administration is influenced by:

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- <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.

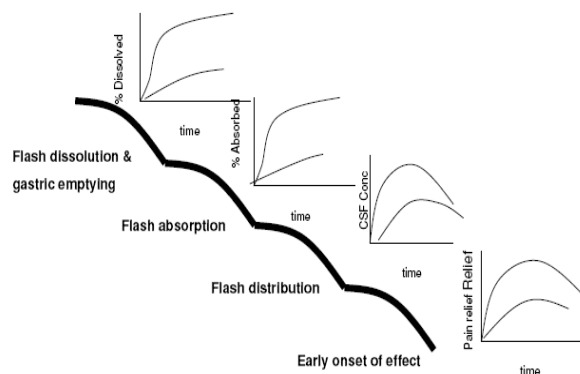
Surge Dose<sup>®</sup> is designed to maximize the extent of drug dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC as summarized below and in Figure 1:

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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**



### 3.3 Proof of concept

#### 3.3.1 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.

#### 3.3.2 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

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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

#### 3.3.3 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

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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

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

With Surge Dose<sup>®</sup>, 76 % subjects had a T<sub>max</sub> equal to or less than 20 min and 100 % reached T<sub>max</sub> within 30 min. By comparison only one Voveran<sup>®</sup>-D subject (5 %) had T<sub>max</sub> 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<sub>max</sub>, 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<sub>max</sub> 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).

## 4 Temazepam as a potential Surge Dose<sup>®</sup> candidate

This report details the consideration of the clinical features of temazepam that suggest Surge Dose<sup>®</sup> formulations will offer faster in vivo dissolution and absorption, with the potential for improved and more consistent therapeutic outcomes. It also describes the preliminary experimental work conducted on temazepam which demonstrates the significantly improved in vitro dissolution that is possible by applying the Surge Dose<sup>®</sup> technology to this drug.

### 4.1 Physicochemistry and solubility

Temazepam has the following chemical structure and a molecular weight of 300.7 as shown in Figure 2.

<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

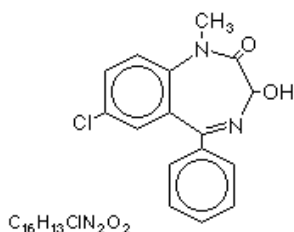
<sup>15</sup> Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arznei-Forsch/Drug Res* (2001) 51(11): 885 – 890



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**Figure 2 Chemical structure of temazepam**



It is described as practically insoluble in water (Ph Eur) and very slightly soluble in water (USP 25). It is an amphoteric molecule with two pKa values, a pKa around 1.3 for deprotonation of the protonated 4-nitrogen atom (base) and around 11.5 for deprotonation of the 3-hydroxy or 1-nitrogen positions (acid). Hence its lowest aqueous solubility will occur at the calculated isoelectric point of pH 6.4 and the solubility will increase on either side of this pH with a solubility of 0.054 mg/mL reported in deionised water at pH 7.09<sup>16</sup>. A higher aqueous solubility of 0.604 mg/mL at ambient temperatures has also been reported<sup>17</sup>.

Based on these two values, a 10 mg dose of temazepam should completely dissolve in between 16 and 185 mL water. These volumes are within the range of 150-200 mL which is a typical volume of co-administered water taken with an oral dosage form. However such solubility data suggest that the rate of dissolution could be absorption rate limiting for this drug particularly when volumes of available liquid are limited.

### 4.2 PK, intestinal permeability and formulation effects

Temazepam is used as a hypnotic in the short-term management of insomnia and for premedication before surgical or investigative procedures. It is a short-acting benzodiazepine which is well absorbed from the gastrointestinal tract. Its general properties are similar to those of diazepam although characterised by a much shorter elimination half-life of 5 – 15 hours which has the advantage of minimal residual sedation which is frequently a problem of other benzodiazepines with longer elimination half-lives of 1 – 2 days.

Temazepam is about 96% bound to plasma protein. It is excreted mainly in the urine in the form of its inactive glucuronide conjugate together with small amounts of the demethylated derivative, oxazepam, also in conjugated form.

<sup>16</sup> Newton DM, Narducci WA, Leet WA, Ueda CT. Lorazepam solubility in and sorption from intravenous admixture solutions. *Am J Hosp Pharm* (1983) **40**:424-7

<sup>17</sup> Loftsson T, Hreinsdottir D. Determination of aqueous solubility by heating and equilibration: A technical note. *AAPS PharmSciTech* (2006) **7**(1):article 4

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Despite temazepam being well absorbed, the rate of absorption depends on the formulation<sup>18</sup> and for solid dosage forms absorption is clearly dissolution rate limited. Slow and variable absorption has been reported from hard gelatin capsules (Restoril<sup>®</sup>, Sandoz) with  $T_{max}$  ranging from 0.75 to 12.0 hours after dosing in fasted subjects where the capsules were administered with 100 – 200 mL tap water<sup>19</sup>. In healthy volunteers, 30 mg temazepam as a solution was found to be absorbed most quickly, with highest peak plasma concentrations which resulted in faster onset of sedation compared with hard gelatin capsules and suppositories<sup>20</sup>. Absorption was rapid from the solution, and  $C_{max}$  around 50 % higher than those obtained with the capsules, were achieved in 20-40 minutes as seen in Figure 3. It was noted that when rapidly absorption of temazepam with rapid achievement of high plasma levels, results in intense sedative effects.

**Figure 3 Mean plasma concentrations of temazepam administered as a solution ( $\Delta$ ), capsules ( $\square$ ) and a suppository ( $\circ$ )**

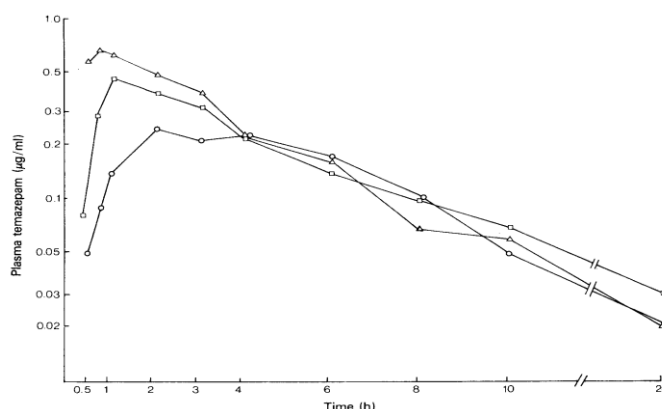


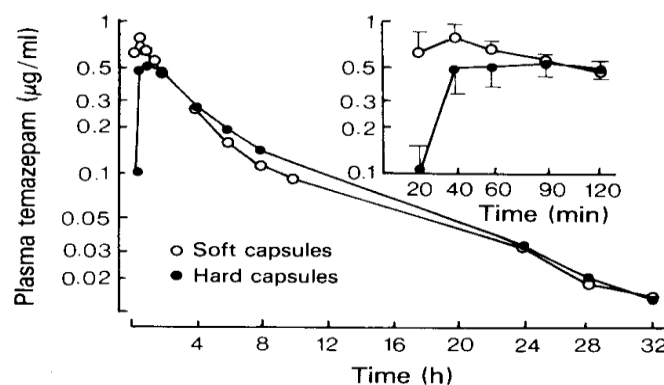
Figure 4 shows the improvement that can be achieved with a liquid filled soft gelatin capsule where the drug is already in solution compared with a conventional powder filled hard gelatin capsule. The liquid filled capsule produced faster absorption with a  $T_{max}$  of 0.83 hours and a higher  $C_{max}$  of 0.892 mcg/mL compared with 1.44 hours and 0.668 mcg/mL<sup>21</sup>.

- <sup>18</sup> Martindale. The complete drug reference. 33<sup>rd</sup> edition Pharmaceutical Press. Editor S C Sweetman
- <sup>19</sup> Divoll M, Greenblatt DJ, Harmatz JS, Shader RI. Effect of age and gender on disposition of temazepam. *J Pharm Sci* (1981) **70**(10):1104-7
- <sup>20</sup> Fuccella LM. Bioavailability of temazepam in soft gelatin capsules. *Br J Clin Pharmacol* (1979) **8**(1):31S-35S
- <sup>21</sup> Fuccella LM, Bolcioni G, Tamassia V, Ferrario L, Tognoni G. Human pharmacokinetics and bioavailability of temazepam administered in soft gelatin capsules. *Eur J Clin Pharmacol* (1977) **12**:383-6

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**Figure 4 Mean plasma concentrations after oral temazepam 20 mg in a hard gelatin capsule (●) and a soft gelatin capsule (○)**



Similar fast absorption for 10 mg temazepam in soft gelatin capsules has been reported in geriatric in-patients with a median  $T_{max}$  of 0.75 hours and mean  $C_{max}$  of 0.306 mcg/mL<sup>22</sup>. This study showed significant inter-subject variation in absorption with  $T_{max}$  values ranging from 0.25 to 1.5 hours indicating that in some subjects, very fast absorption was occurring compared with one subject where no detectable plasma levels were measured until 0.75 hours post dose.

It has been postulated that an elixir where the drug was already in solution and readily available for absorption would result in faster absorption than the soft gelatin capsules where time is required for rupture and emptying of the capsule. However studies on elixirs have shown wide inter-subject variability with similar performance to soft gelatin capsules. In surgical patients, a 30 mg dose pre-operatively gave mean peak plasma concentrations around 800 ng/mL with  $T_{max}$  values around 30 minutes for both dosage forms<sup>23</sup>. There was a high degree of inter-subject variability with peak plasma concentrations achieved within 15 – 105 minutes.

Mean plasma levels of 211 ng/mL were associated with sedation ratings of “awake” with “sedated” ratings associated with concentrations greater than 785 ng/mL. Plasma levels exceeded the reported target levels of about 200 ng/mL required for sedation and anxiolysis.

<sup>22</sup> Klem K, Murray GR, Laake K. Pharmacokinetics of temazepam in geriatric patients. *Eur J Clin Pharmacol* (1986) **30**:745-47

<sup>23</sup> Hosie HE, Nimmo WS. Temazepam absorption in patients before surgery. *Br J Anaesth* (1991) **66**:20-4

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In 60 psychiatric in-patients, 20 mg temazepam produced similar hypnotic effects for both formulations with no significant differences between sleep duration and latency<sup>24</sup>.

The lack of clinical advantage for the elixir may be attributable to the small volume of liquid in which the dose is administered and also to the nature of the formulation. In general, elixirs provide a 5 – 20 mL volume dose to be taken without any additional water, and are complex non-aqueous formulations using solvents and ingredients to dissolve and flavour the drug, many of which ingredients can delay gastric emptying. One elixir formulation containing 10 mg temazepam in 5 mL, is formulated with povidone 25, polyethylene glycol 400, ethanol, glycerol, sodium phosphate, citric acid, chlorophyll (E141), sorbitol solution (70%), peppermint oil and, lemon flavour supara BL2300<sup>25</sup>. Without any co-administered liquid, such small dosage volumes are likely to be caught up in the muscular folds of the stomach, rather than draining into the pyloric region, so that emptying will be dependent on gastric activity even though the drug is in solution. Consideration of these factors could explain why similar performance is seen with both soft gelatin capsules and elixirs despite the disintegration time required for the capsule.

### 4.3 PK-PD relationship

A good correlation has been reported between plasma concentrations of lorazepam and its clinical effect<sup>26</sup> and although cerebrospinal fluid levels correlated well with dose, the correlation with sedation was relatively weak<sup>27</sup>.

In healthy fasted subjects, 20 mg temazepam in soft gelatin capsules was demonstrated to be absorbed faster with higher  $C_{max}$  and greater efficacy than an uncoated tablet formulation<sup>28, 29</sup>. Mean  $C_{max}$  and  $T_{max}$  values for the soft gelatin capsule were 935 ng/mL and 0.9 hours respectively compared with 726 ng/mL and 1.1 hours for an uncoated tablet.

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<sup>24</sup> Patel AG, Gura R, Kurian T, Lambert MT, Steinert J, Priest RG. A comparison of the hypnotic effects of temazepam capsules and temazepam elixir. *Int Clin Psychopharmacol* (1991) **6**:1-9

<sup>25</sup> <http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=1581>

<sup>26</sup> Ratcliff A, Indalo AA, Bradshaw EG, Rye RM. Plasma concentrations and clinical effects of lorazepam after oral administration. *Br J Anaesth* (1981) **53**:517-22

<sup>27</sup> Osborne GA, Badcock NR, McGrath PM, Russell WJ, Frewin DB. The relationship between the concentration of temazepam in cerebrospinal fluid and sedation in man. *Anaesth* (1992) **47**:303-6

<sup>28</sup> Mattila MJ, Mattila M, Toumainen P. Acute pharmacokinetic and pharmacodynamics comparison of two formulations of temazepam. *Med Biol* (1985) **63**(1):21-7

<sup>29</sup> Tuomainen P. A methodological comparison of two formulations of temazepam in pharmacokinetic and pharmacodynamic aspects. *Pharmacol Toxicol* (1989) **64**(1):28-32

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Although there was limited early blood sampling at 30, 60 and 120 minutes, there were more subjects with  $T_{max}$  at 30 minutes with the soft gelatin capsule, 50 % compared with only 30 % with the tablet. The soft gelatin capsule was also shown to have a significantly faster onset of action as a pre-medicant in 60 gynaecological patients<sup>30</sup>

In this study, the central effects of temazepam were measured using digit symbol substitution (DSS), letter cancellation (LC) and Maddox wing (exophoria) tests at baseline and at 1, 2 and 3 hours post dose. The first two tests are sensitive to learning but the last is not. Subjective tests on performance and alertness were also conducted. Although there was no significant difference between the two dosage forms, the soft gelatin capsule was always significantly better than placebo whereas the tablet was not. Hence the interpretation of the results to indicate improved performance with the soft gelatin capsule. The fast absorption from the soft gelatin capsule was associated with a faster return to placebo subjective sedation levels, which tallies with the lack of residual activity reported with this formulation.

## 5 Fast dissolving Surge Dose<sup>®</sup> temazepam tablets

### 5.1 Formulations

As temazepam was not available as a raw material, commercial tablets<sup>31</sup> were reformulated by grinding in a mortar and pestle and passing through a 280 µm screen using Surge Dose<sup>®</sup> formulation principles employing pHMA and WUA. Added excipients were passed through a 280 µm screen and blended with the powdered tablets. The powder blend was then compressed on a BT 50 tablet press fitted with a single set of 8 mm round shallow concave punches to achieve the hardest possible tablet disintegrating within 30 seconds in 0.0033 M HCl at 37 °C.

Batch formulae in Table 1 show the unquantified levels of excipients in the commercial tablets<sup>32</sup> as √. Where additional ingredients are added, these are quantified.

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<sup>30</sup> Salonen M, Aantaa E, Aaltonen L, Hovi-Viander L, Kanto J. A comparison of the soft gelatin capsule and the tablet form of temazepam. *Acta Pharmacol Toxicol* (1986) **58**(1):49-54

<sup>31</sup> Temtabs<sup>®</sup> 10 mg tablets Lot 57209 (Sigma) Manufactured by Fawns & McAllan Pty Ltd, 1408 Centre Road, Clayton, Victoria 3168, Australia.

<sup>32</sup> Prescriber Information for Temtabs<sup>®</sup>, Sigma

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**Table 1 Formulations for temazepam tablets reformulated from Temtabs<sup>®</sup> 10 tablets to demonstrate the effect of Surge Dose<sup>®</sup> on in vitro dissolution**

Formulation	0521110	Temtabs <sup>®</sup>
Temazepam (mg)	10	10
Sodium bicarbonate, fine (mg)	20	0
Citric acid, anhydrous (mg)	10	0
Crospovidone * (mg)	10	0
Microcrystalline cellulose *, Lactose *, Maize starch *, Sunset yellow lake, Magnesium stearate	√	√
Total (mg)	218	178
Tablet description	8 mm round uncoated shallow convex tablet	8 mm round uncoated shallow convex tablet debossed on one side
Hardness	4 – 5 Kp	-
Disintegration time in 0.0033 M HCl at 37 °C	24 seconds	-

\* classified as water uptake agent (WUA)

Key features of the formulations in relation to the levels of pHMA and water uptake agents (WUA) are summarized in Table 2. These are based on the disclosed formulation assuming 165 mg of each 178 mg commercial tablet comprises WUAs and around 1 % w/w magnesium stearate as a tablet lubricant.

**Table 2 Key formulation characteristics for reformulated temazepam tablets**

Ingredients	0521110	Temtabs <sup>®</sup> 10
% bicarbonate (SB)	9.2	0
% pH modulating agents (PHMA)	13.8	0
% water uptake agent (WUA)	~ 81	~ 94
Weight ratio pHMA : drug	3 : 1	n/a
Weight ratio SB : drug	2 : 1	n/a
Weight ratio WUA : drug	~ 18 : 1	~ 17 : 1
Weight ratio WUA : SB	~ 9 : 1	n/a
Weight ratio WUA : pHMA	~ 6 : 1	n/a

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### 5.2 In vitro dissolution

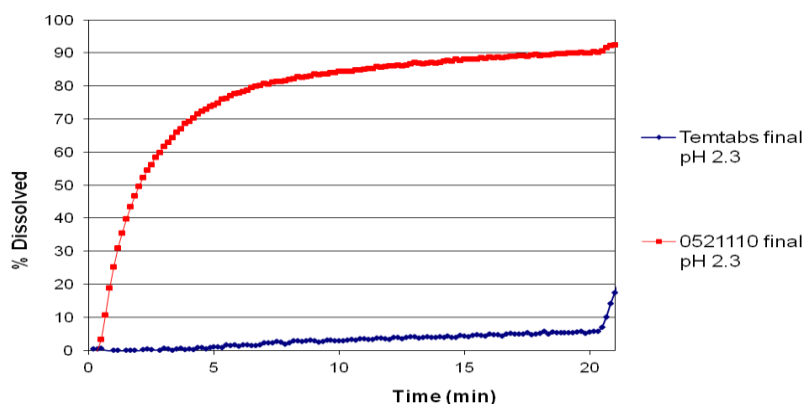
#### 5.2.1 Tablets

Dissolution was measured in 900 mL 0.0033 M HCl at 37 °C in USP dissolution apparatus media at 30 rpm and 0 rpm which conditions were selected to simulate in vivo conditions and also to provide good discrimination for fast dissolving formulations<sup>33</sup>. 900 mL 0.0033 M HCl contains 3 millimoles HCl which is equivalent to the 30 mL residual gastric acid estimated to be present in a fasted subject. When diluted with 170 mL water co-administered with the formulation, the resultant solution contains approximately in 200 mL, approximating 0.015 M HCl. However, when used for dissolution at a volume of 900 mL, 0.015 M HCl contains significantly more acid than present in vivo. Therefore for testing in 900 mL, Imaginot uses 0.0033 M HCl which contains the same absolute amount of acid as 200mL 0.015 M HCl and illustrates the effect of pH changes which would occur when formulations containing pH modulating agents are administered. This low concentration also mimics low gastric acid conditions such as in fed subjects or those with low gastric acid secretion.

Drug concentrations were measured using a Varian Cary 50 UV-Vis Spectrophotometer set at the optimal wavelength, experimentally found to be 230 nm.

Dissolution profiles in 900 mL 0.0033 M HCl for the Surge Dose<sup>®</sup> temazepam tablets show significantly faster dissolution compared with the conventional commercial tablets Temtabs<sup>®</sup> as seen in Figures 5 and 6.

**Figure 5 Dissolution profile in 900 mL 0.0033 M HCl at 30 rpm and 37 °C for Surge Dose<sup>®</sup> temazepam tablets 10 mg (0521110) compared with Temtabs<sup>®</sup>**



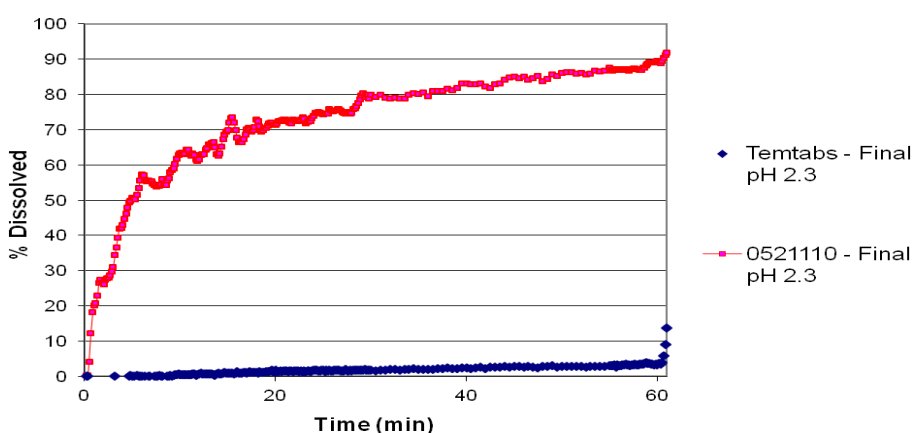
<sup>33</sup> Handbook of Dissolution Testing, 3<sup>rd</sup> edition, R Hanson & V Gray, Dissolution Technologies Inc, 2004

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At 30 rpm, 62 % temazepam dissolves within 3 minutes compared with less than 1 % from the commercial tablet. By 15 minutes, 88 % of the dose in the Surge Dose<sup>®</sup> tablet had dissolved whereas the commercial tablet was still less than 5 % dissolved. This fast dissolution occurs at a relatively low acid concentration typical of subjects with reduced gastric acidity or the fasted state.

**Figure 6** *Dissolution profile in 900 mL 0.0033 M HCl at 0 rpm and 37 °C for Surge Dose<sup>®</sup> temazepam tablets 10 mg (0521110) compared with Temtabs<sup>®</sup>*



At 0 rpm, the inherent activated dissolution of the Surge Dose<sup>®</sup> technology ensures fast and extensive release of 31 % of the drug by 3 minutes and 70 % by 15 minutes compared with less than 1 % dissolution achieved with the standard tablet. Surge Dose<sup>®</sup> formulations ensure that drug dissolution in vivo will be independent of gastro-intestinal mobility and dissolution will occur even during gut stasis.

In both cases, increasing the stirring speed to 250 rpm achieved 100 % dissolution of the drug from the fast dissolving Surge Dose<sup>®</sup> formulation in a few minutes. However dissolution from the commercial tablets was still relatively slow even under high stir conditions and did not reach 100 % indicating a high degree of solubility limitation despite the high dissolution volume of 900 mL. These results mean that for the commercial products, a high level of gastro-intestinal mobility is required to expedite drug dissolution. These results indicate the effect of the Surge Dose<sup>®</sup> technology in controlling the pH of the micro-environment around the dissolving temazepam particles to increase the solubility and rate of dissolution.

#### 5.2.2 Liquid filled soft gelatin capsules

Although liquid filled soft gelatin capsules of temazepam were not available for testing, dissolution profiles for similar liquid filled capsules of other drugs demonstrate that even

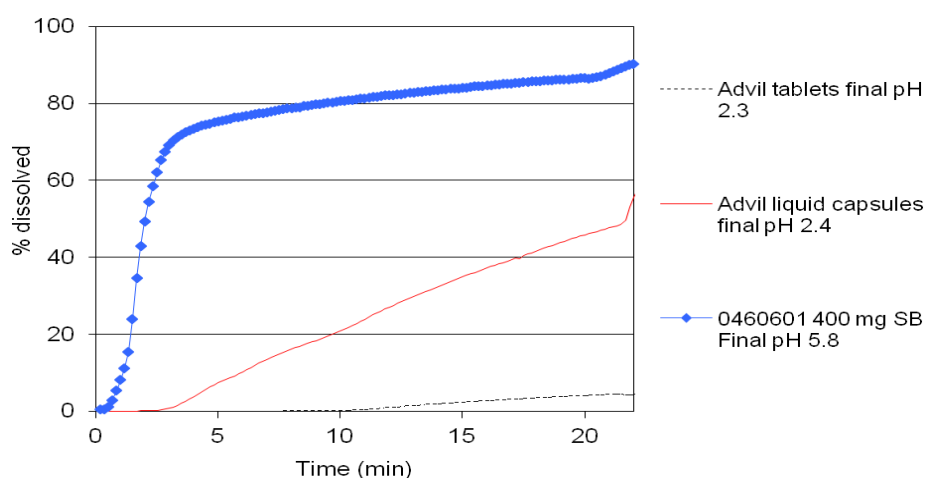


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though the drug is in solution in propylene glycol, dissolution still requires a level of agitation. Figure 7 shows dissolution profiles in 900 mL 0.0033 M HCl at 30 rpm and 37 °C for ibuprofen, a drug which is available as both tablets and liquid filled soft gelatin capsules. Although the soft gelatin capsule showed faster and more extensive dissolution than the commercial tablet, the Surge Dose<sup>®</sup> tablet formulation showed significantly faster and more extensive dissolution than both commercial formulations.

**Figure 7 Dissolution profile in 900 mL 0.0033 M HCl at 30 rpm and 37 °C for Surge Dose<sup>®</sup> ibuprofen tablets compared with Advil<sup>®</sup> tablets and liquid capsules**



### 5.3 Formulation implications

Application of the Surge Dose<sup>®</sup> formulation approach using pH modulating agents using a single low level of sodium bicarbonate and citric acid in a weight ratio of 2:1 has been shown to significantly increase the initial rate and extent of dissolution. Further development is required to optimise a Surge Dose<sup>®</sup> temazepam tablet formulation with respect to the level and composition of pHMA and also WUA.

Surge Dose<sup>®</sup> tablet formulations utilise conventional manufacturing and packaging equipment and processing techniques but require controlled low relative humidity and unit packaging for maximum stability. Although there is a pre-solubilised soft gelatin capsule available which does offer fast absorption, this requires specialist manufacturing capability and will incur the associated increased manufacturing costs. Hence the potential cost advantage of Surge Dose<sup>®</sup> formulations relative to the soft gelatin technology.

The in vitro dissolution profiles suggest that the Surge Dose<sup>®</sup> technology is capable of increasing the extent of solubilisation relative to the soft gel capsule particularly in the first five minutes. It is possible that this would result in faster delivery to the site of absorption but this would need to be investigated in vivo.

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### 6 Conclusions

This review suggests that temazepam is a suitable candidate for the application of Imaginot's Surge Dose<sup>®</sup> technology to significantly increase the rate of in vitro and in vivo dissolution, and subsequently increase the rate of absorption and onset of action:

- The solubility of this amphoteric molecule which displays minimum solubility at its isoelectric point at pH 6 is such that normal doses of the drug will dissolve in typical volumes of co-administered water
- Temazepam is readily absorbed across the intestinal mucosa and there is evidence that if the drug is already in solution it is absorbed faster than if administered in the solid form requiring time for in vivo dissolution to take place
- There is good correlation between the PK and PK with the effects being easily monitored in healthy subjects using non-invasive tests to determine the time to onset of action
- An experimental Surge Dose<sup>®</sup> temazepam 10 mg tablet formulated with small amounts of sodium bicarbonate and citric acid, shows significantly faster in vitro dissolution than commercial tablets even in the absence of extrinsic stirring.