

**IM 03-22-01**

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

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## EXECUTIVE SUMMARY

This report provides a review of oxymorphone hydrochloride (HCl) as a candidate for the application of Imaginot's Surge Dose<sup>®</sup> drug delivery technology to increase this drug's rate of dissolution and absorption resulting in improved clinical outcomes. The technical rationale is presented for an ultra-fast active-dissolving Surge Dose<sup>®</sup> oxymorphone which is expected to provide advantages over the existing immediate release (IR) tablets that do not utilise any rapid dissolution technology. Improved clinical outcomes would include:

- reduction in time to onset of effective pain relief,
- faster achievement of peak analgesia and
- a higher probability of effective analgesia.

Application of the Surge Dose<sup>®</sup> technology would also be suited to the development of a combination paracetamol with oxymorphone tablet with fast absorption of both actives.

Oxymorphone is a short acting opiate analgesic, proposed as one of the options in step 3 pain management where the use of an opioid is appropriate. In moderate to severe acute pain, fast and consistent onset of action is an essential clinical requirement. Oxymorphone is ideal for oral administration being lipophilic and well absorbed by passive diffusion across the intestinal mucosa with good pharmacokinetic – pharmacodynamic (PK–PD) correlation. However, although **median** times to peak plasma concentration ( $T_{max}$ ) around 0.5 h are reported for existing oxymorphone IR formulations, closer analysis of available data indicates that absorption is highly variable with individual  $T_{max}$  values ranging from 15 min to 1.5 h, and the **mean**  $T_{max}$  is longer than the median. Correspondingly  $C_{max}$  values are highly variable with CVs of 40 – 50 % such that a proportion of subjects will not achieve minimum effective plasma concentrations around 2 µg/mL with a 10 mg dose. Slow absorption associated with low peak plasma concentrations ( $C_{max}$ ) is likely to contribute to the relatively high lack of efficacy up to 35 % reported in some clinical trials.

Imaginot's patented Surge Dose<sup>®</sup> technology was developed based on *in vivo* PK studies with paracetamol (acetaminophen) which is a known marker for liquid gastric emptying. In the proof of concept study, around 70 % of subjects experienced slow absorption for the fast release commercial tablet (Tylenol<sup>®</sup> Extra Strength Rapid Release Gels) with median  $T_{max}$  45 min and 16 % of subjects never reaching the minimum therapeutic level of 10 µg/mL. In contrast, two Surge Dose<sup>®</sup> formulations resulted in significantly faster absorption with median  $T_{max}$  values of 17 and 25 min and more than 70 % subjects exceeding 10 µg/mL in the first 15 min compared with only 20 % for the commercial tablet. Based on this

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study, PK-PD modelling predicts that ultra-fast dissolving Surge Dose<sup>®</sup> paracetamol tablets will demonstrate 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> formulations.

Surge Dose<sup>®</sup> has also been shown to significantly reduce  $T_{max}$  and increase  $C_{max}$  for the NSAIDs lornoxicam and diclofenac in fasted subjects as a result of faster and more consistent absorption compared with leading commercial products:

- Absorption from an optimised film coated Surge Dose<sup>®</sup> lornoxicam tablet was twice as fast with comparable mean and median  $T_{max}$  of 0.51 and 0.50 h respectively. Individuals showed more consistent fast absorption with  $T_{max}$  ranging from 0.3 to 1 h and 75 % subjects achieving  $T_{max}$  within the first 0.5 h. The commercial tablet had a mean  $T_{max}$  of 1.06 h and 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> lornoxicam achieved around 40 % higher mean  $C_{max}$  of 1098 ng/mL (CV 18.71 %) compared with only 788 ng/mL (CV 18.69 %) for the reference tablet. Increased and more consistent plasma levels will translate to increased efficacy, and for those drugs where side effects can limit usage, may allow a dose reduction to reduce side effects without compromising efficacy.
- Diclofenac was absorbed 4 – 5 times as quickly from an optimised film coated Surge Dose<sup>®</sup> tablet compared with Voveran<sup>®</sup>-D (Novartis), a dispersible tablet dissolved in water before administration. 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> tablets resulted in significantly higher  $C_{max}$  values, reaching  $3,569 \pm 1,515$  ng/mL compared with  $1,042 \pm 518$  ng/mL for Voveran<sup>®</sup>-D.  $C_{max}$  values for Surge Dose<sup>®</sup> were comparable with those obtained following IV or IM administration whereas as those for Voveran<sup>®</sup>-D were lower than reported for standard tablets of  $1,340 \pm 627$  ng/mL.

Clearly most conventional IR formulation technologies do not deliver the desired fast and consistent onset of action required for drugs taken on demand such as analgesics, migraine therapies, drugs for allergy, anti-nausea drugs, phosphodiesterase inhibitors and other drugs for acute indications. Such formulations exhibit slower and more variable dissolution in gastric fluids and consequently are slower to empty into the small intestine where absorption occurs. The faster absorption of drugs from oral solutions compared

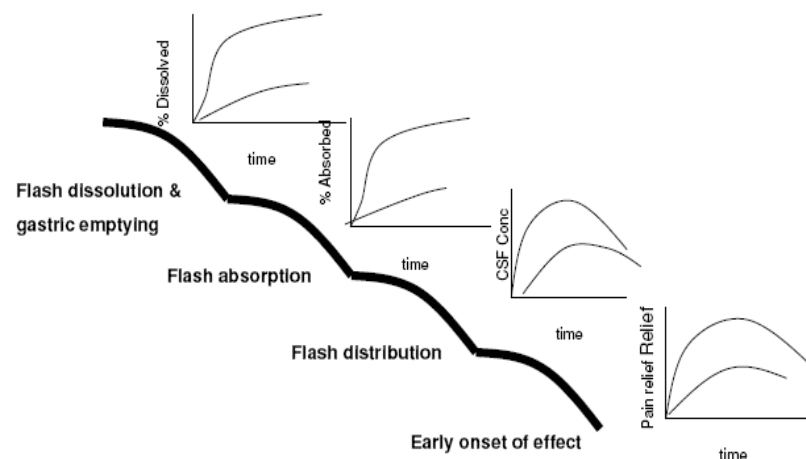
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with solid dosage forms highlights the effects of slow and variable *in vivo* dissolution resulting in slower and more variable absorption.

Surge Dose® enabled ultra-fast *in vivo* dissolution of oxymorphone will result in faster and more consistent absorption reducing mean and median  $T_{max}$  values towards the lower end of the reported range, namely 15 min. It will also reduce the variability of absorption seen in healthy fasted subjects which will be amplified in a normal population sample where gastrointestinal (GI) conditions vary significantly. This will lead to both a more rapid onset of action and increased overall efficacy compared with existing commercial formulations.

To achieve rapid absorption from a solid dose formulation, ultra-fast activated dissolution *in vivo* is essential. Furthermore this must occur in a limited volume of available fluid in the stomach and a 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® formulations are designed to minimise the time for *in vivo* dissolution independent of gastric pH or gastric motility, maximising dissolution into the co-administered water.

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



- The drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents
- The resultant solution empties rapidly and passively from the stomach in both fed and fasted states i.e. the drug empties as fast as if it had been taken as a solution

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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.

Oxymorphone is a basic drug with  $pK_{a1}$  8.17 and  $pK_{a2}$  9.54 which is covered by the broad platform claims in Imaginot's patents. As a basic drug it will demonstrate its maximum solubility under acidic conditions with solubility reducing as the pH increases. Hence while acidic gastric conditions in fasted subjects will favour dissolution, its dissolution rate is likely to be quite variable in the general population where gastric pH will vary significantly at the time a dose is taken. This is likely to result in variable absorption with some slow absorption occasions producing sub-therapeutic peak plasma concentrations particularly when using low drug doses. This may contribute to the lack of analgesia reported by up to 35 % subjects in clinical efficacy studies on oxymorphone.

While no dissolution studies have been conducted on oxymorphone, results for codeine, another opioid analgesic with similar physico-chemical properties, are indicative of the expected improvements for Surge Dose<sup>®</sup> oxymorphone. *In vitro* dissolution for Surge Dose<sup>®</sup> codeine phosphate exceeded 80% in 3 minutes in typical fasted gastric conditions, compared with around 30 % in 3 minutes 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 70 % dissolution in 5 minutes demonstrating the intrinsic activated dissolution of this technology compared with conventional tablets showing negligible dissolution.

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 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-

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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 a basic drug and an acidic drug have been successfully scaled-up for commercial manufacture using direct compression and wet granulation processing and standard film coating techniques.

When key attributes of oxymorphone are compared to other oral opiates used for the control of acute and/or breakthrough pain, oxymorphone has a number of advantages:

- oxymorphone has a longer elimination half life which allows less frequent dosing
- despite its relatively low oral bioavailability as a result of first pass hepatic metabolism, the major metabolite is active with double the elimination half life of the parent compound which effectively extends the duration of action.
- low protein binding allows faster achievement of therapeutic plasma levels.
- no significant GI slowing and resultant constipation which occurs with other opiates and is a major problem particular in elderly patients
- no major drug interactions as the metabolism of oxymorphone does not involve CYP3A4 or CYP2D6 drug metabolising pathways
- absorption and metabolism are unaffected by the polymorphisms in CYP enzyme systems that occur in up to 20 % of the population.

Surge Dose<sup>®</sup> oxymorphone would add to this favourable clinical profile with improved efficacy and safety. Faster  $T_{max}$  values would lead to more consistent  $C_{max}$  values within the therapeutic range of 2 – 4 µg/mL, reducing the frequency of sub-therapeutic dosing that may contribute to the relatively high failure rate of around 35 % with existing formulations where CVs are around 40 – 50 %.

In summary, there is a technically supportable opportunity to develop and register a Surge Dose<sup>®</sup> oxymorphone with clinical benefits over existing IR tablets and the potential for market exclusivity associated with registering a new improved formulation:

- Although existing IR oxymorphone tablets have a low **median**  $T_{max}$  of 30 min, results are highly variable ranging from 15 min to 1.5 h. Surge Dose<sup>®</sup> oxymorphone would produce more  $T_{max}$  values in the region of 15 minutes, reducing the number of slow absorption occasions with  $T_{max}$  greater than 30 minutes.
- Surge Dose<sup>®</sup> oxymorphone could provide enhanced efficacy, reducing the high dropout rate of up to 35 % in some pain studies likely to be associated with slow and

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variable absorption (CV 40 – 50 %) from existing IR products producing sub-therapeutic plasma levels below 2 µg/mL

- Surge Dose<sup>®</sup> oxymorphone with ultra-fast *in vivo* dissolution will demonstrate more fast absorption occasions and less variable absorption with faster and more consistent onset of action

Thus Surge Dose<sup>®</sup> oxymorphone provides an opportunity to effectively compete with other opiates as well as other more expensive drug delivery assisted formulations such as effervescent fentanyl buccal tablets and fentanyl nasal spray. Surge Dose<sup>®</sup> oxymorphone alone or in combination with an NSAID, provides a patented product with the potential for superior clinical efficacy, particularly fast onset of action in breakthrough pain.





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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> has been shown to significantly reduce mean and median times to peak plasma drug concentration ( $T_{max}$ ) and reduce absorption variability for both paracetamol (acetaminophen) 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 and 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 the gastric emptying cycle and/or *in vivo* dissolution seen when comparing aqueous drug solutions with a solid dose form
- a direct temporal relationship between plasma concentrations and PD effects with no significant lag time

Surge Dose<sup>®</sup> will maximize the impact of pH dependent solubility to increase the rate of absorption, and is also suitable 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 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:

- 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

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patent has been granted in Australia and is in examination elsewhere.

- ii. PCT/AU 2005/00759 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. A clean ISR report was issued in Europe.
- iii. PCT/AU 2005/00758 covering paracetamol and paracetamol combinations. This has been assigned to a third party in Australia (granted), Europe, India and Japan. The US and Canadian patents have been granted.

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 producing higher 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 MMC and leading to 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 also 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 prepared by direct compression or wet compression, and so do

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not require any major capital outlay or present any regulatory hurdles by 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 an acidic drug 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, where the pH at 1.2 is similar to that in the fasted stomach, but the volume and total amount of acid is much higher than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.2, containing the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo* – these conditions are used to characterise Surge Dose<sup>®</sup> formulations in the Imaginot patents, under which basic drugs will achieve at least 70 % dissolution in 180 seconds
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, containing 3 mmoles of acid in a volume to simulate the use of 170 mL co-administered water added to around 30 mL acidic gastric contents in the fasted state
- 200 mL 0.0033 M HCl at 30 rpm containing lower levels of acid in a typical physiological volume which simulates lower gastric acidity
- 900 mL 0.0033 M HCl at 0 rpm to simulate gut stasis such as occurs in migraine and the fed state where there is little gastric motility

### 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 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.

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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.

### 1.5 Proof of concept PK studies

#### 1.5.1 Paracetamol

Although paracetamol absorption profiles showed a high degree of variability from one dose to another reflecting MMC activity, fast *in vitro* dissolution was associated with a higher frequency of fast absorption occasions and higher peak plasma concentrations. Slow absorption occasions occurring more frequently with slower dissolving products were associated with lower peak plasma concentrations which sometimes failed to reach the reported minimum therapeutic plasma concentrations for paracetamol. Using PK-PD modelling to quantify pain relief following oral administration, more rapid onset and greater analgesia have been predicted for Surge Dose<sup>®</sup> paracetamol tablets<sup>1</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.

A proof of concept Phase I study in 25 fasted healthy subjects showed that fast dissolving Surge Dose<sup>®</sup> paracetamol tablets achieved faster *in vivo* absorption than conventional slower dissolving commercial tablets marketed as fast absorbing products. Comparator products were Tylenol<sup>®</sup> Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol<sup>®</sup>> and Panadol<sup>®</sup> Rapid (GSK, Aus)<sup>2</sup>. Panadol<sup>®</sup> Rapid contains 630 mg sodium bicarbonate per tablet and shows slower *in vitro* dissolution compared with Surge Dose<sup>®</sup> tablets.

The two preliminary Surge Dose<sup>®</sup> formulations were not optimised but demonstrated fast *in vitro* dissolution. These demonstrated a higher frequency of fast absorption occasions where each fast absorption occasion was associated with a higher peak plasma

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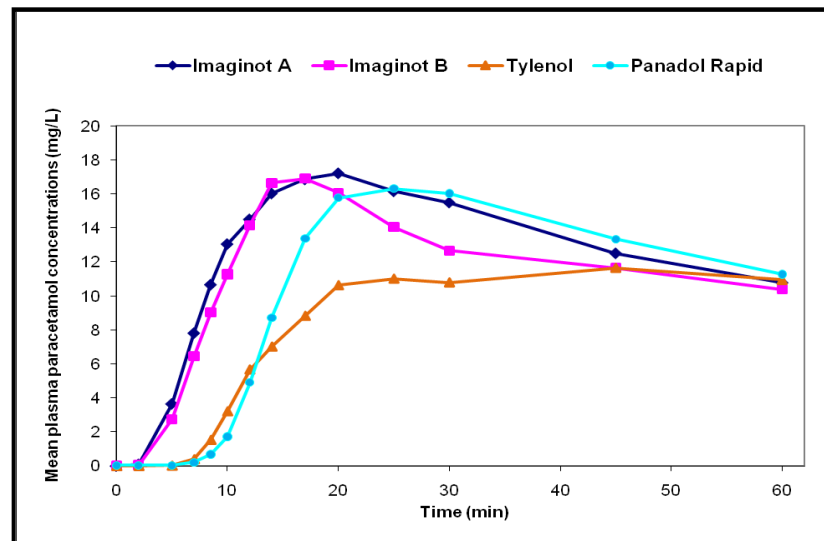
<sup>1</sup> Green B, Chandler S, Macdonald G, Elliott G, Roberts MS. Quantifying pain relief following administration of a novel formulation of paracetamol (acetaminophen), *J. Clin. Pharmacol.* (2010) Online First doi 10.1177/0091270009359181

<sup>2</sup> Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

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concentration ( $C_{max}$ ) compared with slow absorption occasions. Mean absorption profiles for the four products are shown in Figure 1.

**Figure 1** Mean absorption profiles for 1,000 mg paracetamol administered orally as unoptimized Surge Dose formulations and two commercial 'fast absorption' tablets in 25 healthy fasted subjects



- Median  $T_{max}$  values for Surge Dose<sup>®</sup> formulations were 17 and 25 min respectively and for Panadol<sup>®</sup> Rapid 25 min compared with 45 min for Tylenol<sup>®</sup>
- Mean  $C_{max}$  values were lowest for Tylenol<sup>®</sup> at  $19.4 \pm 10.3 \mu\text{g/mL}$  compared with  $23.1 \pm 9.3$  and  $21.8 \pm 11.2 \mu\text{g/mL}$  for the two Surge Dose<sup>®</sup> formulations and  $24.2 \pm 9.3 \mu\text{g/mL}$  for Panadol<sup>®</sup> Rapid
- Although  $AUC_{0-\infty}$  values were similar for all products, Surge Dose<sup>®</sup> formulations achieved significantly more early absorption in the first 10 – 30 minutes with Surge achieving 3 times as much absorbed in the first 30 min compared with Tylenol<sup>®</sup>

This study showed good *in vitro in vivo* correlations (IVIVC) with the best Level A correlation in 900 mL 0.0033 M HCl at 30 rpm which conditions are used to optimize Surge Dose<sup>®</sup> formulations<sup>3</sup>.

Using PK-PD modelling to quantify pain relief following oral administration, more rapid onset and greater analgesia have been predicted for Surge Dose<sup>®</sup> paracetamol tablets

<sup>3</sup> Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401. (2005) QPharm, Imaginot Pty Ltd, Brisbane

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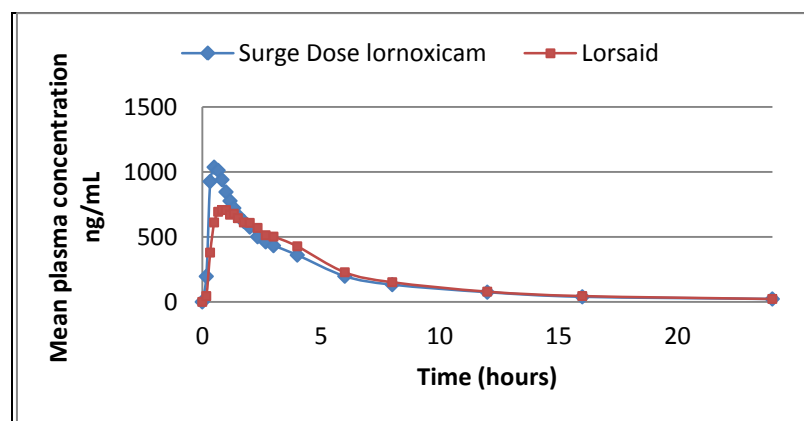
compared with conventional tablets<sup>4</sup>. This can be explained by the number of slow absorption profiles with Tylenol<sup>®</sup>, where  $C_{max}$  failed to reach the documented 10 µg/mL minimum therapeutic plasma concentration for analgesia and antipyresis:

- 64 and 76 % of subjects receiving Surge Dose<sup>®</sup> tablets exceeded the reported minimum therapeutic level of 10 µg/mL in the first 15 min compared with only 20 % for Tylenol
- 16 % of subjects never reached 10 µg/mL indicating sub-therapeutic dosing with Tylenol compared with only 4 % for Surge Dose<sup>®</sup>

#### 1.5.2 Lornoxicam

A film coated Surge Dose<sup>®</sup> lornoxicam 8 mg tablet was developed containing optimized levels of pHMA and WUA to meet the Surge Dose<sup>®</sup> in vitro dissolution specifications. A Phase I PK study in 24 fasted healthy subjects showed significantly faster absorption than Lorsaid<sup>®</sup> (Hetero Drugs Limited) as shown in Figure 2<sup>5</sup>. Compared with other generic lornoxicam tablets, Lorsaid<sup>®</sup> showed more extensive in vitro dissolution but did not meet the Surge Dose<sup>®</sup> specification.

**Figure 2** Mean absorption profiles for 8 mg lornoxicam administered orally as a Surge Dose<sup>®</sup> tablet and Lorsaid<sup>®</sup>



Surge Dose<sup>®</sup> lornoxicam showed faster, less variable absorption with significantly reduced  $T_{max}$  and increased  $C_{max}$  compared with a conventional commercial tablet:

<sup>4</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>5</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 of Lornoxicam Rapid Release 8 mg tablets comparing with Lornoxicam 8 mg tablets in healthy adult human subjects under fasting conditions. 11 Aug 2010

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- Absorption from Surge Dose<sup>®</sup> lornoxicam was twice as fast compared with the commercial product. Mean and median  $T_{max}$  values were comparable at 0.51 and 0.50 h respectively ranging from 0.3 to 1 h. The reference product had a median  $T_{max}$  of 0.83 h ranging from 0.5 to 2.3 h with a longer mean  $T_{max}$  of 1.06 h reflecting the higher number of 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 Lorsaid<sup>®</sup>
- Surge Dose<sup>®</sup> lornoxicam achieved  $C_{max}$  values comparable with parenteral administration<sup>6</sup>, around 40 % higher with a mean  $C_{max}$  of 1098 ng/mL (CV 18.71 %) compared with only 788 ng/mL (CV 18.69 %) for the reference product.
- As with paracetamol, although  $AUC_{0-\infty}$  was the same for both Surge Dose<sup>®</sup> and reference lornoxicam, 4,257.3 and 4,182.6 ng.h/mL respectively, values for  $AUC_{0-10}$ ,  $AUC_{0-20}$  and  $AUC_{0-30}$  demonstrated significantly faster absorption for Surge Dose<sup>®</sup>, respectively 3.9, 2.8 and 2.2 times higher than the reference product.

### 1.5.3 Diclofenac

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

This Phase I PK study in 21 fasted healthy subjects demonstrated faster and more consistent absorption of diclofenac with significantly higher  $C_{max}$  for Surge Dose<sup>®</sup> as shown in Figure 3<sup>7</sup>.

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). By comparison 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> tablets resulted in significantly higher  $C_{max}$  values, reaching  $3,569 \pm 1,515$  ng/mL compared with  $1,042 \pm 518$  ng/mL for Voveran<sup>®</sup>-D.  $C_{max}$  values for Surge Dose<sup>®</sup> were comparable with

<sup>6</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

<sup>7</sup> Piramal Clinical Research. Report No CR-BE-324-DICL-2011 (draft) An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single-dose comparative pharmacokinetic study of Diclofenac Rapid Release tablets 50 mg sodium diclofenac comparing with Voveran D dispersible tablets 46.5 mg diclofenac free acid in healthy adult human subjects under fasting conditions. March 2012

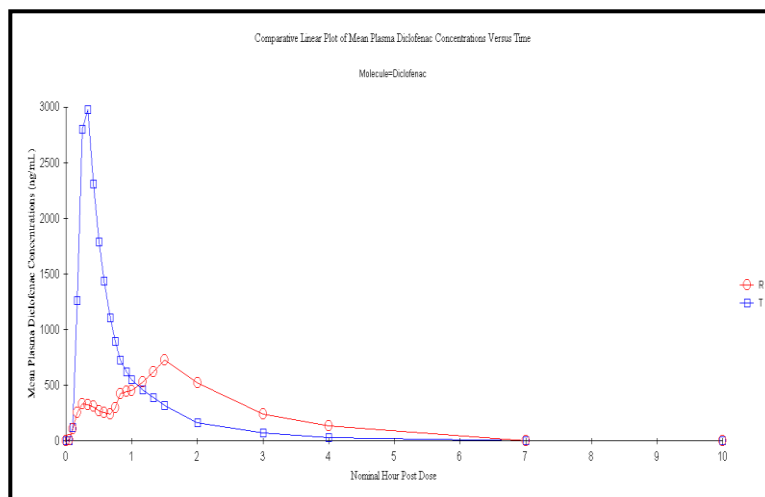


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those obtained following IV<sup>8,9</sup> or IM<sup>10,11</sup> administration whereas as those for Voveran<sup>®</sup>-D were lower than reported for standard tablets of  $1,340 \pm 627$  ng/mL<sup>12</sup>.

**Figure 3 Mean absorption profiles for 50 mg diclofenac sodium administered orally as a Surge Dose<sup>®</sup> tablet and a dispersible commercial tablet (Voveran<sup>®</sup>-D) dispersed in water before administration in 21 healthy fasted subjects**



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).

- <sup>8</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>9</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>10</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>11</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>12</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

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

#### 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

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>13</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.

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<sup>13</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

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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>14</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.

***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 activity***

### 2.1.2 Gastric pH

In addition to the high degree of PK variability attributable to GI motility, gastric pH is another factor affecting the rate of drug dissolution and absorption since pH has a major impact on the solubility and hence rate of dissolution of many orally administered drugs. Increased solubility will increase the amount of drug that will dissolve in the co-administered water before it empties from the stomach, and will increase the dissolution rate. Conversely reduced solubility will slow the rate of dissolution with less drug dissolved and emptied into the small intestine with the co-administered water. Basic drugs which are more soluble under acidic conditions will demonstrate higher solubility and hence faster dissolution at low pH such as in the fasted state. Acidic drugs which are less soluble under acidic conditions will demonstrate lower solubility and hence slower dissolution at low 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

<sup>14</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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diabetes mellitus and autoimmune conditions. Patients taking 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 less acidic.

***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***

### 2.2 Fast dissolution drives fast absorption and clinical benefits

While the physiological conditions of the patient cannot be changed by the dosage form, Imaginot has shown that 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 both favourable and unfavourable conditions reflecting the wide range of physiological conditions that occur in the general population. This is particularly important for drugs taken on demand for immediate effect such as in headache or pain, where delayed absorption can often result from the existing physiological conditions.

Where speed and consistency of *in vivo* dissolution directly impact the clinical outcome, improvement in *in vitro* dissolution profiles relative to currently marketed formulations can offer significantly improved patient outcomes and associated improved compliance. The higher the drug concentration in the small intestine, the greater will be the driving force for absorption across the mucosa resulting in rapid absorption and high peak plasma concentrations. In turn, higher plasma levels drive distribution into the effect compartment 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 providing a low driving force for absorption which will be slow. Such variability is evident in many PK studies where individual subject data are reported and may also explain the lack of efficacy reported by some patients.

Surge Dose<sup>®</sup> is designed to maximize the extent of drug dissolution in the stomach so that it quickly reaches the small intestine in solution independent of the MMC. Any undissolved drug or drug solution retained in the gastric mucosal folds will remain in the stomach until

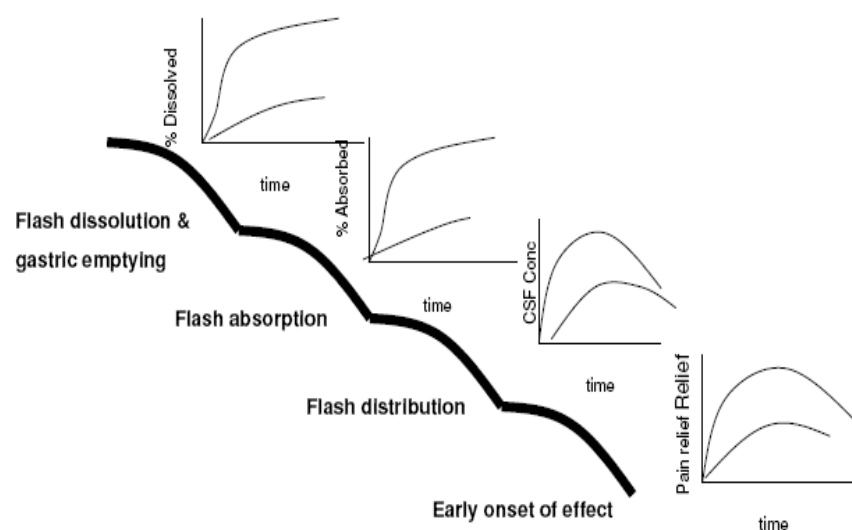
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emptied into the small intestine during Phase III MMC. Depending on the MMC and the sampling frequency, this can show up as multiple peaks in individual subject absorption profiles in PK studies. In such cases, the early peak results from dissolved drug reaching the small intestine by passive drainage, and later peaks result from drug retained in the stomach emptied by MMC activity. The relative sizes of these peaks reflect the dissolution characteristics of the formulation.

In summary, ultra-fast active-dissolving Surge Dose<sup>®</sup> formulations produce the cascade summarized in Figure 4:

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

**Figure 4 Surge Dose<sup>®</sup> cascade resulting in faster onset of action**



### 3 Oxymorphone

#### 3.1 Marketed products

Oxymorphone hydrochloride (HCl) is a short acting opiate analgesic approved since 1959 in the US for the management of moderate to severe acute pain where the use of an opioid is appropriate. Like other short acting opiates, it is also used for rescue analgesia in patients using long-acting opioids for the management of cancer and chronic non-malignant pain<sup>15</sup>.

Secondary pharmacological effects include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression. Adverse effects are dose related and similar to those seen with other opioids, including nausea, pyrexia, vomiting, somnolence and pruritis. Dosage can be limited by adverse effects which prevents the achievement of maximum analgesic efficacy.

OPANA<sup>®</sup> IR (immediate release) and ER (extended release) tablets received FDA approval in Jun 2006<sup>16</sup> (NDA 021611), both manufactured for Endo Pharmaceuticals Inc by Novartis. Endo originally marketed an intravenous (IV) solution (1 and 1.5 mg/mL) and 5 mg rectal suppository as Numorphan<sup>®</sup> but the suppository and 1.5 mg/mL IV product have been discontinued. The drug is not available in Australia or Europe.

OPANA<sup>®</sup> IR contains 5 mg or 10 mg oxymorphone HCl with lactose monohydrate, pregelatinized starch and magnesium stearate. None of these excipients will produce activated dissolution or increase the solubility of the drug.

OPANA<sup>®</sup> IR<sup>17</sup> has an onset of action around 1 h and duration of effect around 4 to 6 h. The recommended dosage is 10–20 mg every 4–6 h in opioid-naïve patients titrated to adequate pain relief. The 5 mg IR tablet allows conservative initiation of therapy particularly in elderly patients, those with mild hepatic impairment, or those with renal impairment. It should be taken at least 1 h before or 2 h after food due to increased bioavailability when taken with high fat meals or alcohol.

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<sup>15</sup> Sloan P. Review of oral oxymorphone in the management of pain. *Ther Clin Risk Manage* (2008) **4(4)**: 777-787

<sup>16</sup> NDA 021611 Opana  
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>  
 accessed on 09/06/2010

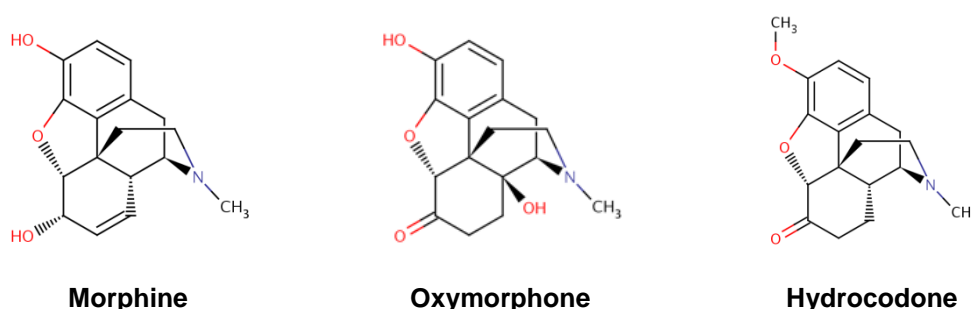
<sup>17</sup> Prescribing Information. OPANA IR (oxymorphone hydrochloride). March 2010

## 3.2 Physicochemical properties

### 3.2.1 Structure

Oxymorphone (14-hydroxydihydromorphinone) HCl ( $C_{17}H_{19}NO_4 \cdot HCl$ , MW 337.80) is a semi-synthetic pyridine-ring unsubstituted pyridomorphinan, more closely related structurally to hydromorphone than morphine as shown in Figure 5.

**Figure 5 Chemical structures of oxymorphone<sup>18</sup>, morphine<sup>19</sup> and hydrocodone<sup>20</sup>.**



### 3.2.2 Solubility

Oxymorphone is a basic compound with  $pK_{a1}$  8.17 and  $pK_{a2}$  9.54 at 37°C<sup>21</sup>. The free base is *freely soluble* in water with a reported aqueous solubility of 24 mg/mL<sup>22</sup>. Oxymorphone is used as the more soluble HCl salt in pharmaceutical formulations which has a reported aqueous solubility of 1g in 4 mL<sup>23</sup>. Hence typical doses of 5 – 20 mg will be soluble in less than 1 mL water, and should readily dissolve in 100–200 mL co-administered water.

As oxymorphone is a basic molecule, it will have a higher solubility under acidic conditions. At higher pH such as in the small intestine or in the achlorhydric or hypochlorhydric stomach, it will be less soluble. The rate of *in vivo* dissolution will therefore vary as a result of pH effects on solubility, slowing as the pH increases and reduces solubility.

**Surge Dose<sup>®</sup> oxymorphone will leverage pH effects on solubility to increase the extent and rate of dissolution**

<sup>18</sup> <http://www.drugbank.ca/drugs/DB01192> Oxymorphone

<sup>19</sup> <http://www.drugbank.ca/drugs/DB00295> Morphine

<sup>20</sup> <http://www.drugbank.ca/drugs/DB00956> Hydrocodone

<sup>21</sup> Prescribing Information. OPANA (oxymorphone hydrochloride). March 2010

<sup>22</sup> Drugbank: <http://www.drugbank.ca/drugs/DB01192>. Accessed 09/06/2010

<sup>23</sup> NDA 021611 Opana – Chemistry Review Section, pg 14 of 121

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### 3.2.3 Permeability

Oxymorphone is slightly lipophilic with an octanol/aqueous partition coefficient at 37°C and pH 7.4 of 0.98<sup>24</sup>. It has greater lipid solubility than morphine as a result of the ketone-group substitution which favours intestinal absorption by passive diffusion and facilitates penetration into the CNS once the drug is dissolved<sup>25, 26</sup>.

With pKa values of 8.17 and 9.54, ionized drug will predominate in the small intestine where the pH is around 6.5 – 7.5 which will facilitate dissolution of any remaining undissolved drug in intestinal secretions. Overall the higher concentration of drug in solution reaching the small intestine as a result of more rapid dissolution, will provide a higher driving force for faster absorption. While the unionized form of the drug will be preferentially absorbed from the small intestine, equilibrium will be maintained between the ionized and unionized forms to drive continued absorption.

**Surge Dose<sup>®</sup> oxymorphone will deliver the drug faster and at a higher concentration into the small intestine, thus driving faster absorption and distribution**

### 3.3 Pharmacokinetics (PK)

#### 3.3.1 Absorption

Rapid absorption of oxymorphone occurs from the small intestine following oral administration. Although opiate transporters have been identified, their role in oxymorphone absorption is unclear<sup>27</sup>. As shown in Table 1, median T<sub>max</sub> values are around 0.5 h ranging from 0.25 – 1.5 h for single IR doses of 5, 10, or 20 mg<sup>28,29</sup>.

<sup>24</sup> Pommer E. Oxymorphone: a review. *Support Care Cancer* (2006) **14**: 109-115

<sup>25</sup> Hale ME, Dvergsten C, Gimbel J. Efficacy and Safety of Oxymorphone Extended Release in Chronic Low Back Pain: Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase III Study. *J Pain* (2005) **6(1)**: 21-28

<sup>26</sup> Sloan P. Review of oral oxymorphone in the management of pain. *Ther Clin Risk Manage* (2008) **4(4)**: 777-787

<sup>27</sup> Smith H. Variations in Opioid Responsiveness. *Pain Physician* (2008) **11**: 237-248

<sup>28</sup> Adams M, Ahdieh H. Single- and Multiple-Dose Pharmacokinetic and Dose-Proportionality Study of Oxymorphone Immediate-Release Tablets. *Drugs* (2005) **6(2)**: 91-99

<sup>29</sup> Gimbel J, Ahdieh H. The Efficacy and Safety of Oral Immediate-Release Oxymorphone for Postsurgical Pain. *Anesth Analg* (2004) **99**: 1472-1477



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**Table 1 PK properties of single dose oxymorphone IR in 23 fasted healthy subjects (Adams and Ahdieh 2005)**

	Oxymorphone IR dose		
	5mg	10mg	20mg
<b>Oxymorphone</b>			
AUC <sub>∞</sub> (μg • h/L)	4.48 (2.07)	9.10 (3.40)	20.07 (5.80)
C <sub>max</sub> (μg/L)	1.10 (0.55)	1.93 (0.75)	4.39 (1.72)
t <sub>max</sub> (h)	0.50 (0.25–1.00) <sup>b</sup>	0.50 (0.25–1.50) <sup>b</sup>	0.50 (0.25–1.00) <sup>b</sup>
CL/F (L/min)	23.53 (13.18)	21.42 (9.92)	18.21 (6.16)
λ <sub>z</sub> (h <sup>-1</sup> )	0.1534 (0.1308)	0.1257 (0.0997)	0.0835 (0.0331)
t <sub>1/2</sub> (h)	7.25 (4.40)	7.78 (3.58)	9.43 (3.36)
<b>6-OH-oxymorphone</b>			
AUC <sub>∞</sub> (μg • h/L)	4.02 (3.18)	9.90 (5.13)	24.37 (10.50)
C <sub>max</sub> (μg/L)	0.95 (0.52)	1.62 (0.75)	3.57 (1.41)
t <sub>max</sub> (h)	0.50 (0.25–1.00) <sup>b</sup>	0.50 (0.50–1.50) <sup>b</sup>	0.50 (0.25–1.00) <sup>b</sup>
λ <sub>z</sub> (h <sup>-1</sup> )	0.1661 (0.1677)	0.0752 (0.0678)	0.0414 (0.0134)
t <sub>1/2</sub> (h)	7.27 (4.76)	13.72 (6.55)	18.35 (5.77)
<b>Oxymorphone-3-glucuronide</b>			
AUC <sub>∞</sub> (μg • h/L)	650.03 (140.05)	1322.72 (261.76)	2672.40 (480.33)
C <sub>max</sub> (μg/L)	134.24 (30.02)	265.78 (63.24)	516.26 (106.53)
t <sub>max</sub> (h)	1.00 (1.00–1.50) <sup>b</sup>	1.00 (1.00–2.00) <sup>b</sup>	1.00 (1.00–1.50) <sup>b</sup>
λ <sub>z</sub> (h <sup>-1</sup> )	0.0936 (0.0360)	0.0805 (0.0218)	0.0763 (0.0178)
t <sub>1/2</sub> (h)	8.48 (3.11)	9.15 (2.18)	9.67 (2.71)

a Mean (SD), unless otherwise specified.  
b Median (range).

λ<sub>z</sub> = the terminal elimination rate constant; AUC<sub>∞</sub> = area under the plasma concentration vs time curve from time zero to infinity; C<sub>max</sub> = maximum plasma concentration, the highest concentration observed during a dosage interval; CL/F = oral clearance; IR = immediate release; t<sub>max</sub> = the time that C<sub>max</sub> was observed; t<sub>1/2</sub> = terminal elimination half-life.

Table 2 shows T<sub>max</sub> values compare favourably with other opioids including transbuccal fentanyl tablets, highlighting a key advantage of faster absorption with oxymorphone.

**Table 2 T<sub>max</sub> values for oxymorphone and other opioids**

Opioid	Oxymorphone	Morphine	Codeine	Hydromorphone	Hydrocodone	Oxycodone	Methadone	fentanyl FENTORA <sup>®</sup> buccal tablet with OraVescent <sup>®</sup> DDT
T <sub>max</sub> (min)	30	30-90	60	45	80	60	60-450	47

Mean C<sub>max</sub> values increase linearly with dose, 1.1, 1.9 and 4.4 ng/mL for 5, 10 and 20 mg doses respectively. The high variability with CVs of 40 – 50 % is consistent with and related to the high variability in T<sub>max</sub> ranging from 0.25 – 1.5 h. Fast absorption occasions with a short T<sub>max</sub> in the region of 15 min will be associated with higher C<sub>max</sub> values compared with slow absorption occasions where the T<sub>max</sub> is 1.5 h producing lower C<sub>max</sub>. For a 5 mg dose, some subjects will have peak plasma concentrations less than 0.5 ng/mL whereas others will exceed 1.6 ng/mL overlapping the C<sub>max</sub> range reported for a 10 mg dose. Whilst recognizing significant inter-individual variations in the response to opiates, there are many subjects who do not respond to treatment which in part may be explained by sub-therapeutic T<sub>max</sub> values and an associated lack of efficacy.

As the impact of genetic polymorphisms associated with CYP450 mediated metabolism is far less for oxymorphone than for many other opioids, major contributors to the observed PK

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variability will be intra- and inter-subject differences in rates of gastric emptying and also *in vivo* variability in drug dissolution and subsequent absorption.

***Surge Dose<sup>®</sup> oxymorphone is expected to produce more short  $T_{max}$  values around 15 min, reducing variability, mean  $T_{max}$  and possibly median  $T_{max}$***

#### 3.3.2 Distribution

Oxymorphone's lipid solubility enables rapid distribution from the plasma across the blood brain barrier to exert its central effect. Protein binding of oxymorphone is low in the range of 10 % to 12 %<sup>30</sup> which is advantageous for acute pain management since the majority of circulating drug will be available for uptake at its site of action.

This also provides a benefit for oxymorphone compared with some other opioids where protein binding is much higher as shown in Table 3.

**Table 3 Comparative % protein binding for oxymorphone and other opioids**

Opioid	Oxymorphone	Morphine	Codeine	Hydromorphone	Hydrocodone	Oxycodone	Methadone	fentanyl FENTORA buccal tablet with OraVescent <sup>®</sup> DDT
Protein Binding (%)	10-12	20-35	7-25	8-19	Not Known	38-45	85-90	80-85

The volume of distribution of oxymorphone is 3 L/Kg<sup>31</sup> which is greater than 0.9 L/kg corresponding to total body water indicating uptake by tissue membranes such as the CNS and consistent with the known lipid solubility of the molecule.

***Surge Dose<sup>®</sup> oxymorphone will saturate protein binding sites more quickly adding to the pre-existing low protein binding advantages of oxymorphone, allowing a faster increase in plasma and effect compartment concentrations and faster onset of action***

#### 3.3.3 Metabolism

The oral bioavailability of oxymorphone is approximately 11 % as a result of extensive hepatic metabolism<sup>32</sup>. There is no evidence of saturable metabolic pathways over the

<sup>30</sup> Sloan PA, Barkin RL. Oxymorphone and oxymorphone extended release: A pharmacotherapeutic review. *J Op Manag* (2008) **4:3** 131-144

<sup>31</sup> Sloan P. Review of oral oxymorphone in the management of pain. *Ther Clin Risk Manage* (2008) **4(4)**: 777-787

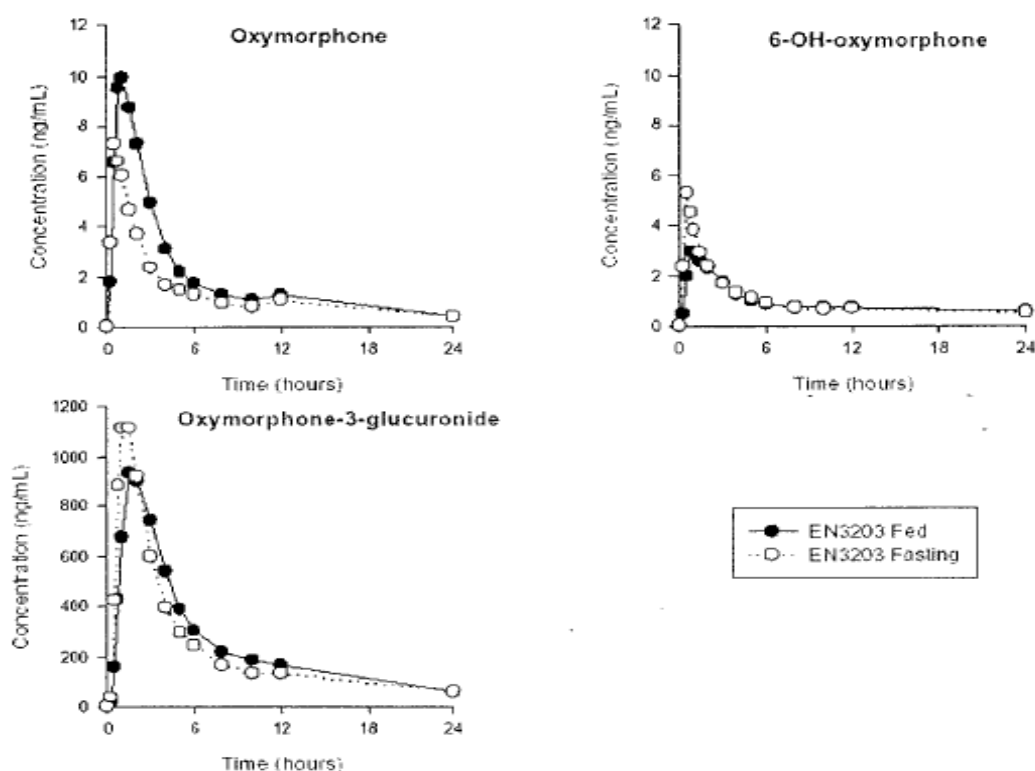
<sup>32</sup> Adams M, Ahdieh H. Pharmacokinetics and Dose-Proportionality of Oxymorphone Extended Release and Its Metabolites: Results of a Randomized Crossover Study. *Pharmacotherapy* (2004) **24(4)**: 468-476

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

therapeutic range, levels of both oxymorphone metabolites increasing linearly with dose. Metabolism is predominantly through glucuronide conjugation involving the uridine diphosphate glucuronosyl transferase enzymes UGT 2B7 and UGT 1A3<sup>33</sup>. The oxymorphone-3-glucuronide metabolite is inactive with an AUC some 90-fold higher than the parent compound<sup>34</sup>. Oxymorphone is also converted to the active metabolite 6-OH-oxymorphone by reduction of the keto-group.

Plasma concentrations for oxymorphone and its two metabolites are shown in Figure 6 following the oral administration of four 10mg IR tablets. The  $T_{max}$  of 6-OH-oxymorphone is equivalent to oxymorphone indicating rapid metabolism of the parent drug. However its elimination half-life ( $t_{1/2}$ ) is approximately double that of the parent drug<sup>35</sup>. Since this metabolite has similar potency to the parent drug, this will potentially extend the duration and extent of oxymorphone analgesia.

**Figure 6 Plasma levels of oxymorphone HCl and its two metabolites in healthy volunteers (○ fasted; ● after high fat meal)**



<sup>33</sup> Pommer E. Oxymorphone: a review. *Support Care Cancer* (2006) **14**: 109-115

<sup>34</sup> Chamberlain KW, Cottle M, Neville R, Tan J. Oral Oxymorphone for Pain Management. *Annals Pharmacotherapy* (2007) **41**: 1144-1151

<sup>35</sup> Adams M, Ahdieh H. Single- and Multiple-Dose Pharmacokinetic and Dose-Proportionality Study of Oxymorphone Immediate-Release Tablets. *Drugs* (2005) **6(2)**: 91-99

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A common complication in pain management, particularly post-operatively, involves drug interactions resulting from the concomitant use of drugs such as antinauseants, antibiotics and anticoagulants.

As seen in Table 4, oxymorphone does not have any clinically significant CYP450 interactions compared with other opiates which is a major point of difference. Oxymorphone is not metabolised by the major drug metabolizing iso-enzymes, CYP2D6 which catalyses opioid O-dealkylation, and CYP3A4 which catalyses opioid N-demethylation. This significantly reduces the potential for variations in plasma concentrations associated with drug-drug interactions caused by competition for the same enzyme systems. This can lead to delayed metabolism and increased plasma levels of one or both medications resulting in adverse events particularly toxicity.

**Table 4 Clinically-relevant metabolic pathways for oxymorphone and other opioids**

Opioid	Oxymorphone	Morphine	Codeine	Hydromorphone	Hydrocodone	Oxycodone	Methadone	fentanyl FENTORA buccal tablet with OraVescent® DDT
Conjugation	Yes	Yes	Yes	Yes	Yes	Yes	No	No
CYP3A4	No	No	Yes	No	Yes	No	Yes	Yes
CYP2C19	No	No	No	No	No	No	Yes	No
CYP2D6	No	No	Yes	No	Yes	Yes	Yes	No

In addition there is no evidence of metabolic enzyme polymorphisms affecting oxymorphone metabolism compared with other opioids such as hydrocodone, oxycodone, methadone, fentanyl and codeine where polymorphisms of CYP 450 isoenzymes produce fast and slow metabolizers within the general population<sup>36</sup>. Slow metabolizers may accumulate drug to toxic levels. In the case of codeine, this analgesic is ineffective in about 10 % of the Caucasian population due to CYP2D6 polymorphisms, as this enzyme is necessary to O-methylate codeine to morphine, the active metabolite. Fast metabolism leads to a rapid elimination of drugs such that drug concentrations do not reach therapeutic levels or only reach therapeutic levels for a short period of time requiring re-medication.

**Surge Dose<sup>®</sup> oxymorphone will add to the pre-existing metabolic advantages of oxymorphone over other opioids particularly fentanyl**

<sup>36</sup> Smith H. Variations in Opioid Responsiveness. *Pain Physician* (2008) **11**: 237-248

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#### 3.3.4 Elimination

Oxymorphone's longer elimination half life ( $t_{1/2}$ ) approximately 8 h ranging from 7 to 10 h<sup>37</sup> provides an advantage compared with other opioids as shown in Table 5 and supports the use of less frequent dosing such as 6 hourly which is preferable to 4 hourly. Less than 2 % of the parent compound is excreted in the urine<sup>38</sup>.

**Table 5 Elimination half lives ( $t_{1/2}$ ) for oxymorphone and other opioids**

Opioid	Oxymorphone	Morphine	Codeine	Hydromorphone	Hydrocodone	Oxycodone	Methadone	fentanyl FENTORA buccal tablet with OraVescent <sup>®</sup> DDT
$t_{1/2}$ h	7.3-9.4	2-3	1.9-3.9	2-4	1.25-3	3.5-5.6	8-59	2.6-11.7

**Surge Dose<sup>®</sup> oxymorphone will add to this advantage over other opioids and compares favourably with transbuccal fentanyl**

#### 3.3.5 Formulation effects

No published data have been found for oxymorphone solutions to estimate the effect of *in vivo* dissolution on its absorption rate. The only PK data on a solution of oxymorphone 10 mg administered with 240 mL water is a comparison with oxymorphone ER tablets in fasted and fed subjects<sup>39</sup>. No numerical data are provided and although difficult to extrapolate a  $T_{max}$  value from the graph, it appears to be around 30 min, similar to that for IR tablets. PK studies submitted in the NDA used 0.25, 0.5, 1, 1.5 and 2 h as the five sampling points in the first 2 hours, and it is reasonable to assume that the same schedule is used here. As oxymorphone has relatively fast absorption under ideal conditions, the sparse sampling schedule is probably insufficiently discriminating to show any difference. A reduction in  $T_{max}$  from 40 to 25 min which would be associated with a significant clinical benefit in terms of faster onset of action, would be missed with such a sampling schedule.

Based on  $T_{max}$  values ranging from 15 min to 1.5 h for the IR tablets, it is expected that oxymorphone solutions will demonstrate faster absorption with less variability than tablets. Fast dissolving Surge Dose<sup>®</sup> oxymorphone tablets would be expected to behave more like a

<sup>37</sup> Adams M, Ahdieh H. Single- and Multiple-Dose Pharmacokinetic and Dose-Proportionality Study of Oxymorphone Immediate-Release Tablets. *Drugs* (2005) **6(2)**: 91-99

<sup>38</sup> Adams M, Ahdieh H. Pharmacokinetics and Dose-Proportionality of Oxymorphone Extended Release and Its Metabolites: Results of a Randomized Crossover Study. *Pharmacotherapy* (2004) **24(4)**: 468-476

<sup>39</sup> NDA 021611 Opana (Study EN3202-003: Clin Pharm Review p 22-23)

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

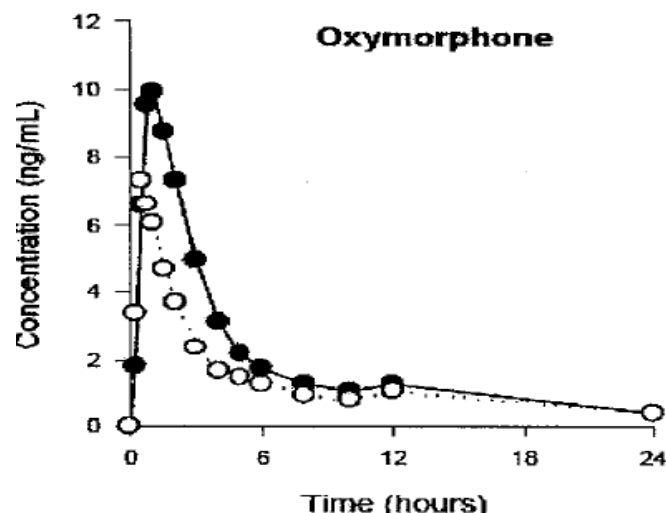
solution than a tablet with a correspondingly higher frequency of short  $T_{max}$  values. With a more frequent early sampling schedule, a higher frequency of  $T_{max}$  values closer to 15 min would be expected for Surge Dose<sup>®</sup> oxymorphone compared with existing IR tablets.

**Surge Dose<sup>®</sup> oxymorphone's expected PK profile will be closer to that of a solution than existing IR tablets, producing more  $T_{max}$  values around 15 min**

### 3.3.6 Effect of food

Food has a significant effect on oxymorphone absorption increasing  $C_{max}$  and AUC by ~38% following a high fat meal as shown in Figure 7 for a 40 mg IR dose. However the delay in  $T_{max}$  is relatively short, around 30 min, delayed from 0.5 to 1 h<sup>40</sup>.

**Figure 7 Effect of food on plasma levels of oxymorphone HCl following administration of four 10 mg IR tablets ○ fasted; ● after high fat meal**



As seen earlier, the increase in absorption is associated with reduced levels of the two main metabolites 6-hydroxymorphone and oxymorphone-3-glucuronide in the fed state compared with the fasted state. This suggests that there may be reduced hepatic metabolism, either by faster blood flow or competition for metabolic enzymes resulting in higher oral bioavailability after food. Although higher bioavailability after food for some poorly soluble drugs results from improved solubility in the lipid components of the meal, this is usually associated with a significant delay in  $T_{max}$  in the region of 1 – 2 h as a result of delayed gastric emptying in the fed state. The delay is only around 30 min for oxymorphone taken after food.

Similar increased plasma levels and bioavailability have been reported for alcohol administered as 240 mL of 40 %, 20 %, and 4 % solutions with OPANA<sup>®</sup> ER 40 mg.  $C_{max}$

<sup>40</sup> SBA NDA 021611 Opana (Study EN3202-003: Clin Pharm Review p 22-25)

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

increased on average by 70% and up to 270% in individuals<sup>41</sup>. The reason has not been elucidated but *in vitro* studies confirmed that alcohol does not cause premature drug release from the formulation leading to dose dumping. No studies have been conducted with OPANA<sup>®</sup> IR but similar results would be expected. Although alcohol may promote absorption by disruption of the intestinal lipid membranes, it is possible that increased blood flow could reduce the extent of metabolism, particularly as oxymorphone levels increase as the dose of alcohol increases.

Given that oxymorphone would be taken as required in response to acute moderate to severe pain with or without food, a Surge Dose<sup>®</sup> tablet that undergoes activated dissolution in the presence or absence of food will leverage the effects of faster differential and exponential drainage of liquids. This should achieve faster and more predictable absorption in the fed state with a reduction in  $T_{max}$  values towards fasted values.

***Surge Dose may provide a true 'on demand' presentation without limitations associated with food consumption***

### 3.4 Pharmacodynamics (PD)

#### 3.4.1 Mechanism of action

Opioid drugs produce CNS effects through interaction with the 7-transmembrane G-protein-coupled opioid receptors<sup>42</sup>. Although the analgesic mechanism is unknown, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord which play a role in the analgesic effects of this drug<sup>43</sup>. Opioid receptors also occur in the peripheral nervous system which will be accessible to circulating oxymorphone without crossing the blood brain barrier<sup>44</sup>.

The anti-nociceptive effects of oxymorphone in reducing the sensitivity to painful stimuli are mediated predominantly through the  $\mu_1$  and  $\delta$  opioid receptors with the affinity for the latter thought to potentiate  $\mu_1$ -mediated analgesia. Although on a mg to mg basis oral oxymorphone is some 3 fold more potent than oral morphine, its reduced affinity for  $\kappa$ -receptors reduces its potential for sedation, respiratory depression and histamine release<sup>45</sup>.

<sup>41</sup> NDA 021611 Opana (Study EN3202-033: Clin Pharm Review p 19-22; 60-77)

<sup>42</sup> Pommer E. Oxymorphone: a review. *Support Care Cancer* (2006) **14**: 109-115

<sup>43</sup> Trescott AM, Datta S, Lee M, Hansen H. Opioid Pharmacology *Pain Physician* (2008) **11**: S133-153

<sup>44</sup> Intrussi CE. Clinical Pharmacology of Opioids for Pain. *Clin J Pain* (2002) **18**: S3 – S13

<sup>45</sup> Gimbel JS. Oxymorphone: A mature molecule with a new life. *Drugs of Today* (2008) **44(10)**: 767-782



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### 3.4.2 PK-PD correlation

There is relatively good PK-PD correlation for oxymorphone. Although there is high variability in PK data for the IR tablets, there is no evidence of any significant lag time for CNS equilibration.

Analgesia following oral oxymorphone IR tablets is dose-related with an analgesic plateau at 20 mg and  $C_{max}$  around 4 µg/L with CVs around 40 %<sup>46, 47</sup>. While the FDA did not accept that 5 mg was effective with  $C_{max}$  around 1 µg/L, it was approved as a lower initial dose for opiate naïve patients. Reported plasma concentrations of oxymorphone associated with trough and peak pain intensity are from 2.08 ng/mL at trough and 4.42 ng/mL at peak, all with large CVs around 100 %<sup>48</sup>.

***Faster absorption of Surge Dose<sup>®</sup> oxymorphone should result in faster onset of action compared with existing IR tablets with more high peak plasma concentrations and improved efficacy***

### 3.4.3 Onset and duration of action

Onset of analgesia following IV administration of oxymorphone is very rapid, subjectively reported to occur within 5 – 10 min<sup>49</sup> demonstrating that the lipid solubility of oxymorphone allows rapid penetration into the CNS to exert its effect.

Comparative mean pain relief – time profiles for IM and oral oxymorphone are shown in Figure 8<sup>50</sup> using Numorphan<sup>®</sup> tablets enclosed in a hard gelatin capsule packed with starch and lactose. Albeit limited by sampling points at only 1 and 2 h, maximum pain relief was around 30 min later for oral doses of 5 and 15 mg oxymorphone compared with IM dosing.

Of note is that encapsulation of the tablet for oral administration in this study would be expected to slow *in vivo* dissolution, in turn delaying absorption and onset of action. For comparison, efficacy studies on oral non-encapsulated OPANA<sup>®</sup> IR tablets showed faster effects, with first perceptible pain relief reported in 15 – 23 min and meaningful pain relief at

<sup>46</sup> Gimbel J, Ahdieh H. The Efficacy and Safety of Oral Immediate-Release Oxymorphone for Postsurgical Pain. *Anesth Analg* (2004) **99**: 1472-1477

<sup>47</sup> Adams M, Ahdieh H. Single- and Multiple-Dose Pharmacokinetic and Dose-Proportionality Study of Oxymorphone Immediate-Release Tablets. *Drugs* (2005) **6(2)**: 91-99

<sup>48</sup> NDA 021611 Opana (Study EN3202-033: Clin Pharm Review p 30)

<sup>49</sup> Sinatra RS, Hyde NH, Harrison DM. Oxymorphone revisited. *Semin Anesth* (1988) **7**:209-215

<sup>50</sup> Beaver WT, Wallenstein SL, Houde RW, Rogers A. Comparisons of the analgesic effects of oral and intramuscular oxymorphone and of intramuscular oxymorphone and morphine in patients with cancer. *J Clin Pharmacol* (1997) **17**:186-198

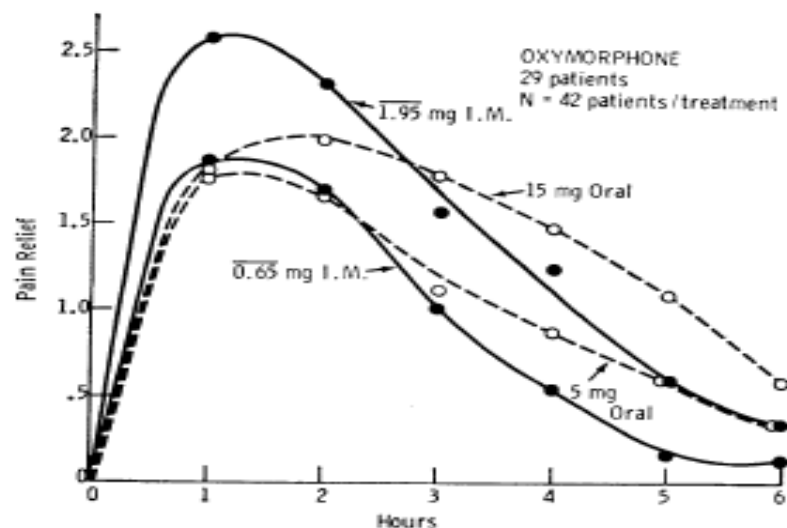


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around 1 h post dosing<sup>51</sup>. Oral administration produced a lower peak effect than IM but the duration of action was longer.

**Figure 8 Mean pain relief – time profiles for 5 and 15 mg oxymorphone following IM (solid lines) and oral (dotted lines) administration (Beaver et al 1977)**

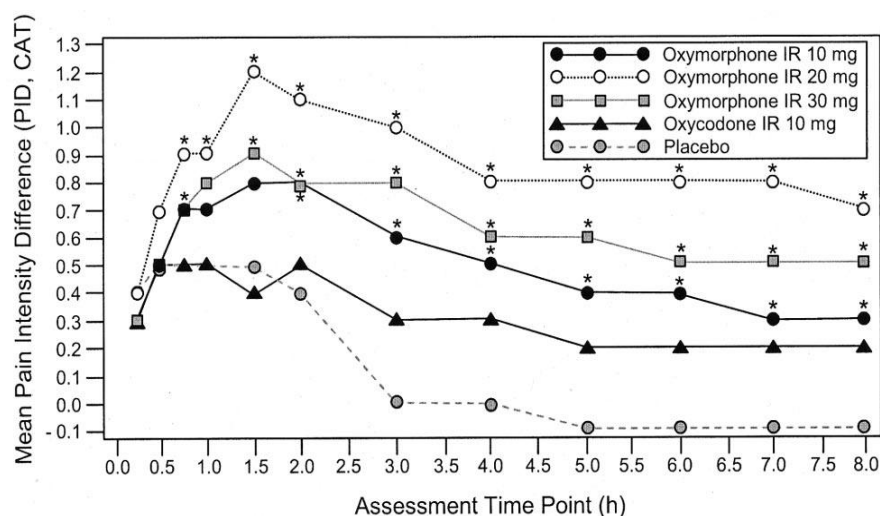


In a multicenter, double-blind, randomized, placebo controlled, parallel-group, dose-ranging study with 258 patients undergoing hip and knee replacements, median time to meaningful pain relief was 1 hour for 10, 20 and 30 mg doses of oxymorphone IR compared with 1.5 h for placebo as shown in Figure 9<sup>52</sup>.

**Figure 9 Summary of pain intensity differences (PID; categorical) for efficacy evaluable patients. \* $P < 0.05$  versus placebo (from Gimbel and Ahdieh 2004)**

<sup>51</sup> NDA 021611 Opana (Studies EN 3203-004, EN 3202-005)

<sup>52</sup> Gimbel J, Ahdieh H. The Efficacy and Safety of Oral Immediate-Release Oxymorphone for Postsurgical Pain. *Anesth Analg* (2004) **99**: 1472-1477



All three doses of oxymorphone were superior to 10 mg oxycodone IR, and both were superior to placebo based on pain assessments at 15, 30, 45, 60, 90 and 120 min and then hourly to 8 h post dose. Statistically significant pain reduction was reported after around 45 min and full analgesia after approximately 1 h. The median times to onset of analgesia for oxymorphone were 40 min for 10 mg, 34 min for 20 mg, both faster than 45 min for 15 mg oxycodone<sup>53,54</sup>. These results are consistent with those found for oxymorphone IR 5 mg in acute post-surgical pain where times to onset and peak analgesia were reported at 0.5 and 1.0 h respectively<sup>55</sup>.

As shown in Table 6, this relatively fast onset of action for oxymorphone compares favorably with that obtained for other opioids, and it has the advantage of a longer duration of action. If used for breakthrough pain, the potentially faster onset of action for oxymorphone provides a clinical benefit over transbuccal fentanyl.

**Table 6 Pharmacodynamic comparison of oxymorphone with other opioids**

Opioid	Oxymorphone	Morphine	Codeine	Hydromorphone	Hydrocodone	Oxycodone	Methadone	fentanyl FENTORA buccal tablet with OraVescent® DDT
Onset (min)	15 -45	15-30	30-60	15-30	10-20	10-15	30-60	30

<sup>53</sup> Aqua K, Gimbel JS, Singla N, Ma T, Ahdieh H, Kerwin R. Efficacy and Tolerability of Oxymorphone Immediate Release for Acute Postoperative Pain After Abdominal Surgery: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group Trial. *Clin Ther* (2007) **29(6)**: 1000-1012

<sup>54</sup> NDA 021611 Opana (Medical Review P2 p 16)

<sup>55</sup> NDA 021611 Opana (Medical Review P3 Page Study EN3203-008 p 56)

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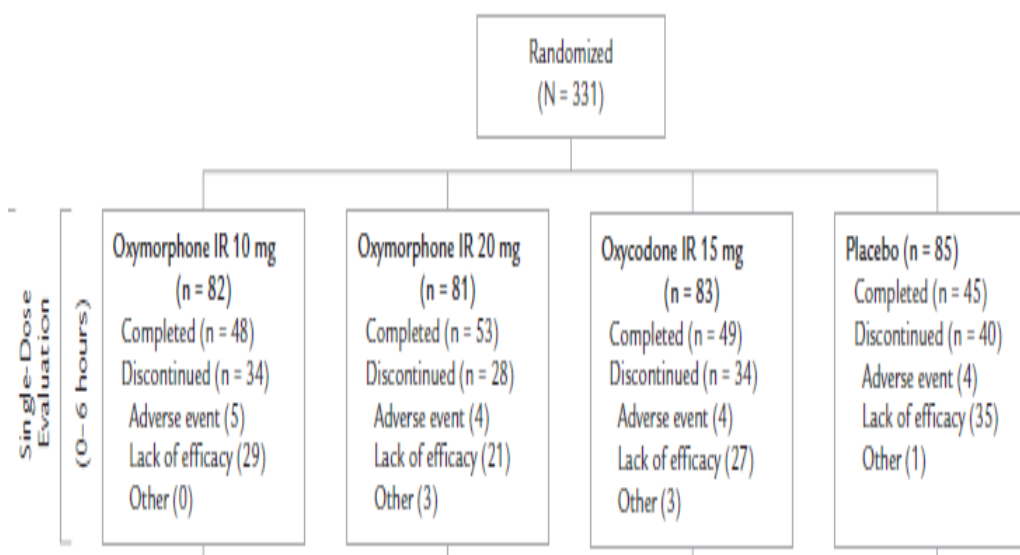
Duration (h)	4-6	3-4	3-4	3-4	3-4	3-4	4-8	2-3
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***Faster absorption of Surge Dose<sup>®</sup> oxymorphone should result in faster onset of action and faster peak effect***

#### 3.4.4 Lack of efficacy

Although the FDA declined to use the 5 mg OPANA IR study to support efficacy<sup>56</sup>, those studies accepted by the FDA demonstrate relatively high drop-out rates which are likely to be associated with variable absorption. In one pivotal study, 15.3 % to 33.8 % (average 27 %) patients withdrew across the three doses of 10, 20 and 30 mg citing lack of efficacy compared with 42 % for placebo<sup>57</sup>. In another randomized, double-blind, placebo- and active-controlled, parallel single- and multiple-dose study in 331 patients with moderate to severe pain following abdominal surgery, lack of efficacy was the leading cause of drop out in 35 % and 26 % of subjects dosed with 10 mg or 20 mg oxymorphone IR respectively as summarized in Figure 10<sup>58</sup>.

**Figure 10 Patient disposition following the initial dose of study medication for oxymorphone, oxycodone and placebo (Aqua et al 2007)**



<sup>56</sup> NDA 021611 Opana (Medical Review P2 Study EN3203-008 p 5)

<sup>57</sup> Gimbel J, Ahdieh H. The Efficacy and Safety of Oral Immediate-Release Oxymorphone for Postsurgical Pain. *Anesth Analg* (2004) **99**: 1472-1477

<sup>58</sup> Aqua K, Gimbel JS, Singla N, Ma T, Ahdieh H, Kerwin R. Efficacy and Tolerability of Oxymorphone Immediate Release for Acute Postoperative Pain After Abdominal Surgery: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group Trial. *Clin Ther* (2007) **29**(6): 1000-1012

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

A variety of different factors will be contributing to this high drop out rate, including the inter-individual variation that exists with opiate use where the minimum effective concentration varies widely between individuals and is influenced by the extent of previous opioid use, age and general medical condition. However, regardless of whether patients are opioid tolerant or opioid-naïve patients, there will be differences in GI motility and pH that will affect dissolution and absorption and could result in sub-therapeutic plasma levels in some patients. This is supported by the reported significant variation in  $C_{max}$  values and minimum therapeutic levels which appear to be in the region of 1 - 2 ng/mL.

Since dose and plasma concentrations of oxymorphone are linearly related and analgesic response is linearly related to dose, it follows that greater efficacy may be possible if higher and more consistent plasma levels can be achieved.

***Faster absorption of Surge Dose<sup>®</sup> oxymorphone should result in more peak plasma concentrations exceeding minimum effective plasma concentrations***

## 4 Surge Dose<sup>®</sup> oxymorphone

### 4.1 Clinical considerations

Analysis of available data on oxymorphone PK and PD suggests it is a suitable candidate for Imaginot's Surge Dose<sup>®</sup> technology which would offer significant clinical benefits:

- Oxymorphone is used for the treatment of moderate - severe pain where fast and consistent onset of action is a clinical pre-requisite whether used over an extended period or for the acute episodic indication of breakthrough pain
- Although highly soluble, there is evidence that absorption is dissolution rate limited so that there is the opportunity to increase the *in vitro* dissolution rate as shown with codeine phosphate, another opiate drug
- The drug is readily absorbed by passive diffusion across the intestinal mucosa and readily crosses the blood brain barrier
- Although median  $T_{max}$  is 0.5 h, there is significant variability with individual values ranging from 15 min to 1.5 h, which identifies the potential for increasing the frequency of low  $T_{max}$  values to reduce mean  $T_{max}$
- $C_{max}$  values are highly variable and there is a high drop out rate due to lack of efficacy which could be a result of slow absorption and associated low peak plasma concentration below minimum therapeutic plasma levels
- There is good PK-PD correlation with peak plasma levels around 30 min and peak effect at around 1 h with a linear relationship between dose and effect

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

Based on the available information, faster *in vivo* dissolution of a Surge Dose<sup>®</sup> oxymorphone tablet should increase the rate and consistency of absorption which should be associated with increased speed of onset of analgesia and increased efficacy with fewer doses resulting in slow absorption and peak plasma concentrations below therapeutic levels.

### 4.2 Technical considerations

Based on the physicochemistry of oxymorphone, it appears to be a suitable candidate for application of Imaginot's Surge Dose<sup>®</sup> technology:

- It has high water solubility and should completely dissolve in the volumes of water used for swallowing a tablet
- As a basic drug, its solubility will be higher under acidic conditions which in turn will increase the rate of dissolution

While Imaginot has not done any work on oxymorphone HCl per se, it has shown that the technology significantly increases the *in vitro* dissolution rate of codeine phosphate<sup>59</sup>, another opiate drug with similar physicochemical properties as summarised in Table 7.

**Table 7 Comparative data for oxymorphone and codeine phosphate**

Parameter	Oxymorphone HCl	Codeine phosphate
Dosage	10 – 20 mg	10 – 60 mg
Solubility in water	24 mg/mL	9 mg/mL
Volume water to dissolve dose	0.83 mL	7 mL
pKa	8.17, 9.54	8.21

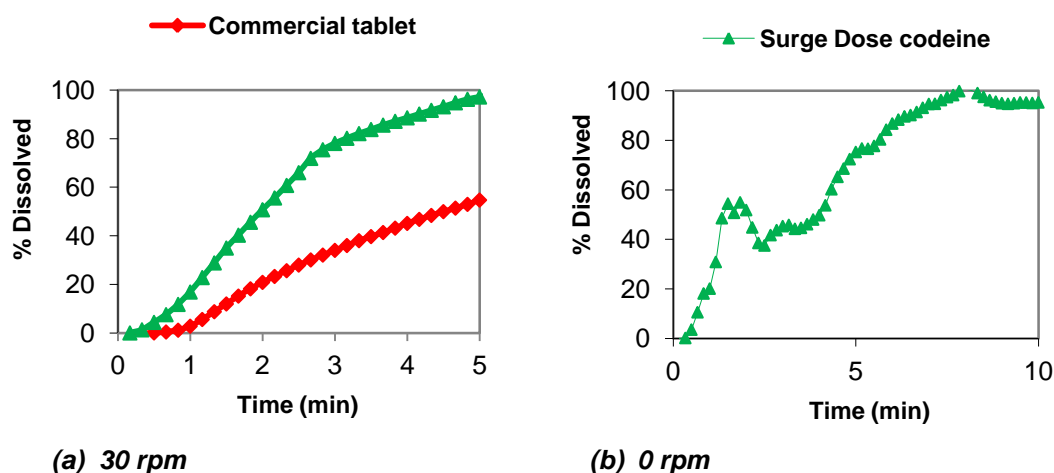
Only limited work was conducted with codeine phosphate but preliminary results from tablets containing 20 mg sodium bicarbonate with an organic acid indicate that optimization would further increase the rate and extent of dissolution. Both are acid salts of a basic drug and will have higher solubility under acidic conditions such as in the fasted stomach, and lower solubility in the slightly alkaline intestinal conditions. As oxymorphone HCl has a higher solubility than codeine phosphate, faster dissolution would be expected with an optimized Surge Dose<sup>®</sup> oxymorphone tablet.

Figure 11 shows the rapid dissolution reaching 80 % in 3 min for Surge Dose<sup>®</sup> codeine phosphate tablets in 900 mL 0.0033 M HCl compared with much slower dissolution for the commercial codeine tablet where only 34 % dissolved in the first 3 min.

<sup>59</sup> Imaginot Pty Ltd, May 2006. DR 03-12-01 Fast dissolving tablets containing codeine phosphate 30 mg

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

**Figure 11** Dissolution profiles for Surge Dose<sup>®</sup> codeine phosphate 30 mg compared with a commercial 30 mg tablet in USP dissolution apparatus II using 900 mL 0.0033 M HCl at (a) 30 rpm and (b) 0 rpm at 37 °C



This also demonstrates the intrinsic activated dissolution of Surge Dose<sup>®</sup> codeine tablets where 70 % dissolution is achieved in 5 min even in the absence of external stirring. Such conditions mimic gut stasis as often occurs during severe pain and migraine attacks, and are also typical of the low gastric motility in Phase I MMC which is generally triggered by food delaying gastric emptying. While the commercial tablet was not tested under these conditions, it would be expected to show negligible dissolution based on testing of standard formulations of other basic drugs.

Based on these results and the higher solubility of oxymorphone HCl, an optimized Surge Dose<sup>®</sup> oxymorphone tablet should achieve 70 – 80 % dissolution within the first 3 min in both stirred and unstirred conditions. This would translate to faster *in vivo* dissolution under a range of favorable and unfavorable GI conditions, resulting in faster delivery to the small intestine and subsequently faster absorption relative to the current commercial product.

### 4.3 IP considerations

The only listed US FDA Orange Book<sup>60</sup> patents relate to OPANA<sup>®</sup> ER; US 7276250 expiring 4 Feb 2023; US 5958456 expiring 9 Sep 2013; US 5662933 expiring 9 Sep 2013. No patents have been found relating to oxymorphone IR or other fast acting formulations and there is currently no patented OPANA<sup>®</sup> IR product. A Surge Dose<sup>®</sup> reformulation provides the opportunity for a patented position with an improved IR tablet, and also with the development of a combination analgesic such as paracetamol with oxymorphone within the claims of the Imaginot patents.

<sup>60</sup> FDA Orange Book, Oxymorphone and Opana  
[http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl\\_No=021610&Product\\_No=001&table1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021610&Product_No=001&table1=OB_Rx) accessed 09/06/2010

## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

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### 4.4 Competitive potential

#### 4.4.1 Improved IR tablet

Oxymorphone is a rapidly absorbed opioid which has a number of advantages compared with other opioids. It has a longer half life and duration of effect than oxycodone, codeine, hydrocodone and morphine and as a result of its metabolic pathways, does not have the same problems of drug interactions and variable metabolic rates associated with CYP450 polymorphisms which result in significant variability between patients. In the absence of these polymorphisms, the high incidence of lack of efficacy reported in the pivotal clinical trials is likely to be caused at least in part by variable absorption where slow absorption results in low sub-therapeutic plasma concentrations. A Surge Dose<sup>®</sup> oxymorphone reformulation would address this potential limitation and take advantage of the benefits of oxymorphone that would be combined with faster onset of action and improved efficacy.

#### 4.4.2 Fast acting combination analgesic

Given the undesirable side effects of opiates, they are frequently used at lower doses in combination with analgesics having different mechanisms of action such as paracetamol which is widely recognised as an opiate sparing agent. Combination analgesic products containing paracetamol or other non-steroidal anti-inflammatory drug (NSAIDs) with opioids such as codeine, hydrocodeine and oxycodone, offer clinical benefits such as<sup>61</sup>:

- prolonged analgesia when there are different rates of absorption
- synergistic efficacy via different mechanisms of action to elevate pain thresholds
- use of lower doses for active components, reducing the potential for adverse reactions including particularly opioid tolerance and dependency

No combinations appear to have yet been registered with oxymorphone so there is the opportunity to develop a Surge Dose<sup>®</sup> paracetamol with oxymorphone combination, where the dissolution rates of the two components can be optimized for fast absorption and effect.

#### 4.4.3 Effective alternative to fentanyl in breakthrough pain

The recent introduction of the effervescent transbuccal fentanyl tablet Fentora<sup>®</sup> (Cephalon Inc) and the intranasal fentanyl formulation Instanyl<sup>®</sup> (Nycomed Danmark SpA), both positioned for the treatment of breakthrough pain, demonstrates that faster efficacy can be achieved with faster and more consistent absorption.

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<sup>61</sup> Smith HS. Combination Opioid Analgesics. *Pain Phys.*(2008) 11:201-214



## Application of Surge Dose<sup>®</sup> fast dissolution technology to oxymorphone

Fentora<sup>®</sup> transbuccal tablets achieve median  $T_{max}$  values around 47 min (range 35 – 90 min) and onset of action as early as 10 min with the first assessment at 5 min post dose<sup>62,63</sup>.

This transbuccal system provides faster absorption than the original sugar based lozenge Actiq<sup>®</sup> with maximum effect recorded in 46 min compared with 91 min<sup>64</sup>. Instanyl<sup>®</sup> nasal spray demonstrates similar fast absorption with doses of 50 – 200 µg achieving  $C_{max}$  values of 0.35 – 1.2 ng/mL in 10 – 15 min<sup>65</sup>.

Clearly, with the benefits of fast and consistent absorption, a Surge Dose<sup>®</sup> oxymorphone could effectively compete with other drug delivery assisted opioids in the management of breakthrough pain.

## 5 Conclusions

Based on this review, oxymorphone is a suitable candidate for Imaginot's Surge Dose<sup>®</sup> technology where the addition of pH modulating agents and water uptake agents would be customised to maximize the dissolution rate of the drug. A Surge Dose<sup>®</sup> oxymorphone should reduce the contribution of variable *in vivo* dissolution to the apparent PK and PD variability observed with existing OPANA<sup>®</sup> IR tablets. This will result in faster and more consistent absorption where mean PK and PD measures will be closer to median values and patients should experience a faster onset of action. This should be associated with improved efficacy reducing the incidence of slow absorption which results in a very slow onset of action or lack of efficacy occurring in up to one third of patients.

Given the current regulatory and patent landscape in the US, an improved faster absorbed Surge Dose<sup>®</sup> oxymorphone would provide an opportunity to create an improved patented oxymorphone IR tablet, which will effectively compete with other oral opioids, and will provide a viable competitive alternative to the Fentora<sup>®</sup> transbuccal fentanyl tablets. A combination analgesic containing oxymorphone with paracetamol is a commercial option which could further enhance efficacy.

<sup>62</sup> Blick SA & Wagstaffe AJ. Fentanyl buccal tablet in breakthrough pain in opioid tolerant patients with cancer. *Drugs* (2006) **66**(18):2387-2393

<sup>63</sup> Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablets for the relief of breakthrough pain in opiate tolerant adult patients with chronic neuropathic pain: a multi-centre randomized, double-blind, placebo-controlled study. *Clin Ther* (2007) **29**(4):588-601

<sup>64</sup> Taylor DR. Fentanyl buccal tablets: rapid relief from breakthrough pain. *Expert Opin Pharmacother* (2007) **8**(17):3043-3057

<sup>65</sup> Electronic Medicines Compendium Instanyl<sup>®</sup> nasal spray, Nycomed Danmark SpA [http://www.medicines.org.uk/emc/medicine/22242#PHARMACOKINETIC\\_PROPS](http://www.medicines.org.uk/emc/medicine/22242#PHARMACOKINETIC_PROPS)