

IM 03-26-01

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

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EXECUTIVE SUMMARY

This report provides a review of nalmefene as a candidate for the application of Imaginot's Surge Dose[®] drug delivery technology to improve its absorption characteristics achieving faster *in vivo* dissolution and absorption. Nalmefene is related to naltrexone and both are opioid receptor ligands which differ in their degree of specificity. Unlike naltrexone which is a μ -opioid receptor antagonist with some agonist activity, nalmefene is a pure universal antagonist binding with all three subtypes of opioid receptors, μ , δ and κ . IV nalmefene is used for the reversal of opioid-induced anesthesia, respiratory depression and overdose. Compared with naltrexone, nalmefene has good oral bioavailability (around 40 %) and is well tolerated with a lower incidence of side effects which are mild and transient. Nalmefene also has a much longer duration of action than naltrexone due to its slow dissociation from the opioid receptors with effects lasting up to 72 hours.

The opioidergic system plays an important role in mediating the reward effects of alcohol partly by modulating dopaminergic neurotransmission in the brain. Oral nalmefene provides a useful treatment to block the effects of alcohol in the treatment of alcohol dependency and heavy drinking which are leading risk factors affecting some 10 % of the population. Oral nalmefene at 20 – 80 mg taken when the urge to drink is recognized has shown reduced relapse rates and reduced alcohol consumption. Clearly fast onset of action in this indication provides a clear clinical benefit and may improve the efficacy. Nalmefene 40 mg daily is also effective in pathological gambling which affects some 1 % of adults and where a family history of alcoholism appears to predict response to an opiate antagonist.

Imaginot's patented ultra-fast dissolving Surge Dose[®] technology was developed based on *in vivo* studies with paracetamol, a known marker for liquid gastric emptying. In the proof of concept study, 70 % subjects experienced slow absorption for the fast release commercial tablet (Tylenol[®] Extra Strength Rapid Release Gels) with a median T_{max} (time to peak plasma concentration C_{max}) of 45 min and 16 % of subjects never reaching the minimum therapeutic level of 10 $\mu\text{g/mL}$. In contrast, two Surge Dose[®] formulations resulted in significantly faster absorption with median T_{max} of 17 and 25 min. More than 70 % subjects exceeded 10 $\mu\text{g/mL}$ in the first 15 min compared with only 20 % for Tylenol[®]. PK-PD (pharmacokinetic-pharmacodynamic) modelling predicts that Surge Dose[®] paracetamol will demonstrate significantly faster onset of action and improved clinical efficacy with 20 % more patients achieving target end points than Tylenol[®]. This is consistent with fewer sub-therapeutic absorption profiles with Surge Dose[®] formulations and confirmed by the lower NNT (Number Needed to Treat) of 2.8 predicted for Surge Dose[®] paracetamol compared with 4.2 for Tylenol[®].

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Surge Dose[®] 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[®] 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[®] 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.
- Diclofenac was absorbed 4 – 5 times as quickly from an optimised film coated Surge Dose[®] tablet compared with Voveran[®]-D (Novartis), a dispersible tablet dissolved in water before administration. Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (± 5.0) and 19.5 min (range 5 – 30 min). Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h). Surge Dose[®] tablets resulted in significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. C_{max} values for Surge Dose[®] were comparable with those obtained following IV or IM administration whereas as those for Voveran[®]-D were lower than reported for standard tablets of $1,340 \pm 627$ ng/mL.

Increased and more consistent plasma levels will translate to increased efficacy, and for drugs such as NSAIDs and bisphosphonates where side effects can limit usage, may allow a use of a lower dose to reduce side effects without compromising efficacy.

Dosage forms such as liquid filled soft capsules, ODTs (orally disintegrating or dissolving tablets) and absorption enhanced tablets have been developed to meet the recognized need for fast absorption, but in general fail to deliver the desired fast and consistent onset of action required for drugs taken on demand. Such dosage forms exhibit slow and variable dissolution in gastric fluids and consequently empty slower into the small intestine whence absorption occurs. The faster absorption of drugs from oral solutions compared with solid dosage forms highlights the effects of slow and variable *in vivo* dissolution resulting in slower and more variable absorption. However liquid dosage forms tend to be less stable, require additional formulation to provide a product with acceptable organoleptic properties and satisfactory preservation against microbial spoilage, are less convenient and bulkier, may require controlled storage and may be more expensive to manufacture than traditional solid

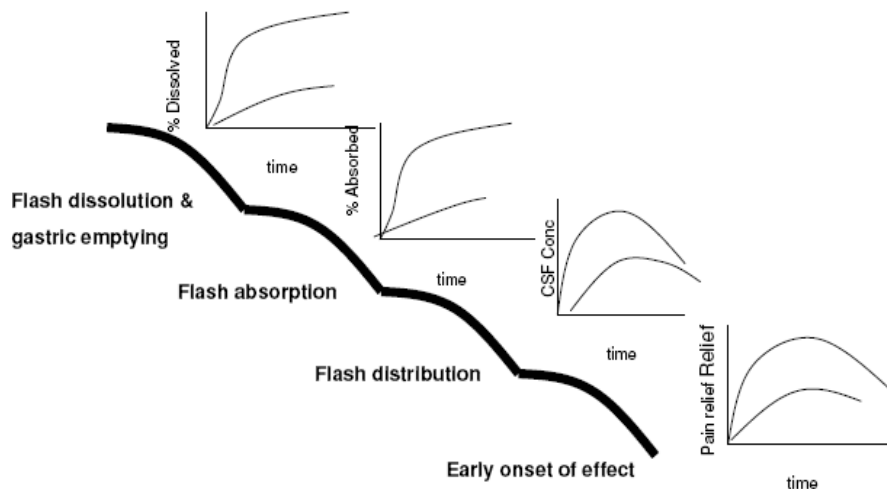
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dosage forms. In contrast, Surge Dose[®] provides a convenient, portable easy-to-swallow tablet that can be easily manufactured.

To achieve rapid absorption from a solid dosage formulation, ultra-fast activated dissolution *in vivo* is essential. Furthermore this must occur in the limited volume of available fluid in the highly variable gastric environment in terms of 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 motility, maximising dissolution into co-administered water.

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



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

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- High plasma concentrations drive rapid distribution to the effect compartment resulting in rapid onset of action and rapid peak effect

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

Nalmefene is a basic drug, with a pKa of 7.6 which is covered by the broad platform claims in Imaginot's patents for this class of drugs. It has good permeability and high lipid permeability which facilitates rapid absorption and distribution to central opioid receptors. As a basic drug it will demonstrate its maximum solubility under acidic conditions with solubility reducing as the pH increases. While acidic gastric conditions in fasted subjects will favour dissolution, its dissolution rate in the general population is likely to be quite variable as gastric pH will vary significantly at the time of dosing. This will result in variable absorption with some slow absorption occasions.

In vitro dissolution studies conducted on the physico-chemically similar molecule codeine indicates that the dissolution rate can be significantly increased with Surge Dose[®] formulations compared with conventional tablets. An unoptimized Surge Dose[®] codeine reached around 80 % dissolution in 3 min in typical fasted gastric conditions compared with around 40 % for the commercial tablet. Even under the most unfavourable *in vitro* test conditions, in the absence of stirring (0 rpm), Surge Dose[®] achieved 40 % dissolution in 3 min demonstrating intrinsic activated dissolution independent of gastric motility.

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[®] formulations using controlled low relative humidity (RH) conditions and unit packaging in moisture-impervious laminates for maximum stability. Small scale batches of a wide range of different drugs and a drug combination have been manufactured with accelerated stability indicating a shelf life of at least 2 years. To date formulations of a basic drug and two acidic drugs have been successfully scaled-up for commercial manufacture using direct compression and wet granulation processing and standard film coating techniques.

This review concludes that nalmefene, a universal opioid receptor antagonist, is a suitable candidate for Imaginot's Surge Dose[®] activated dissolution technology with pH modulating agents and water uptake agents used to maximise the dissolution rate of the drug.

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Furthermore there is a technically supportable opportunity to develop and register an improved Surge Dose[®] nalmefene formulation that will offer faster and more consistent onset of action benefits over current tablets and the potential for market exclusivity associated with registering a new formulation as well as extended patent protection.

In summary:

- Surge Dose[®] nalmefene will provide faster and more consistent absorption with more subjects with T_{max} in less one hour independent of GI conditions
- Higher concentrations of dissolved drug in the GI tract will produce higher plasma levels which will drive early distribution into the CNS to achieve early blockade of opioid receptors
- Once the receptors are blocked, the effects of Surge Dose[®] nalmefene will last for up to 72 hours as the molecule slowly dissociates from the receptors
- Surge Dose[®] nalmefene will maximise clinical efficacy and may allow use of lower doses with an associated improved tolerability and lower incidence of side effects

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1 Introduction

1.1 Surge Dose[®] drug delivery technology

The Surge Dose[®] 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[®] drug formulations provide faster and more consistent absorption resulting in faster and more reliable onset of action. Surge Dose[®] significantly reduces mean and median times to peak plasma drug concentration (T_{max} , C_{max}) and reduces absorption variability as demonstrated for paracetamol (acetaminophen, APAP), lornoxicam and diclofenac in pharmacokinetic (PK) studies in man. Based on PK-PD (pharmacodynamic) modelling, Surge Dose[®] paracetamol is predicted to achieve improved efficacy as the variable absorption of currently marketed tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy.

The Surge Dose[®] technology is well positioned to provide a clinical benefit for drugs with:

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

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

1.2 IP status

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

- i. PCT/AU 2006/001798 published as WO/2007/059591 covering acidic and unionized

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therapeutic agents claiming priority from the Australian provisional filed on 28 Nov 2004. Originally this patent application was cognated with others to cover acids, bases, amphoteric and unionized compounds. It has now been amended in all jurisdictions to cover only acidic and unionized compounds. This patent has been granted without limitation in Australia and examination is progressing in US under the PPH and Japan

- ii. PCT/AU 2005/00759 published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. This has been granted in Australia and Canada without limitation and is under examination elsewhere.
- iii. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations has been assigned to a third party in Australia (granted), Europe, India and Japan. This patent has been granted in US and Canada.

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

1.3 Technical strategy

Formulation optimization is aimed at achieving total dissolution of the drug in available liquid in the stomach to provide a high concentration gradient for rapid absorption from the small intestine driving high plasma concentrations. Surge Dose® uses optimized levels and ratios of pH modulating agents (pHMA) and water uptake agents (WUA) for each drug or drug combination to provide a pH-controlled 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 dissolving drug particles independent of the gastric pH, whilst controlling the pH to maximize solubility. This provides a higher concentration of drug in solution in the first few minutes after administration with the resultant drug solution draining from the stomach independent of the Migrating Motility Complex (MMC) and driving faster absorption. In contrast, traditional tablet formulations release drug into solution by passive diffusion across stagnant boundary layers around dissolving drug particles which provide a barrier to fast dissolution. Such slow dissolving tablets produce only low concentrations of dissolved drug and rely on MMC gastric emptying for drug absorption.

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

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

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

Testing is conducted using a range of highly discriminating *in vitro* dissolution methods as a development rather than a QC tool. These use standard dissolution equipment with different media at 37 °C, different volumes and different stirring speeds to simulate *in vivo* conditions:

- 900 mL 0.05 M HCl at 30 rpm is frequently used in pharmacopoeial test methods, where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.2, contains the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo*, and are the conditions used to characterise Surge Dose[®] formulations in the Imaginot patents
- 200 mL 0.015 M HCl at 30 rpm, pH 1.7, contains 3 mmoles of acid in a typical physiological volume based on 170 mL co-administered water with around 30 mL acidic gastric contents in the fasted state
- 200 mL 0.0033 M HCl at 30 rpm simulates a typical physiological volume with lower gastric acidity as occurs in many subjects in the general population
- 900 mL 0.0033 M HCl at 0 rpm simulates gut stasis such as occurs in migraine and the fed state where there is little gastric motility

1.4 Commercialization

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

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delivery company (Ethypharm SA), India's largest pharmaceutical company (Abbott Healthcare Pvt Ltd) and Piramal Healthcare Ltd <Piramal>, an international drug delivery technology contract development and manufacturing company. Piramal can undertake formulation development, biostudies and contract manufacture of products based on the Surge Dose[®] technology for interested parties.

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

2 Clinical premise for Surge Dose[®]

2.1 Key sources of physiological variability affecting drug absorption

2.1.1 Gastrointestinal (GI) motility

Drug absorption following oral administration is influenced by:

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

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

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

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 respectively¹.

¹ 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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When a drug is administered to a fasted subject, they may be in any phase of the MMC. In late Phase II or Phase III, relatively fast absorption will occur as the total gastric contents are rapidly emptied into the small intestine. However, in Phase I or early Phase II, there will be slower absorption although there will be an initial fast absorption phase for any dissolved drug that passively drains from the stomach where the amount of dissolved drug will depend on its solubility and the dissolution characteristics of the dosage form. Initial absorption will be followed by a later absorption phase when the remaining gastric contents are emptied into the small intestine by Phase III MMC. This often results in double or multiple peaks in the plasma concentration – time profiles seen in many subjects particularly when there is sufficiently frequent sampling. These gastric emptying peaks occurring during the first two hours differ from later peaks due to entero-hepatic recycling.

Hence the underlying MMC will influence gastric emptying and drug absorption contributing to the inter- and intra-subject variability seen in PK studies with orally administered solid dosage forms and solutions. For the same formulation, a subject in Phase I will absorb the drug slower than if they were in Phase II, with the fastest absorption occurring when the subject is in Phase III. It should be noted that the variability resulting from the underlying MMC is significant and can mask differences between formulations and other variables particularly in fasted PK studies. Delayed absorption and reduced variability seen in fed studies result from the fact that the underlying MMC is interrupted by the ingestion of food which generally triggers Phase I MMC².

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

2.1.2 GI pH

2.1.2.1 Stomach

Although gastric contents are acidic in the fasted healthy state, there is significant variability in inter- and intra-subject gastric pH. Gastric pH typically varies between 1 and 7 during the

² 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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course of the day in the general population depending on age, presence of food, concomitant medication and pathophysiology:

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

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

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

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

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

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

2.1.2.2 Small intestine

Conditions in the small intestine which is the primary site for absorption of most drugs, differ to those in the stomach, with a more consistent higher pH and high secretion rates of relatively alkaline intestinal fluids. Under such conditions, poorly soluble drugs which are weak bases and are more soluble under acidic conditions in the stomach may precipitate out. This will slow absorption and may be responsible for long T_{max} values seen for weakly basic drugs.

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This problem is well recognized and *in vitro* methods have been developed to predict the impact of such behaviour on drug absorption^{3,4,5}.

Where a basic drug has not already completely dissolved in the stomach, the alkaline secretions will reduce solubility and hence delay dissolution and slow absorption. There is also the potential for precipitation of the less soluble form on the surface of undissolved drug which will further slow dissolution and absorption. This is demonstrated for the antifungal agent itraconazole, where use of hydroxypropyl methylcellulose as a precipitation inhibitor improved its oral bioavailability by some 60 % in rats⁶.

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

2.2 Clinical rationale

Drug absorption following oral administration is influenced by:

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

While the physiological conditions of the patient cannot be changed by the dosage form, strategic formulation design can improve the probability of rapid absorption by modifying the pH of the dissolution reaction and creating a mechanism for activated dissolution *in vivo*.

-
- ³ Kostewicz ES, Brauns U, Becker R, Dressman JB. Forecasting the oral absorption behaviour of poorly soluble weak bases using solubility and dissolution studies in biorelevant media Pharm Res (2002) 19:345-9
 - ⁴ Kostewicz ES, Wunderlich M, Brauns U, Becker R, Bock T, Dressman JB. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. JPP (2004) 56:43-51
 - ⁵ Gu C-H, Rao D, Gandhi RB, Hilden J, Raghavan K. Using a novel multicompartiment dissolution system to predict the effect of gastric pH on the oral absorption of weak bases with poor intrinsic solubility. J Pharm Sci (2005) 94(1):199-208
 - ⁶ Van Speybroeck M, Mols R, Mellaerts R, Thi TD, Martens JA, van Humbeeck J, Annaert P, van den Mooter G, Augustijns P. Combined use of ordered mesoporous silica and precipitation inhibitors for improved oral bioavailability of the poorly soluble weak base itraconazole. Eur J Pharm Biopharm (2010) 75:354-65

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Surge Dose[®] formulations are designed to achieve ultra fast dissolution under the wide range of favourable and unfavourable conditions that occurs in the general population. This is important for drugs taken 'on demand' for immediate effect where delayed absorption often results from prevailing physiological conditions.

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

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

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

Surge Dose[®] is designed to maximize the rate and extent of drug dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC. The following cascade is shown in Figure 1:

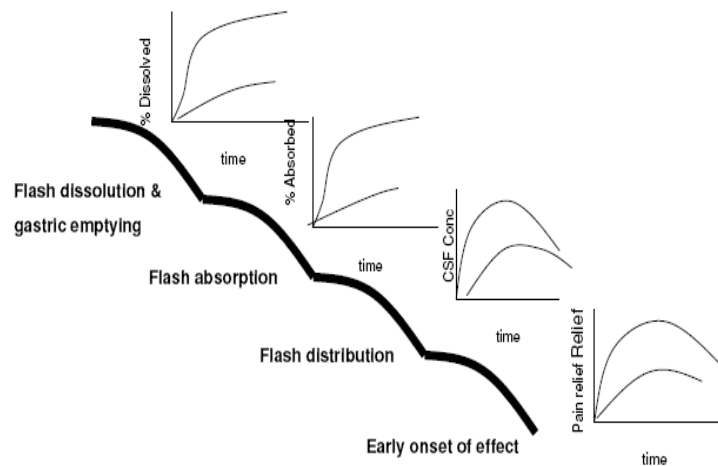
- i. Drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents
- ii. Resultant solution empties rapidly and passively from the stomach in fed and fasted states independent of the MMC i.e. empties as fast as when taken as a solution
- iii. The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption
- iv. Fast absorption quickly saturates any protein binding sites and saturable metabolic and transport processes leading to earlier achievement of therapeutic plasma concentrations with short T_{max} and high C_{max} as well as reduced intra- and inter-subject variability

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- v. High plasma concentrations drive rapid distribution to effect compartments resulting in rapid onset of action and rapid peak effect

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



2.3 Proof of concept

2.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects⁷ demonstrated significantly faster absorption with two fast dissolving Surge Dose[®] paracetamol formulations that have subsequently been improved, compared with Tylenol[®] Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol[®]>:

- Median T_{max} values for the Surge Dose[®] formulations were 17 and 25 min compared with 45 min for Tylenol[®]
- Surge Dose[®] AUC_{0-30} values indicated 3 times as much absorbed in the first 30 min compared with Tylenol[®]
- 64 and 76 % subjects receiving Surge Dose[®] tablets exceeded the reported minimum therapeutic level for paracetamol of 10 $\mu\text{g/mL}$ in the first 15 min compared with only 20 % subjects receiving Tylenol[®]
- 16 % subjects taking Tylenol[®] never reached 10 $\mu\text{g/mL}$ indicating sub-therapeutic dosing compared with only 4 % for Surge Dose[®] formulations

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

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This study showed good *in vitro in vivo* correlations (IVIVC). Although paracetamol absorption was variable from one dose to another reflecting MMC activity, fast *in vitro* dissolution was associated with a higher frequency of fast absorption occasions and higher C_{max} values. Slow absorption occasions were more frequent with Tylenol[®], and were associated with lower C_{max} values sometimes failing to reach reported minimum therapeutic plasma levels. PK-PD modelling to quantify pain relief following oral administration predicted more rapid onset and greater analgesia with Surge Dose[®] paracetamol tablets than Tylenol[®] tablets⁸. Improved clinical efficacy is predicted for Surge Dose[®] formulations as a result of fewer sub-therapeutic absorption profiles with 20% more patients achieving target end points than Tylenol[®]. This is reflected in the predicted lower NNT (Number Needed to Treat) of 2.8 for Surge Dose[®] compared with 4.2 for Tylenol[®].

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

2.3.2 Lornoxicam

A PK study in 24 fasted subjects with the NSAID lornoxicam has demonstrated the *in vivo* benefits of Surge Dose[®] increasing *in vitro* drug dissolution compared with a conventional commercial tablet⁹. An optimized Surge Dose[®] tablet formulation significantly reduced T_{max} and resulted in significantly higher C_{max} levels similar to parenteral administration¹⁰. Faster and more consistent absorption has the potential to improve efficacy.

Absorption from Surge Dose[®] lornoxicam tablets was twice as fast as from the reference commercial product:

⁸ 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

⁹ 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

¹⁰ Radhofer-Welte S, Dittrich P, Simin M, Branebjerg PE. Comparative bioavailability of lornoxicam as single doses of quick release tablet, standard tablet and intramuscular injection – a randomized, open-label, crossover Phase I study in healthy volunteers. *Clin Drug Invest.* (2008) **28**(6): 345-51

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- Mean and median T_{max} values for Surge Dose[®] lornoxicam were comparable at 0.51 and 0.50 h respectively, ranging from 0.3 to 1 h
- Median T_{max} for the reference tablet was 0.83 h ranging from 0.5 to 2.3 h with a longer mean T_{max} of 1.06 h indicating more subjects with slow absorption
- 75 % subjects on Surge Dose[®] lornoxicam achieved T_{max} within the first 0.5 h compared with only 8 % for the reference tablet
- Surge Dose[®] lornoxicam achieved peak plasma concentrations comparable with parenteral administration, around 40 % higher than the reference tablet with mean C_{max} 1098 ng/mL (CV 18.71 %) compared with 788 ng/mL (CV 18.69 %)
- Although $AUC_{0-\infty}$ was the same for both Surge Dose[®] and reference lornoxicam tablets with values around 4,200 ng.h/mL, early exposure AUC values after 10, 20 and 30 min demonstrated significantly faster absorption with Surge Dose[®] lornoxicam, respectively 3.9, 2.8 and 2.2 times higher than with the reference tablet

2.3.3 Diclofenac

A film coated Surge Dose[®] diclofenac sodium 50 mg tablet with optimized levels of pHMA and WUA to meet the Surge Dose[®] in vitro dissolution specifications was compared with Voveran[®]-D (Novartis), a dispersible tablet dissolved in water before administration. 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[®]¹¹.

It was notable that despite Voveran[®]-D dispersible tablets being promoted 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. Absorption from Surge Dose[®] diclofenac tablets was 4 – 5 times faster:

- Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (\pm 5.0) and 19.5 min (range 5 – 30 min) with reduction in the frequency of slow absorption profiles. By comparison Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h).

¹¹ 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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- Surge Dose[®] tablets resulted in significantly higher C_{\max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. C_{\max} values for Surge Dose[®] were comparable with those obtained following IV^{12,13} or IM^{14,15} administration whereas as those for Voveran[®]-D were lower than reported for standard tablets of $1,340 \pm 627$ ng/mL¹⁶.
- With Surge Dose[®], 76 % subjects had a T_{\max} equal to or less than 20 min and 100 % reached T_{\max} within 30 min. By comparison only one Voveran[®]-D subject (5 %) had T_{\max} equal to or less than 20 min and 3 (18 %) less than 30 min. With Voveran[®]-D, 70 % subjects had to wait at least 1 h to reach T_{\max} , with 6 (30 %) waiting at least 2 h.

3 Nalmefene

3.1 Patents

US 3,814,768¹⁷, GB 1411129 and equivalents (priority 26 Nov 1971) cover a range of 6-methylene-6-desoxy-dihydro morphine or codeine derivatives including nalmefene that have higher oral activity and a longer duration of activity of 8 – 12 hours as narcotic antagonists. These represent an improvement over naltrexone which is less active orally than by parenteral administration with a shorter duration of action, only 4 hours following oral use compare with 6 hours when injected. Uses of nalmefene for the treatment of alcoholism and gambling are covered by US 5,086,058 (Alko, Finland, priority 04 Jun 1990). These patents have expired.

More recent current patents and applications cover:

- prodrugs of nalmefene such as US 2011/0034502 (Johnson & Johnson, priority 24 Apr 2008) and US 2011/0053971 (Janssen Pharma NV, priority 23 Apr 2009)

¹² 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

¹³ 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

¹⁴ 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

¹⁵ 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

¹⁶ 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

¹⁷ US 3,814,768, Fishman J et al, 6-METHYLENE-6-DESOXY DIHYDRO MORPHINE AND CODEINE DERIVATIVES AND PHARMACEUTICALLY ACCEPTABLE SALTS

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- transdermal patches that provide sustained release levels of nalmefene such as US 5,086,058, US 2006/0235038 and US 2002/0037313 .

3.2 Regulatory status and therapeutic indication

Nalmefene has been registered in the US as Revex[®] marketed by Baxter Healthcare Group since 17 April 1995 for the reversal of opiate-induced respiratory depression and treatment of suspected opioid overdose. It is available as a parenteral solution for IV, IM or SC administration containing 100 µg or 1 mg free base per 1 mL. Nalmefene is not currently registered for alcohol dependency and is not registered as an oral dosage form.

Alcoholism or alcohol dependency is a major public health problem in the west estimated to affect some 10 % of the population. 10% of deaths and 25% of emergency room admissions are directly alcohol related. It has potentially fatal consequences such as liver cirrhosis and cancer as well as huge social and economic costs estimated to be at least EUR 200 billion per annum. In the UK there are 150,000 hospital admissions and 20,000 premature deaths directly due to alcohol, 1.2 million alcohol related violent incidents, with the annual costs of alcohol abuse estimated at around GBP 1.4 -1.7 billion¹⁸. Although alcohol dependency is severely under-diagnosed with only around 13% receiving treatment, more than 30 million people are treated each year in the US, Europe and Japan¹⁹. The WHO estimates some 60 million people in Europe at risk with excess alcohol consumption more than double the recommended daily limits of 2-3 standard drinks for women and 3-4 standard drinks for men²⁰.

Drugs registered for alcohol dependency in the US are disulfuram (Antabuse[®]), naltrexone (ReVia[®]) and acamprosate (Campral[®]) with off-label use of topiramate (Topamax[®]) and ondansetron (Zofran[®])²¹. Nalmefene, a universal opioid receptor in the same class as naltrexone but with improved oral bioavailability and reduced hepato-toxicity, is being evaluated as a treatment for alcohol dependency where there is a significant unmet medical need for an effective oral treatment²². An alcohol dependent person continually craves alcohol, is unable to limit their drinking, needs to drink greater amounts for the same effect and has withdrawal symptoms after stopping use.

¹⁸ The Impact of alcohol on the NHS, Institute of Alcohol Studies 05 May 2009
<http://www.ias.org.uk/resources/factsheets/nhs.pdf>

¹⁹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020459s006lbl.pdf

²⁰ Global Status Report on Alcohol and Health 2011
http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf

²¹ Collins GB, McAllister MS, Adury K. Drug adjuncts for treating alcohol dependence. Cleveland Clinic J Med (2006) 73(7):641-56

²² Datamonitor 04/2002

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Biotie Therapies Corp <Biotie> has conducted a number of studies on the safety and efficacy of oral nalmefene including two phase 3 studies in the UK and Finland in over 1,200 patients suffering from alcoholism and alcohol dependence. In November 2006, Biotie granted an exclusive licence to H Lundbeck A/S <Lundbeck> for worldwide marketing and distribution rights excluding North America, Mexico, UK, Ireland, Turkey, and South-Korea for nalmefene as a prescription medicine for the treatment of substance abuse and impulse control disorders. Under the deal valued at EUR 88 million with upfront (EUR 15 million) and milestone payments plus royalties on sales, Lundbeck is responsible for manufacturing and registration.

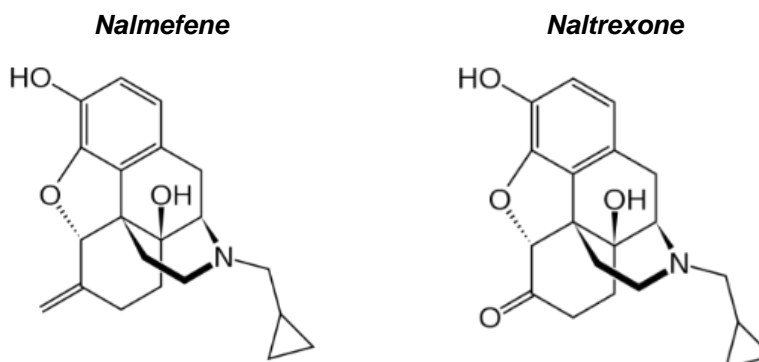
Biotie has submitted the first Marketing Authorisation Application (MAA) on nalmefene for the treatment of alcohol dependence to the Medicines and Healthcare Regulatory Authority (MHRA) in the UK as reference state in the Mutual Recognition Process for EU approval. Lundbeck has now completed an extensive Phase 3 development program in 2,000 alcohol dependent subjects to demonstrate safety and tolerability over 12 months comparing 18 mg oral nalmefene on demand with placebo. A European MAA was filed for Selincro[®] tablets containing 18 mg nalmefene in December 2011²³.

3.3 Physicochemical properties

3.3.1 Structure

Nalmefene, 17-cyclopropylmethyl-4,5 α -epoxy-6-methylenemorphinan-3,14-diol, has the chemical formula C₂₁H₂₅NO₃ and a molecular weight of 375.9. Nalmefene is closely related to naltrexone with the ketone (-C=O) group at the 6-position replaced with a methylene (-CH₂-) group, which significantly increases the binding affinity to the μ -opioid receptor. Its chemical structure compared with naltrexone is shown in Figure 2.

Figure 2 Chemical structures of nalmefene and naltrexone



²³ Biotie Therapies Corp. Stock Exchange Release 21 December 2011. Biotie's partner Lundbeck submits European Marketing Authorization Application for Selincro(TM) (nalmefene)

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3.3.2 Solubility

Nalmefene hydrochloride (HCl) has high aqueous solubility to the extent of 130 mg/mL²⁴. Doses up to 80 mg equivalent to the free base will dissolve in less than 1 mL water, so solubility should not be dissolution rate limiting. As a basic molecule with a pKa of 7.6, solubility will be higher under acidic conditions than at higher pH such as in the small intestine. By comparison naltrexone which has the ionizable keto-group, has a much higher pKa at 13.56 but similar solubility at 100 mg/mL and will be more reactive²⁵.

3.3.3 Permeability

Nalmefene would be expected to be more lipophilic and less ionizable than naltrexone consistent with its higher logP of 1.125 compared with 0.7 for naltrexone²⁶.

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

3.3.4 In vitro dissolution

With its high solubility and high permeability, nalmefene would be classified as BCS class I.

3.4 Pharmacokinetics (PK)

3.4.1 Absorption and distribution

Nalmefene is readily absorbed with on oral bioavailability of 40 – 50 % as a result of extensive first-pass hepatic metabolism, mainly to an inactive glucuronic acid conjugate and to a N-de-alkylated metabolite with slight pharmacological activity. This is much higher than naltrexone which has an oral bioavailability around 5 % with extremely high hepatic first-pass metabolism. Less than 5% of the dose is excreted unchanged in the urine with some 60 % excreted as the β -glucuronidase / sulphatase hydrolysable conjugate. The elimination half-life is around 7 – 15 hours with a mean of 11 hours. Nalmefene is around 45 % protein bound with a steady state volume of distribution around 8-9 L/kg and clearance around 1,100 mL/min.

²⁴ WO/2002/067916 Pharmaceutical salts. Grünenthal GmbH. Priority 28 Feb 2001 p43

²⁵ Naltrexone DB00704 <http://www.drugbank.ca/drugs/DB00704>

²⁶ <http://www.druglead.com/cds/nalmefene.html>

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Key PK parameters were similar after single and multiple intravenous (IV) administration of nalmefene 2 mg in healthy Chinese subjects, with T_{max} 0.08 h, C_{max} $7.34 \pm 1.56 \mu\text{g/L}$ and AUC $32.23 \pm 9.94 \mu\text{g/L}\cdot\text{h}$ ²⁷. Following IV doses of 1 – 2 mg nalmefene, there is evidence of age related effects with higher C_{max} and a 30 – 40 % lower central compartment volume of distribution in the elderly ($2.8 \pm 1.1 \text{ L}$ vs $3.9 \pm 1.1 \text{ L}$)²⁸. The distribution half-life was faster in the elderly, around 42 minutes compared with 1.3 ± 0.8 hours in young volunteers. No association was evident between high plasma levels and adverse events. Systemic clearance of 2 mg nalmefene IV was reduced and elimination $t_{1/2}$ increased by 31 % in patients with hepatic disease from 8 to 10.5 hours with reduced nalmefene glucuronide formation²⁹. Volume of distribution and protein binding were unchanged.

Oral nalmefene shows linear PK over the dose range 50 – 300 mg³⁰. Table 1 summarizes the key PK parameters for 50, 100, 200 and 300 mg doses in fasted healthy males and Table 2 shows the estimated individual PK data. These data highlight the significant variability in T_{max} ranging from 1 to 2 hours for the 50 mg dose with SDs indicating that some subjects experienced T_{max} by the first sample at 30 minutes. As this variability is high in fasted subjects where nalmefene has higher solubility under acidic conditions, it would be expected that variability would be even higher when gastric conditions are less acidic, in light of reduced solubility and slower dissolution at higher pH.

Table 1 Mean (\pm SD) PK parameters for oral administration of 50, 100, 200 and 300 mg nalmefene HCl to healthy men (from Dixon et al 1986)

Dose (mg)	t_{max} (hr)	C_{max} (ng/mL)	k (hr ⁻¹)	$t_{1/2}$ (hr)	AUC _{0-∞} (hr·ng/mL)
50	2.50 ± 0.58	24.3 ± 11.0	0.068 ± 0.018	10.3*	274 ± 97
100	1.5 ± 1.0	57.9 ± 49.0	0.061 ± 0.004	11.4	647 ± 212
200	1.25 ± 0.50	155 ± 8	0.071 ± 0.025	9.8	$1,320 \pm 357$
300	1.50 ± 0.58	177 ± 18	0.059 ± 0.014	11.7	$1,876 \pm 87$

²⁷ Liao RF, Zeng ZP, Wen YG. Pharmacokinetics of nalmefene after a single or multiple intravenous doses in Chinese healthy volunteers. J Southern Medical University (2008) 28(10):1816-9

²⁸ Frye RF, Matzke GR, Jallad NS, Wilhelm JA, Bikhazi GB. The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. Brit J Clin Pharmacol (1996) 42(3):301-6

²⁹ Frye RF, Matzke GR, Schade R, Dixon R, Rabinovitz M. Effects of liver disease on the disposition of the opioid antagonist nalmefene. Clin Pharmacol Ther (1997) 61(1):15-23

³⁰ Dixon R, Gentile J, Hsu HB, Hsiao J, Howes J, Garg D, Weidler D. Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. J Clin Pharmacol (1987) 27:233-9

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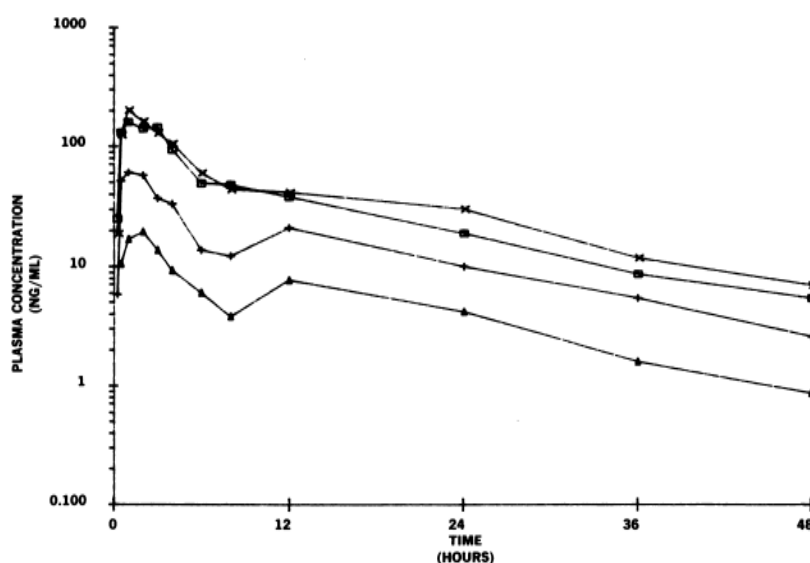
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Table 2 Individual PK parameters for oral administration of 50 mg nalmefene HCl to 6 healthy men (from Dixon et al 1986)

Parameters	Subject						Mean \pm SD
	1	2	3	4	5	6	
C_{max} (ng/mL)	37	51	38	39	39	32	39.3 ± 6.3
t_{max} (hr)	1	2	1	2	1.5	1.5	1.50 ± 0.45
k (hr ⁻¹)	0.105	0.137	0.082	0.068	0.087	0.061	0.090 ± 0.028
$t_{1/2}$ (hr)	6.6	5.1	8.5	10.2	8.0	11.4	7.7*
AUC_{0-t} (hr-ng/mL)	364	257	491	307	270	405	349 ± 89
$AUC_{0-\infty}$ (hr-ng/mL)	375	264	507	318	287	418	361 ± 91

Figure 3 shows a typical log plasma concentration – time plot for one subject with the secondary peak around 12 hours attributed to enterohepatic recycling of the glucuronide.

Figure 3 Log plasma concentration- time curves for oral nalmefene 50, 100, 200 and 300 mg (from Dixon et al 1986)



3.5 Pharmacodynamics (PD)

3.5.1 Mechanism of action

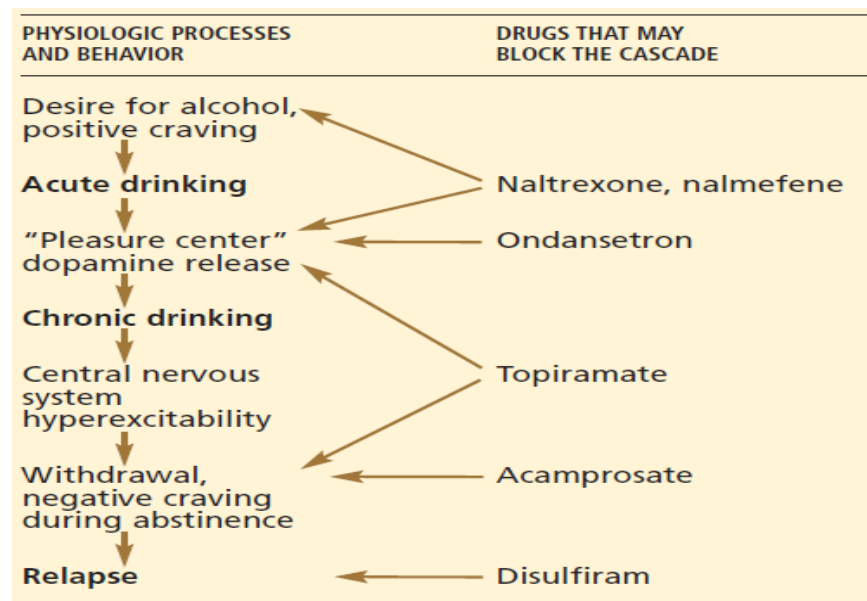
Alcohol dependency involves a cascade of effects on different systems in the brain which can be blocked at different levels by the various drugs used for the treatment of this condition as

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shown in Figure 4³¹. Alcohol increases the activity of opioid pathways mediated by endogenous β -endorphin which activates the reward effects of alcohol by modulating dopaminergic neurotransmission in the brain. As opioid receptor antagonists, nalmefene and naltrexone block opioid transmission and so have the potential to modulate drinking behaviour by blocking the urge to drink and to block the effects of alcohol³².

Figure 4 *Blocking the cascade of alcohol dependence (from Collins et al 2006)*



Unlike naltrexone which is a selective μ -opioid receptor antagonist with some agonist activity, nalmefene is a pure 'universal' antagonist binding with all three subtypes of opioid receptors, μ , δ and κ . Thus nalmefene has the potential for efficacy at lower doses than naltrexone with a corresponding reduction in side effects and no abuse potential. The δ and κ receptors reinforce alcohol consumption. Nalmefene is around twice as potent as naltrexone when used for the treatment of addictions. At low doses nalmefene is more effective than naltrexone in suppressing ethanol intake in rats³³.

³¹ Collins GB, McAllister MS, Adury K. Drug adjuncts for treating alcohol dependence. *Cleveland Clinic J Med* (2006) 73(7):641-56

³² Soyka SM & Rosner S. Nalmefene for treatment of alcohol dependence. *Exp Opin Invest Drugs* (2010) 19(11):1451-9

³³ Walker BM & Koob GF. Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. *Neuropsychopharmacol* (2008) 33(3):643-52

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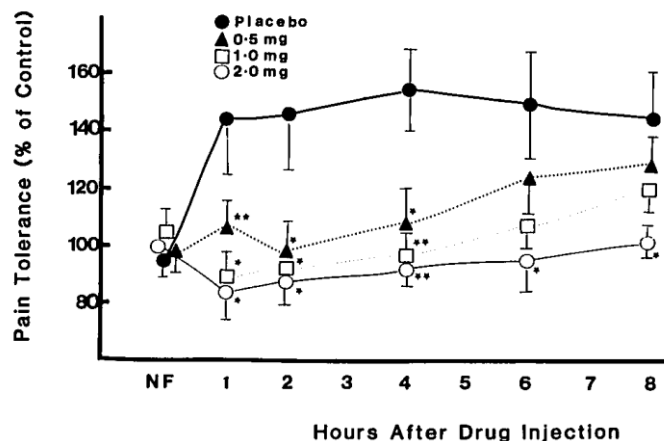
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3.5.2 Duration of action

Longer duration of occupancy of opioid receptors by nalmefene compared with naloxone has been demonstrated consistent with the longer effect of nalmefene in reversing narcotic anesthesia and side effects and treating opiate overdose³⁴. Mean clearance half-time from opioid receptors was 28.7 ± 5.9 h for 1 mg nalmefene IV compared with 2.0 ± 1.6 h for 2 mg naloxone. Brain clearance time was 21.1 times longer than plasma clearance time for nalmefene, and only 3.4 times for naloxone which has a much shorter half-life of 60 – 90 minutes compared with 11 hours for nalmefene.

Both IV and oral nalmefene produce prolonged blockade of opioid receptors with the effects in blocking fentanyl analgesia and preventing fentanyl-induced respiratory depression lasting longer than 72 hours^{35,36,37}. This prolonged effect shown in Figures 5 and 6 means that there is not a direct correlation between effect and plasma concentrations although the faster absorption occurs, the faster blockade of the opioid receptors can commence. This prolonged duration is consistent with the structure of nalmefene which is lipophilic and once bound to the opioid receptors dissociates very slowly.

Figure 5 Duration of effect after IV nalmefene 0.5, 1 and 2 mg in blocking analgesic effects of fentanyl 2 µg/kg IV compared with placebo (from Gal et al 1986)



³⁴ Kim S, Wagner HM, Villemagne VL, Kao PF, Dannals RF, Ravert HT, Joh T, Dixon RB, Civelek AC. Longer occupancy of opioid receptors by nalmefene compared to naloxone as measured in vivo by a dual-detector system. J Nucl Med (1997) 38(11):1726-31

³⁵ Gal TJ & DiFazio CA. Prolonged antagonism of opioid action with intravenous nalmefene in man. Anesthesiol (1986) 64(2):175-80

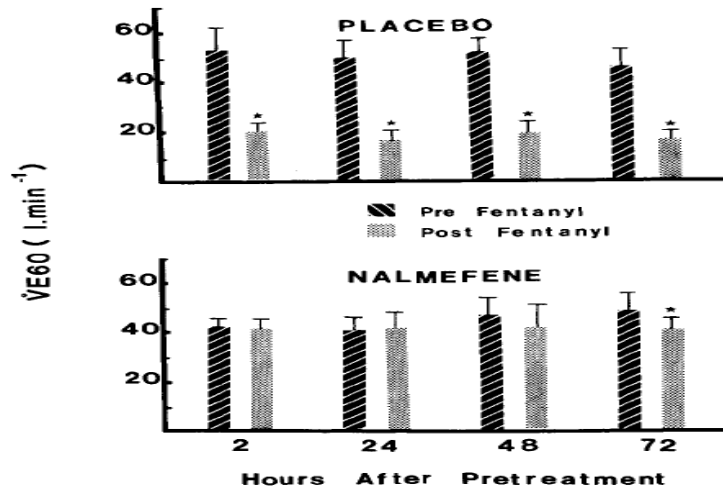
³⁶ Gal TJ & DiFazio CA. Prolonged blockade of opioid effects with oral nalmefene. Anesthesiol (1986) 65(3A):A343

³⁷ Gal TJ, DiFazio CA, Dixon R. Prolonged blockade of opioid effect with oral nalmefene. Clin Pharmacol Ther (1986) 40(5):537-42

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Figure 6 Duration of effect after oral nalmefene 50 mg in blocking respiratory depression of fentanyl 2 µg/kg IV measured as minute ventilation at PCO₂ 60 mm Hg during rebreathing compared with placebo (from Gal et al 1986)



Other studies have confirmed this extended blockade of opioid receptors for nalmefene. A double-blind placebo-controlled study in patients with opioid induced sedation showed that nalmefene had longer lasting effects than naloxone with effects lasting at least 210 minutes compared with 15 minutes for naloxone³⁸.

Single and repeated dosing of 20 mg nalmefene over 7 days in 12 healthy subjects resulted in 87–100% occupancy at μ -opioid receptors³⁹. The decline in occupancy was slower than the decline in the plasma concentration of nalmefene or metabolites with 83–100% occupancy persisting 26 h after dosing indicating slow dissociation of the drug from μ -opioid receptors. This supports the rationale of administering nalmefene when needed before alcohol drinking, with once daily being an effective dosage regimen.

3.5.3 Efficacy

Biotie has conducted three Phase 2 and two Phase 3 studies in alcohol dependence with oral nalmefene 20-80 mg per day. One study in 400 alcoholic patients demonstrated reduced average alcohol intake and reduced number of heavy drinking days (> 5 standard drinks). Three randomized placebo-controlled Phase 3 studies by Lundbeck involving 2,000 individuals

³⁸ Barsan WG, Seger D, Danzi DF, Ling LJ, Bartlett R, Buncher R, Bryan C. Duration of antagonist effects of nalmefene and naloxone in opiate-induced sedation for emergency department procedures. *Amer J Emerg Med* (1989) 7(2):155-61

³⁹ Ingman K, Hagelberg N, Aalto S, Nägren K, Juhakoski A, Karhuvaara S, Kallio A, Oikonen V, Hietala J, Scheinin H. Prolonged Central μ -Opioid Receptor Occupancy after Single and Repeated Nalmefene Dosing. *Neuropsychopharmacol* (2005) 30:2245–53.

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into two groups studied nalmefene 20 mg as needed compared with placebo to demonstrate efficacy (6 months) and to confirm safety and tolerability (12 months). Primary and secondary endpoints included number of heavy drinking days per month, total alcohol consumption, proportion of responders based on drinking measures, alcohol dependence symptoms and clinical status, liver function and other laboratory tests, pharmaco-economic outcomes and treatment discontinuation. All assessments favoured nalmefene over placebo, although not always statistically significant^{40,41}. Overall, nalmefene reduced heavy drinking days and total alcohol consumption by more than 50% compared to pre-treatment baseline. The 12-month safety study confirmed that the treatment effect of nalmefene was maintained and even improved after 1 year compared with the usual relapse rates of 40 – 70 % within 12 months⁴².

In general there is little difference in efficacy between the lower and higher dosages, and lower doses are better tolerated, with fewer side effects. In a double-blind placebo-controlled trial in 105 alcohol dependent volunteers, 20 or 80 mg oral nalmefene daily for 12 weeks produced similar effects with fewer relapses compared with placebo after 1 week⁴³.

Oral nalmefene inhibited ethanol-induced flushing in Asians caused by endogenous prostaglandins and opiates whereas indomethacin, a cyclooxygenase inhibitor, did not⁴⁴.

Nalmefene at 40 mg/day is also effective in pathological gambling which affects some 1 % of adults and where a family history of alcoholism appears to predict response to an opiate antagonist such as nalmefene⁴⁵.

3.5.4 Adverse events

Nalmefene is very well tolerated and has no apparent abuse potential⁴⁶. Although in a multi-centre study of 5, 20 and 40 mg oral nalmefene compared with placebo over 12 weeks, there

⁴⁰ Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, Mantero-Atienza E. A double-blind placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcoholism: Clin Exper res* (1994) 18(5):1162-7

⁴¹ Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, McCaul ME, Anthenelli R, Salloum I, Galloway G, Garbutt J, Swift R, Gastfriend D, Kallio A, Karhuvaara S. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* (2004) 24:421-8

⁴² Collins GB, McAllister MS, Adury K. Drug adjuncts for treating alcohol dependence. *Cleveland Clinic J Med* (2006) 73(7):641-56

⁴³ Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* (1999) 56(8):719-24

⁴⁴ Ho SB, DeMaster EG, Schafer RB, Levine AS, Morley JE, Go VL, Allen JL. Opiate antagonist nalmefene inhibits ethanol-induced flushing in Asians: a preliminary study. *Alcoholism, Clin Exper Res* (1988) 12(5):705-12

⁴⁵ Grant JE, Kim SW, Hollander E, Potenza MN. Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. *Psychopharmacol* (2008) 200 (4):521-7

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were more side effect related discontinuations in the active groups, the rates did not differ significantly from those in the placebo group⁴⁷. The 20 mg group experienced more insomnia, dizziness and confusion compared with more nausea in the 40 mg group.

At oral doses from 25 – 100 mg the most common side effects were drowsiness, sleepiness, agitation, irritability and muscle tremor. Mild and transient dizziness, insomnia and nausea have also been reported. Frequencies of reported adverse events with IV nalmefene compared with naloxone and placebo are summarized in Table 3⁴⁸. Nausea and vomiting after IV administration are more prevalent than reported for oral administration and appear to be dose related based on reports for the 40 mg oral dose compared with lower doses.

Table 3 Frequency of reported side effects for IV nalmefene, naloxone and placebo

Adverse Event	Nalmefene	Naloxone	Placebo
Number of patients	1127	369	77
Nausea	18%	18%	6%
Vomiting	9%	7%	4%
Tachycardia	5%	8%	-
Hypertension	5%	7%	-
Postoperative pain	4%	4%	N/A
Fever	3%	4%	-
Dizziness	3%	4%	1%
Headache	1%	1%	4%

4 Surge Dose[®] nalmefene

4.1 Clinical considerations

Nalmefene offers several therapeutic advantages over naltrexone which is well established as a treatment for alcohol dependency. Although naltrexone and nalmefene have comparable

⁴⁶ Fudala PJ, Heishman SJ, Henningfield JE, Johnson RE. Human pharmacology and abuse potential of nalmefene. Clin Pharmacol Ther (1991) 49: 300-6

⁴⁷ Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, McCaul ME, Anthenelli R, Salloum I, Galloway G, Garbutt J, Swift R, Gastfriend D, Kallio A, Karhuvaara S. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol (2004) 24:421–8

⁴⁸ Revex[®] Product label http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020459s006lbl.pdf

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potency, nalmefene is not associated with dose-dependent hepato-toxicity, has better oral bioavailability, has a longer duration of antagonist effect, and is a universal antagonist binding with all three opioid receptor subtypes instead of just the μ receptor⁴⁹.

Based on the physicochemical properties, PK and PD of nalmefene, it appears to be a suitable candidate for Imaginot's ultra-fast activated dissolution Surge Dose[®] technology:

- its use to block the desire to drink alcohol where fast and consistent onset of action is a clinical pre-requisite
- ready absorption by passive diffusion across the intestinal mucosa and blood brain barrier where high concentration of dissolved drug in the small intestine provide the driving force for fast absorption and distribution into the CNS
- prolonged action once nalmefene reaches the opioid receptors that lasts for up to 72 hours in the absence of significant circulating plasma levels
- highly variable absorption in both healthy subjects and patients with CVs for C_{max} and T_{max} values ranging from 20 – 70 %

Overall faster *in vivo* dissolution of a Surge Dose[®] nalmefene tablet should achieve faster and more consistent absorption with fewer cases of slow absorption which will be associated with faster onset of action and blockade of opioid receptors to inhibit the desire for alcohol. This would also have application to reverse opioid blockade.

Improved efficacy may allow the use of lower doses with the associated benefit of further improvement in the safety profile of this drug. Any increases in C_{max} due to faster absorption from Surge Dose[®] formulations should be within the range reported for IV nalmefene.

A Surge Dose[®] nalmefene would also achieve activated dissolution in the presence or absence of food, and so would leverage the effects of faster exponential drainage of liquids independent of solids and MMC activity. This would achieve faster and more predictable absorption in the fed state, with faster fed T_{max} values closer to fasted values.

4.2 Technical considerations

The physicochemical properties of nalmefene are suitable for application of Imaginot's Surge Dose[®] technology to increase its rate of dissolution under alkaline and acidic conditions. It has high water solubility and should completely dissolve in the volumes of water used for

⁴⁹ Mason BJ, Salvata FR, Williams LD, Ritvo EC, Cutler RB. A double-blind placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry (1999) 56(8):719-24

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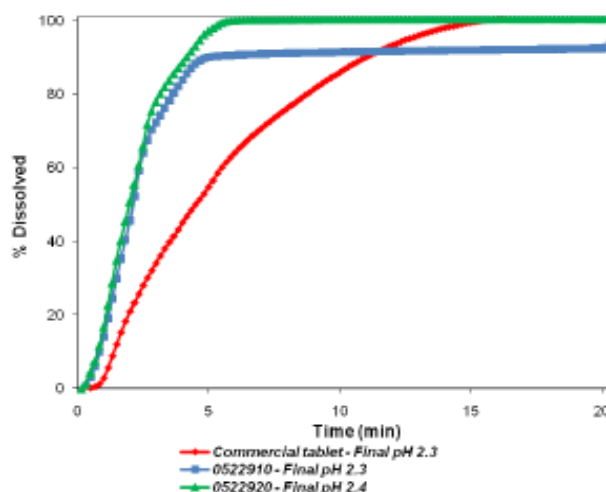
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swallowing a tablet. As a basic drug it will be more soluble in acidic conditions which in turn will increase the dissolution rate in the fasted stomach.

While Imaginot has not worked on nalmefene formulations, it has shown that Surge Dose[®] formulations significantly improve the *in vitro* dissolution of codeine phosphate in 900 mL 0.0033 M HCl in USP dissolution apparatus II at 30 rpm and 37 °C compared with a standard commercial codeine tablet⁵⁰. Codeine phosphate has a similar pKa at 8.2 to nalmefene but a lower solubility around 9 mg/mL. Although codeine is classified as a BCS class III compound based on its low permeability, the *in vitro* dissolution is independent of permeability and so is indicative of how a Surge Dose[®] nalmefene tablet would be expected to behave relative to a standard tablet formulation.

Dissolution profiles for codeine phosphate 30 mg tablets are shown in Figure 7 demonstrating the effect of 20 mg sodium bicarbonate per tablet alone (0522910) and with 42 mg ascorbic acid (0522920) compared with the commercial tablet. Both experimental formulations dissolved around twice as fast as the commercial tablets exceeding 70 % dissolution in 3 minutes compared with only 34 %.

Figure 7 *Comparative dissolution profiles for codeine phosphate 30 mg tablets in USP apparatus II in 900 mL 0.0033 M HCl at 30 rpm and 37°C demonstrating the effect of Surge Dose[®] technology*



The final pH of the dissolution medium was 2.3 – 2.4 for both the commercial product and the experimental formulations (0522910, 0522920) consistent with the low levels of pH modulating agents (PHMA) used in these tablets. The increased dissolution rate results from the activated

⁵⁰ IM 03-13-02 Application of Surge Dose fast dissolution technology to codeine Imaginot Pty Ltd July 2011

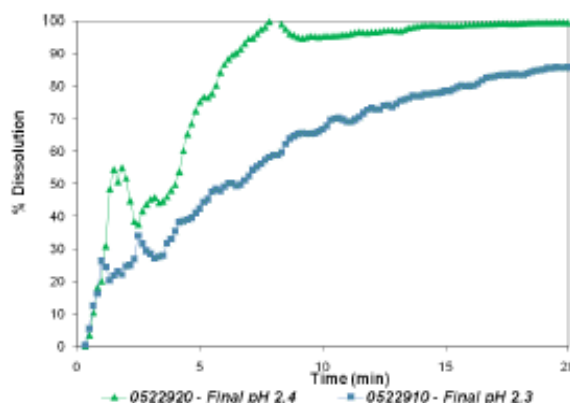
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dissolution and pH control in the vicinity of the dissolving drug particles. The addition of ascorbic acid did not have a significant effect on the initial dissolution rate but reached a plateau at around 90 % until the stirring speed was increased to achieve 100 % dissolution.

Figure 8 demonstrates the activated Surge Dose[®] dissolution with the tablet containing 20 mg sodium bicarbonate and 42 mg ascorbic acid which exceeds 20 % dissolution in the first 5 minutes even in the absence of external stirring.

Figure 8 *Dissolution of codeine phosphate 30 mg in the absence of stirring (0 rpm) comparing the effect of 20 mg sodium bicarbonate alone (0522910) and with 42 mg ascorbic acid (0522920) in 900 mL 0.0033 M HCl*



4.3 IP considerations

While nalmefene is not named in the Imaginot patents it is a basic compound and so a Surge Dose[®] nalmefene would be covered by the broad claims in WO/2005/115345 covering basic and amphoteric actives with a priority date of 28 May 2004.

Additionally there is the opportunity for drug specific patents to be filed on optimized formulations identified during development of a Surge Dose[®] nalmefene tablet.

4.4 Commercial opportunities

Nalmefene is already an established drug administered IV for the treatment of opiate overdose and to reverse opiate induced respiratory depression. It is rapidly and readily absorbed orally and has a good side effect profile with no evidence of abuse potential. With validation of its use in IR treatments to reduce the urge to drink in alcohol dependency, there is an opportunity for a fast acting tablet that will provide consistent and rapid absorption which will drive rapid distribution to the central opioid receptors. Once these receptors are blocked, nalmefene continues to exert its effect for up to 72 hours as a result of its slow dissociation from the receptors.

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5 Conclusion

- ✓ *Surge Dose[®] nalmefene will maximise the rate of dissolution, even under unfavourable conditions, to ensure rapid delivery of dissolved drug to the small intestine to drive absorption and distribution in the CNS*
- ✓ *Surge Dose[®] nalmefene will reduce the variability in T_{max} with more fast absorption profiles with T_{max} values less than 1 h, reducing mean and median T_{max} values*
- ✓ *Surge Dose[®] nalmefene will reduce the variability in C_{max} , reducing the frequency of sub-therapeutic dosing which will improve efficacy*
- ✓ *Surge Dose[®] nalmefene will provide faster onset of action taking advantage of the extended duration of action as a result of strong binding with all three opioid receptors and subsequent slow dissociation*
- ✓ *Surge Dose[®] nalmefene may allow the use of lower doses with further benefits of reduced adverse events*
- ✓ *Surge Dose[®] nalmefene will provide a true 'on demand' presentation without the delays associated with food consumption*