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Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

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Executive Summary

Imaginot Pty Ltd <Imaginot> has a portfolio of three patent families patents covering its Surge Dose[®] technology offering fast dissolution and fast absorption of drugs from swallow tablets. Surge Dose[®] formulations achieve ultra fast activated dissolution under favourable and unfavourable *in vitro* test conditions reflecting the wide range of physiological conditions which exist within the general population. These include gut stasis in migraine and neutral gastric conditions as in patients with impaired gastric function or those taking proton pump inhibitors or antacids. *In vitro*, Surge Dose[®] has been exemplified with more than 30 commonly used drugs including acidic, basic, amphoteric and unionized molecules. *In vivo* fast dissolving Surge Dose[®] formulations of three drugs, paracetamol, lornoxicam and diclofenac, have been shown to result in significantly faster absorption than conventional products.

Published data can provide evidence to assess if faster *in vitro* dissolution is likely to result in faster *in vivo* absorption and faster onset of action. Faster *in vivo* dissolution particularly under less favourable conditions may also lead to reduced inter- and intra-patient variability in absorption seen with many drugs that can result in sub-therapeutic plasma concentrations. Reduced variability can potentially result in increased efficacy.

Physiological basis of Surge Dose[®]

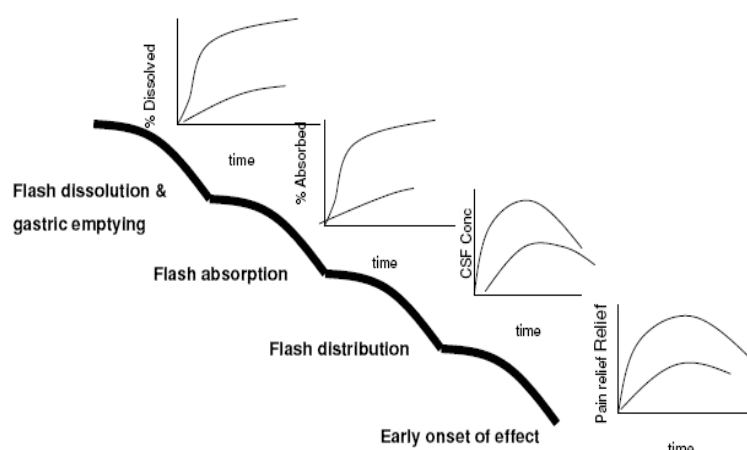
To achieve rapid absorption from a solid dosage form, ultra-fast activated dissolution *in vivo* is essential. This must occur in the limited volume of available fluid in the stomach and the highly variable environment in relation to both pH and gastric motility. **Gastric pH** can vary from highly acidic 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

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

- 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[®] PK proof of concept

Surge Dose[®] formulation technology was developed from *in vivo* PK data with **paracetamol** which is a known marker for liquid gastric emptying. In the proof of concept study, around 70 % subjects experienced slow absorption for the fast release commercial tablet (Tylenol[®] Extra Strength Rapid Release Gels) with a median T_{max} of 45 min and 16 % subjects never reached the minimum therapeutic level of 10 µg/mL. In contrast, two Surge Dose[®] formulations resulted in significantly faster absorption with median T_{max} values of 17 and 25 min and more than 70 % subjects exceeded 10 µg/mL in the first 15 min compared with only 20 % for the commercial tablet. Based on these PK data, PK-PD modelling predicts that ultra-fast dissolving Surge Dose[®] 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[®] formulations and confirmed by the lower NNT (Number Needed to Treat) for 50 % pain relief at 45 min of 2.8 predicted for Surge Dose[®] paracetamol compared with 4.3 for the commercial tablet.

A PK study in 24 fasted subjects with **lornoxiam** 8 mg tablets, further demonstrates the *in vivo* benefits of Surge Dose[®] through maximizing the drug's *in vitro* dissolution rate. The Surge Dose[®] ultra-fast activated dissolution formulation demonstrated significantly reduced T_{max} and increased C_{max} as a result of faster and more consistent absorption compared with a reference commercial tablet:

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

- Absorption from Surge Dose[®] lornoxicam was twice as fast with comparable mean and median T_{max} values of 0.51 and 0.50 h respectively, and individual subject values ranging from 0.3 to 1 h
- Median T_{max} for the reference tablet was 0.83 h with values ranging from 0.5 to 2.3 h with the longer mean T_{max} of 1.06 h indicating more subjects with slow absorption
- With Surge Dose[®] lornoxicam, 75 % subjects 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 administration¹, 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 %)
- $AUC_{0-\infty}$ 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 minutes demonstrated significantly faster absorption with Surge Dose[®] lornoxicam, respectively 3.9, 2.8 and 2.2 times higher than the reference tablet

With optimized Surge Dose[®] **diclofenac** sodium 50 mg tablets, absorption was 4 – 5 times as fast as a dispersible tablet dissolved in water before administration which is promoted for fast pain relief (Voveran[®]-D, Novartis).

- Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (\pm 5.0) and 19.5 min (range 5 – 30 min). Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h).
- Surge Dose[®] resulted in significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. Surge Dose[®] C_{max} values were comparable with those following IV or IM administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets.
- With Surge Dose[®], 76 % subjects had a T_{max} equal to or less than 20 min and 100 % reached T_{max} within 30 min. By comparison only one Voveran[®]-D subject (5 %) had T_{max} equal to or less than 20 min and 3 (18 %) less than 30 min. With

¹ 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

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

Voveran[®]-D, 70 % subjects had to wait at least 1 h to reach T_{max} , with 6 (30 %) waiting at least 2 h.

Overall these data demonstrate increased and more consistent plasma levels which will translate to increased efficacy, and where side effects can limit usage, this may allow dose reduction to reduce side effects without compromising efficacy.

Surge Dose[®] formulation development

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 activated pH-controlled dissolution *in vivo*. Ultra-fast drug dissolution of from Surge Dose[®] formulations is independent of gastric pH or gastric motility at the time of dose.

In vitro dissolution studies on a range of different acidic drugs demonstrate that dissolution rates can be significantly improved compared with existing tablets by use of the Surge Dose[®] activated dissolution technology. *In vitro* dissolution for Surge Dose[®] formulations typically exceed 70 % in 3 min compared with less than 10 % in 30 minutes for commercial tablets in test conditions simulating the fasted state. Even under the most unfavourable *in vitro* test conditions, in the absence of stirring (0 rpm), Surge Dose[®] achieved 80 % dissolution in 3 min demonstrating intrinsic activated dissolution compared with negligible dissolution from conventional tablets.

Formulation optimization is aimed at achieving total dissolution of the drug in available co-administered water and gastric fluids to provide a high concentration gradient for rapid absorption from the small intestine which in turn produce 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 (10 – 20 % 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 an acidic drug have been successfully scaled-up for commercial manufacture using direct compression and wet granulation processing and standard film coating techniques.

Naproxen

Naproxen, an non-steroidal anti-inflammatory drug (NSAID), has analgesic, antipyretic and anti-inflammatory properties and is used in prescription and OTC products for the treatment of acute inflammatory pain, migraine and dysmenorrhoea where fast onset of action is desirable, as well as chronic usage for osteoarthritis, rheumatoid arthritis, and chronic

Application of Surge Dose® ultra-fast dissolution technology to naproxen

inflammatory pain. Brand names include Aleve® (Bayer), Naprosyn®, Naprogesic®, Naprelan® and Anaprox®. Daily doses range from 375 – 1000 mg administered once or twice daily which is an advantage compared with some other NSAIDs because of its long elimination half-life. Effective plasma levels for meaningful pain relief are in the region of 15,000 ng/mL. The gastrotoxicity common to drugs in this class, requires that naproxen be taken with food. It is also available in combination formulations with sumatriptan for migraine, with pseudoephedrine for colds and congestion, and esomeprazole to reduce gastrotoxicity.

Naproxen is a weak acid with a pKa of 4.2, used as the free acid or the more soluble sodium salt. As a weak acid, naproxen solubility is pH dependent with higher solubility at higher pH which results in opposing pH effects on dissolution and absorption. The solubility of naproxen sodium in water at pH 7.8 is 222 mg/mL so a 440 mg dose will dissolve completely in only 2 mL water. The solubility of the free acid naproxen is much lower reaching 1.8 mg/mL at pH 6.5 and 10.3 mg/mL at pH 7.3 still requiring more than 200 mL for complete dissolution of a 400 mg dose at pH 6.5.

Oral solid dosage forms of naproxen demonstrate relatively slow and highly variable absorption. T_{max} values for the less soluble free acid naproxen are in the region of 1 – 2 h whereas the more soluble sodium naproxen is absorbed faster with T_{max} values around 1 h. In both cases, some subjects achieve T_{max} in 0.33 – 0.5 h whereas others demonstrate slow absorption with T_{max} values as late as 3 h. Absorption is further delayed by food with lower C_{max} and T_{max} values as late as 12 h. It is likely that this variable and delayed absorption is a function of slow and variable *in vivo* dissolution. Onset of action is also variable, but analgesia is reported as early as 30 min post dose which is consistent with achievement of effective plasma levels of 15,000 ng/mL in reported PK studies.

Sodium naproxen formulations have largely replaced naproxen products in order to provide faster absorption and faster onset of action. More recently liquid filled soft gelatine capsules have been introduced as an improved next generation oral dosage form, positioned for fast onset of action. However PK studies indicate that these liquid filled capsules result in slower absorption than existing Aleve® tablets of sodium naproxen particularly in the fed state.

Surge Dose® Naproxen

This review considers naproxen as a candidate for the application of Imaginot's Surge Dose® technology to increase this drug's rate of dissolution and absorption with the potential for improved clinical outcomes. Naproxen is exemplified in Imaginot patent WO/2007/059591 and is covered by claims relating to acidic molecules. The rationale is

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

presented here for an ultra-fast active-dissolving Surge Dose[®] naproxen which is expected to provide improved clinical outcomes. Advantages over existing products include:

- reduced time to peak plasma concentrations in fed as well as fasted conditions,
- faster onset of action, and
- reduced potential for gastrotoxicity.

The Surge Dose[®] technology could also be applied to combination products containing naproxen with fast absorption of both actives.

Although lower solubility at low pH will not favour dissolution, a higher proportion of the more readily absorbed ionized species is present providing a higher driving force for absorption. For NSAIDs such as naproxen this is undesirable as gastric absorption results in local toxicity. Conversely higher pH such as produced by Surge Dose[®] formulations of acidic drugs, increases the proportion of less readily absorbed ionized species reducing the potential for absorption. This will minimise local gastric damage in the stomach and favour faster dissolution. As naproxen is a highly permeable drug, the effects of increased solubility at higher pH should outweigh any effects of reduced levels of the more permeable unionized species which exist in equilibrium with the ionized form. As unionized species are absorbed from the small intestine, the equilibrium will be maintained.

As raw material was not available, preliminary screening of naproxen used reformulated commercial tablets, Naprosyn[®] (film coated 250 mg naproxen) and Naprogesic[®] (uncoated 275 mg naproxen sodium). Surge Dose[®] formulations demonstrate that the extent and rate of *in vitro* dissolution of both forms of drug can be significantly increased.

Naprosyn[®] and Naprogesic[®] tablets show slow and limited dissolution in 900 mL 0.0033 M HCl containing 3 millimoles of acid, using USP apparatus 2 at 30 rpm and 37 °C, achieving less than 20% dissolution in the first 20 min. For formulations containing 400 - 500 mg bicarbonate, significantly faster and more extensive dissolution can be achieved for both naproxen and naproxen sodium, reaching around 80 and 40 % dissolution respectively in 3 min and increasing the pH of the dissolution medium to 6.2 – 6.4. Addition of an organic acid to the bicarbonate with sodium naproxen shows the fastest dissolution at 0 rpm exceeding 80 % in 3 min. Results at both 30 and 0 rpm indicate faster dissolution with naproxen than with sodium naproxen highlighting the importance of the reaction between bicarbonate and the free acid naproxen in maximising dissolution. Further formulation optimization and process development will be required to maximize dissolution under a range of *in vitro* test conditions simulating adverse physiological conditions.

Conclusion

Based on this review, it is expected that a Surge Dose[®] naproxen tablet will provide faster *in vivo* dissolution which will drive faster absorption and faster onset of action than conventional solid dosage forms. Faster and more consistent absorption will reduce inter- and intra-subject variability which will reduce the time to onset of action.

Improved consistency of absorption may also improve efficacy by reducing sub-therapeutic C_{\max} occasions below 15,000 ng/mL particularly in the fed state where mean C_{\max} values for a 440 mg dose of sodium naproxen are only around 30 % above effective plasma levels.

Surge Dose[®] naproxen tablets would be expected to reduce mean T_{\max} values from around 2 h for naproxen and around 1 h for sodium naproxen, to closer to 0.5 h with a higher frequency of fast absorption occasions.

In turn improved PK lead to improved clinical outcomes with faster onset of action and the potential to reduce doses without compromising efficacy to reduce the potential for gastrotoxicity particularly important for chronic usage

Table of Contents

Executive Summary

1	INTRODUCTION	1
1.1	Surge Dose [®] drug delivery technology	1
1.2	IP status	1
1.3	Technical strategy	2
1.4	Commercialization.....	3
2	CLINICAL PREMISE FOR SURGE DOSE[®]	4
2.1	Clinical rationale.....	4
2.2	Key sources of physiological variability affecting drug absorption	6
2.2.1	Gastrointestinal (GI) motility	6
2.2.2	Gastric pH	8
2.3	Proof of concept	9
2.3.1	Paracetamol.....	9
2.3.2	Lornoxicam	10
2.3.3	Diclofenac	11
3	NAPROXEN.....	12
3.1	Physicochemical properties.....	12
3.2	Marketed products	13
3.3	Pharmacokinetics (PK)	13
3.4	Pharmacodynamics (PD)	16
4	SURGE DOSE[®] NAPROXEN.....	17
4.1	Clinical considerations	17
4.2	Technical considerations	18
4.3	Development & manufacturing considerations.....	20
4.3	IP considerations.....	21
4.4	Competitive positioning.....	23
5	CONCLUSIONS	23
	APPENDIX 1 SURGE DOSE[®] NAPROXEN FORMULATIONS.....	25
A1.1	Naproxen sodium tablets.....	25
A1.2	Naproxen tablets.....	25
A1.3	Methods	25

1 Introduction

1.1 Surge Dose[®] drug delivery technology

The Surge Dose[®] formulation technology for ultra-fast dissolution and fast absorption of oral drugs has been developed by Imaginot Pty Ltd <Imaginot>, a privately owned drug delivery company based in Queensland, Australia. Surge Dose[®] formulations provide faster and more consistent drug 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}) and reduces absorption variability as demonstrated for paracetamol (acetaminophen, APAP) and lornoxicam in pharmacokinetic (PK) studies in man. Based on PK-PD (pharmacodynamic) modelling, Surge Dose[®] 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 in some patients.

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

- a clinical requirement for fast and reproducible onset of action when taken on demand for acute episodic indications
- high passive absorption without significant intestinal metabolism or active efflux
- evidence of variable absorption associated with 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 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, 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 filed on 13 May 2005. Claims have now been limited to cover only acidic and unionized drugs. This patent has been granted in Australia and expedited examination is progressing in the US under the PPH and in Japan.

- ii. PCT/AU 2005/00759 published as WO/2005/115345 covering basic and amphoteric actives claiming priority from 28 May 2004. A clean ISR report was issued in Europe. Patents have been granted in Australia and Canada without limitation and examination is progressing in Europe, India, Japan and the US.
- iii. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations. This patent has been granted in Australia, Canada and US and assigned to a third party in Australia, Europe, India and Japan.

Patents are based on *in vitro* dissolution and *in vivo* PK results for paracetamol 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 and water uptake agents for each drug or drug combination to provide an activated dissolution system which will maximize the extent and rate of dissolution as demonstrated by *in vitro* testing.

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

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

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

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 prepared by direct compression or wet granulation, and so do 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 10 - 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 such as USP dissolution apparatus II with paddles using 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, containing the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo*, is the dissolution medium 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 delivery company (Ethypharm SA), one of India's largest pharmaceutical companies (Abbott Healthcare Pvt Ltd). Imaginot has an agreement with Piramal Healthcare Ltd. in India for the contract development and manufacture of Surge Dose[®] formulations. Piramal can undertake

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

formulation optimisation, scale, up, stability studies and Phase I studies comparing a Surge Dose[®] formulation to an existing formulation to demonstrate the improved kinetics, at low cost for companies interested in exploring the use of the Surge Dose[®] technology for their drugs.

A number of Surge Dose[®] formulations have been developed which demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low RH conditions, with the first Surge Dose[®] product, lornoxicam 4 and 8 mg launched in 2011 and a second product to be launched late 2012. Additional drugs are under development with formulation and process optimization in progress.

2 Clinical premise for Surge Dose[®]

2.1 Clinical rationale

Drug absorption following oral administration is influenced by:

- i. the rate at which the drug will dissolve from the dosage form into available fluids in the stomach including any co-administered liquid,
- ii. the underlying GI motility or phase of the MMC (migrating motor complex) 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 respectively².

To maximize the rate of absorption, complete dissolution of the drug from a solid dosage form into the co-administered liquid and gastric contents is required. This allows the total dose of drug in solution to reach the small intestine quickly independent of gastric motility. Total

² 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

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

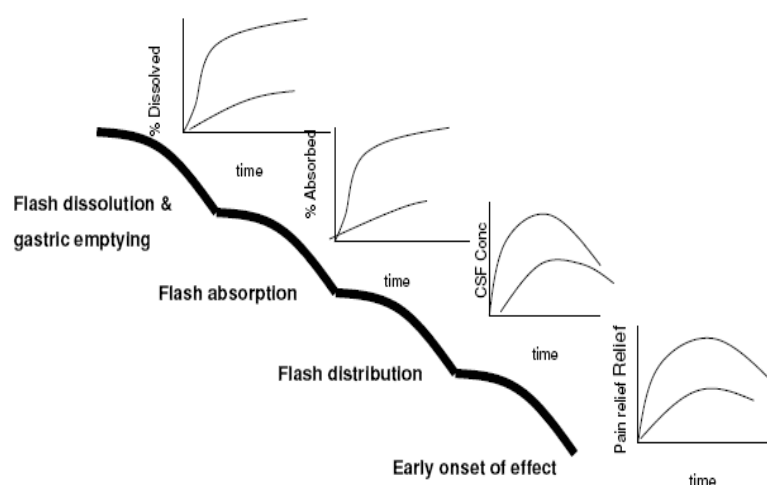
dissolution of the drug provides the maximum concentration to drive absorption and distribution to the effect compartment by passive diffusion.

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 (C_{max}). 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[®] 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. In summary, ultra-fast active-dissolving Surge Dose[®] formulations produce the following cascade of effects which are summarized in Figure 1:

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



- i. The drug undergoes ultra-fast activated dissolution in the co-administered water and available gastric contents
- ii. 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
- 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 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
- v. High plasma concentrations drive rapid distribution to the effect compartment resulting in rapid onset of action and rapid peak effect

2.2 Key sources of physiological variability affecting drug absorption

2.2.1 Gastrointestinal (GI) motility

The underlying MMC influences 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. MMC effects are 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 food which generally triggers Phase I MMC³.

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

Gastric emptying effects are responsible for the double or multiple absorption peaks often seen in individual subject PK profiles particularly when there is sufficiently frequent sampling. Multiple gastric emptying peaks occurring during the first two hours differ from later peaks due

³ Rees WD, Go VL, Malagelada JR. Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. *Gut* (1979) **20** (Nov):963-970

to entero-hepatic recycling. They are frequently associated with longer T_{\max} values and have been reported for many drugs including the NSAID diclofenac^{4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14}.

In late Phase II or Phase III, fast absorption will occur as the gastric contents are rapidly emptied into the small intestine resulting in a short T_{\max} . However, in Phase I or early Phase II, there will be slower absorption with a high T_{\max} . When subjects are in Phase I or II, there is fast absorption of any dissolved drug that drains passively from the stomach followed by a later absorption phase when remaining gastric contents are emptied by Phase III MMC. This includes any dissolved drug retained in the mucosal folds of the stomach as well as any tablet fragments and undissolved drug particles. The amount of dissolved drug in the initial

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- ⁴ Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Szelenyi I, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* (2005) **59**:80-84
 - ⁵ Mummaneni V, Amidon GL, Dressman JB. Gastric pH influences the appearance of double peaks in the plasma concentration-time profiles of cimetidine after oral administration in dogs *Pharm Res* (1995) **12**(5):780-786
 - ⁶ Metsugi Y, Miyaji Y, Ogawara K, Higaki K, Kimura T. Appearance of double peaks in plasma concentration-time profile after oral administration depends on gastric emptying profile and weight function. *Pharm Res* (2008) **25**(4):886-95
 - ⁷ Yin OQ, Tomlinson B, Chow AH, Chow MS. A modified two-portion absorption model to describe double-peak absorption profiles of ranitidine. *Clin Pharmacokinet* (2003) **42**(2):179-92
 - ⁸ Takamatsu N, Welage LS, Hayashi Y, Yamamoto R, Barnett JL, Shah VP, Lesko LJ, Ramachandran C, Amidon GL. Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility. [erratum appears in *Eur J Pharm Biopharm* (2002) 54(2):255]. *Eur J Pharm Biopharm* (2002) **53**(1):37-47
 - ⁹ Marathe PH, Sandefer EP, Kollia GE, Greene DS, Barbhuiya RH, Lipper RA, Page RC, Doll WJ, Ryo UY, Digenis GA. In vivo evaluation of the absorption and gastrointestinal transit of avitriptan in fed and fasted subjects using gamma scintigraphy. *J Pharmacokinet Biopharm* (1998) **26**(1):1-20
 - ¹⁰ Langguth P, Lee KM, Spahn-Langguth H, Amidon GL. Variable gastric emptying and discontinuities in drug absorption profiles: dependence of rates and extent of cimetidine absorption on motility phase and pH. *Biopharm Drug Dispos* (1994) **15**(9):719-46
 - ¹¹ Charman WN, Rogge MC, Boddy AW, Barr WH, Berger BM. Absorption of danazol after administration to different sites of the gastrointestinal tract and the relationship to single- and double-peak phenomena in the plasma profiles. *J Clin Pharmacol* (1993) **33**(12):1207-13
 - ¹² Suttle AB, Pollack GM, Brouwer KL. Use of a pharmacokinetic model incorporating discontinuous gastrointestinal absorption to examine the occurrence of double peaks in oral concentration-time profiles. *Pharm Res* (1992) **9**(3):350-6
 - ¹³ Oberle RL, Amidon GL. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J Pharmacokinet Biopharm* (1987) **15**(5):529-44
 - ¹⁴ Lunell E, Andersson KE, Borga O, Fagerstrom PO, Johannesson N, Kjellin G, Persson CG, Sjölund K. Absorption of enprofylline from the gastrointestinal tract in healthy subjects. *Eur J Clin Pharmacol* (1984) **27**(3):329-33

absorption phase and the relative sizes of these peaks will depend on its solubility and the dissolution characteristics of the dosage form.

In addition to the MMC, 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 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 activity

2.2.2 Gastric pH

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

- A significant proportion of the population has low gastric acidity such as those with achlorhydria where gastric pH does not drop below pH 4, and hypochlorhydria which affects up to 50 % of the population increasing with age or pathology such as diabetes mellitus and autoimmune conditions.
- Patients taking 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.

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. Conversely, 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 and absorption of an orally administered drug depending on its physicochemical properties. Increased solubility

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

increases the amount of drug that will dissolve in the co-administered water before it empties from the stomach, and this increases the dissolution rate. Conversely reduced solubility will slow the rate of dissolution with less drug dissolved and emptied into the small intestine with any co-administered water.

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

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

2.3 Proof of concept

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[®] 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.

2.3.1 Paracetamol

Data from a proof of concept Phase I study in 25 fasted healthy subjects¹⁵ demonstrated significantly faster absorption with two fast dissolving Surge Dose[®] paracetamol formulations compared with a rapid release commercial product (Tylenol[®] Extra Strength Rapid Release Gels). This study showed good *in vitro in vivo* correlations (IVIVC). Noting that the Surge Dose[®] formulations in this study have subsequently been improved:

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

¹⁵ Hooper WD. The Comparative Pharmacokinetics of Paracetamol Formulations IM0401, (2005) QPharm, Imaginot Pty Ltd, Brisbane

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

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[®] paracetamol tablets¹⁶.

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 further PK study in 24 fasted subjects with the acidic non-steroidal anti-inflammatory drug (NSAID) lornoxicam, has also demonstrated the benefits of Surge Dose[®] applied to an 8 mg tablet to maximise the drug's *in vitro* dissolution rate. The Surge Dose[®] ultra-fast activated dissolution significantly reduced T_{max} and resulted in significantly higher C_{max} levels similar to those following parenteral administration¹⁷. Absorption from Surge Dose[®] lornoxicam was twice as fast compared with the commercial reference product and the faster and more consistent absorption has the potential to improve efficacy:

- 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

¹⁶ 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

¹⁷ 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

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

- 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 %)
- $AUC_{0-\infty}$ 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 demonstrate significantly faster absorption with Surge Dose[®] lornoxicam, respectively 3.9, 2.8 and 2.2 times higher than those for the reference tablet

2.3.3 Diclofenac

An optimized film coated Surge Dose[®] diclofenac sodium 50 mg tablet was compared with Voveran[®]-D (Novartis), a dispersible tablet dissolved in water before administration containing 46.5 mg diclofenac free acid equivalent to 50 mg diclofenac sodium. Despite the marketing of the Voveran[®]-D dispersible tablets for fast pain relief, this dispersed product showed slow absorption, low C_{max} and multiple peaks indicating that gastric emptying was absorption rate limiting. Although some dissolved drug emptied into the small intestine and was quickly available for absorption, a significant proportion of each dose was retained in the stomach until emptied during Phase III MMC.

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

- Mean and median T_{max} values were similar for Surge Dose[®] tablets 19.5 min (\pm 5.0) and 19.5 min (range 5 – 30 min) indicating fewer slow absorption profiles with a high T_{max} . Voveran[®]-D showed much slower and more variable absorption with a median T_{max} of 1.5 h (range 15 min – 4 h) indicating a tail of slow absorption profiles.
- Surge Dose[®] produced significantly higher C_{max} values, reaching $3,569 \pm 1,515$ ng/mL compared with $1,042 \pm 518$ ng/mL for Voveran[®]-D. Surge Dose[®] C_{max} values were comparable with those obtained following IV^{18,19} or IM^{20,21} administration whereas

¹⁸ 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

¹⁹ 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

²⁰ 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

those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets²².

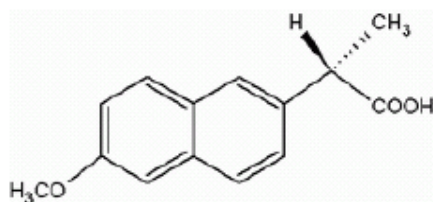
- With Surge Dose[®], 76 % subjects had a T_{max} equal to or less than 20 min and 100 % reached T_{max} within 30 min. By comparison only one Voveran[®]-D subject (5 %) had T_{max} equal to or less than 20 min and 3 (18 %) less than 30 min. With Voveran[®]-D, 70 % subjects had to wait at least 1 h to reach T_{max} , with 6 (30 %) waiting at least 2 h.

3 Naproxen

3.1 Physicochemical properties

Naproxen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) with a pKa of 4.2 with the chemical structure shown in Figure 2.

Figure 2 Chemical structure of naproxen



It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. Additionally it is used for acute episodic indications such as dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever, where rapid relief of symptoms will provide a clinical advantage.

Naproxen is usually given by mouth as the free acid or sodium salt, both of which are readily absorbed from the gastrointestinal tract, at daily doses of 375 – 1,000 mg.. The solubility of the naproxen sodium in water at pH 7.8 is 222 mg/mL which means that a 400 mg dose can completely dissolve in 2 mL water. In contrast the solubility of the free acid naproxen is much lower and is pH dependent with very low solubility in acidic conditions, increasing to 1.8 mg/mL at pH 6.5 and 10.3 mg/mL at pH 7.3. However at pH 6.5, around 222 mL will be required for complete dissolution of a 400 mg dose of naproxen. This suggests that naproxen is more likely to demonstrate solubility limited dissolution *in vivo* which in turn will lead to slower and more variable absorption.

²¹ 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

²² 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

3.2 Marketed products

Naproxen and its more soluble sodium salt are available as prescription and over-the-counter products in a wide range of different oral dosage forms including immediate and delayed release and enteric coated tablets, capsules, liquid filled soft gelatine capsules and suspensions. Common brands are Aleve[®] (Bayer), Anaprox[®], Naprogesic[®], Naprosyn[®] (Roche Products) and Naprelan[®] (Elan Corp), with many generic versions available.

Naproxen is also used in combination products with sumatriptan succinate for migraine (Treximet[®], GSK), with esomeprazole for reduced adverse gastro-intestinal effects (Vimovo[®], AstraZeneca) and pseudoephedrine.

3.3 Pharmacokinetics (PK)

A review undertaken by an independent CRO concluded that naproxen is a suitable candidate for the application of Surge Dose[®] technology to increase the rate of absorption compared with existing products with a resultant faster onset of action²³. The following key points support their conclusions:

- Naproxen has high oral bioavailability of 100 % being absorbed from the small intestine by passive diffusion and readily distributed into synovial fluid and joints.
- At therapeutic concentrations, naproxen is more than 99% bound to plasma proteins exhibiting concentration-dependent binding. Plasma concentrations increase proportionally with doses up to 500 mg daily with an increase in renal clearance at higher doses caused by saturation of plasma proteins.
- Naproxen has a long mean plasma elimination half-life ($t_{1/2}$) of 14 - 15 h which is highly variable (10 – 30 h) and allows once or twice daily dosing.
- Time to peak plasma concentrations (T_{max}) shows high variability between subjects ranging from 0.5 to 2.5 h for naproxen in fasted subjects (mean 1.5 h \pm SD 0.68)²⁴. There is also evidence of intra-subject variability²⁵.
- Despite wide variability, the more soluble naproxen sodium is absorbed faster with mean T_{max} values around 1 – 2 h compared with around 2 h for the free acid.

²³ Tetra Q IMG01-FR-Part 5 Physiochemical properties, pharmacokinetics and pharmacodynamics of naproxen in humans. 30 June 2006

²⁴ Vree TB, Van den Biggelaar-Martens M, Verwey-Van Wissen CPWGM, Vree JB, Guelen PJM. Pharmacokinetics of naproxen, its metabolite o-desmethylnaproxen, and their acyl glucuronides in humans. *Biopharm Drug Dispos* (1993) **14**:491-502

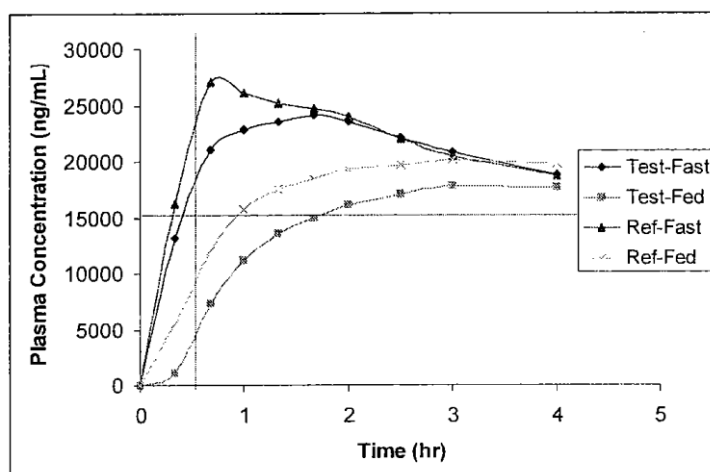
²⁵ Aarbakke J, Gadeholt G, Hoylandskjaer A. Pharmacokinetics of naproxen after oral administration of two tablet formulations in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* (1983) **21**(6):281-3

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

- When naproxen 250 mg was administered to fasted children as a liquid suspension containing 25 mg/mL, T_{max} values were 0.67 – 7.97 h (mean 2.16 h \pm SD 2.11) compared with 1.0 to 8.00 h (mean 2.67 h \pm SD 2.01) for a tablet²⁶. Although the suspension does not require time for *in vivo* disintegration, the free acid has low solubility in acidic gastric contents which would be expected to result in slow *in vivo* dissolution and absorption. Small volumes also have the potential to be retained in the gastric mucosal folds delaying gastric emptying and slowing absorption.
- Food reduces the rate of absorption delaying mean T_{max} from ~ 2 h to 2 – 4 h. Delays in mean T_{max} from ~ 2 h to ~ 3 h have been reported during migraine attacks which are associated with gut stasis.

More detailed PK data on the first liquid filled soft gelatine capsule approved in the US highlight the slow and variable absorption seen with existing products, where ultra-fast dissolving Surge Dose[®] tablets could offer significantly improved absorption. This dosage form was registered following a 505(b)(2) submission²⁷ with two bioequivalence studies in 30 healthy fasted and fed subjects comparing the new dosage form to Aleve[®] tablets (Bayer)²⁸. Both products contained 220 mg naproxen sodium. In the soft gelatine capsule, the drug was solubilized with lactic acid, propylene glycol, povidone and polyethylene. Mean PK profiles are shown in Figure 3 and PK data summarized in Table 1.

Figure 3 Comparative PK profiles for 440 mg doses of naproxen sodium administered as soft gelatine capsules (test) and tablets (ref) under fasted and fed conditions (from ANDA #21-929)



²⁶ Wells TG, Mortensen ME, Dietrich A, Walson PD, Blasier RD, Kearns GL. Comparison of the pharmacokinetics of naproxen tablets and suspension in children. *J Clin Pharmacol* (1994) **34**:30-33

²⁷ NDA #21-920 Naproxen sodium soft gelatine capsules, Banner Pharm Inc

²⁸ NDA #20-204 Aleve[®] tablets, Bayer

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

Table 1 Key PK parameters for naproxen sodium 440 mg administered as liquid filled soft gelatine capsules and Aleve[®] tablets under fasted and fed conditions (from ANDA #21-929)

Parameter	Fasted		Fed	
Product	Soft gel	Aleve [®]	Soft gel	Aleve [®]
Mean T _{max} (h)	1.42	0.99	3.7	2.5
CV %	55.5	47.1	78.7	63.2
Median T _{max} (h)	1.33	0.67	3	2
Min T _{max} (h)	0.33	0.33	1	0.67
Max T _{max} (h)	3	2	12	8
C _{max} (ng/mL)	53,625	57,210	21,719	24,499
CV %	19.1	12.6	28.6	18.1
AUC _{inf} (ng.h/mL)	830,462	830,822	444,744	451,526
CV %	16.4	20.8	19.8	19.9

Overall while the capsule met the AUC and C_{max} bioequivalence criteria in the fasted state, C_{max} was below the lower limit of 80 – 125 % in the fed state. Notably absorption was much slower from the soft gelatine capsule in both fasted and fed states, and food appeared to have a much greater slowing effect on the capsule. A high degree of absorption variability was evident for both products which was greater in the fed state.

These data indicate that the liquid filled capsules do not offer any advantage of faster absorption compared to the existing Aleve[®] tablets, and that slow absorption occasions lead to lower C_{max} levels particularly in the fed state. Longer mean T_{max} compared with median T_{max} indicates a non-parametric distribution with a tail of slow absorption occasions. In the fasted state, both products show some T_{max} values as fast as 0.33 h indicative of fast absorption occasions associated with high MMC activity in the stomach. The maximum T_{max} values indicate cases of slow absorption that suggest delayed *in vivo* dissolution. This is greater for the capsules where rupture of the shell needs to occur before the drug can be released to mix with gastric contents and pass into the small intestine for absorption. For tablets, *in vivo* dissolution commences as soon as any film coat ruptures allowing disintegration of the tablet and dissolution of the drug.

Delayed absorption with the capsules is more evident in the fed state indicating that gastric motility plays a key role in the *in vivo* release of the drug from this dosage form. Food triggers Phase I MMC, so the soft gelatine capsule is likely to be retained in the stomach with the food. Delayed rupture of the capsule means that the dissolved drug inside the capsule cannot mix with and drain from the stomach with any co-administered water. This results in longer T_{max} values which are highly dependent on gastric emptying. In contrast, early disintegration of the

tablet allows drug to start dissolving in available liquids which will readily empty from the stomach allowing earlier absorption.

These results highlight the potential to increase the rate and extent of dissolution for naproxen sodium in order to achieve a higher distribution of T_{max} values in the region of 0.33 h in the fasted state. In turn, this will reduce both mean and median values reducing the difference as the distribution of T_{max} values becomes less skewed with fewer slow absorption occasions. More fast absorption occasions which will be associated with higher C_{max} values would be expected to increase mean C_{max} overall. A similar effect would be expected in the fed state but an ultra-fast dissolution product would still produce more faster absorption occasions than seen with Aleve[®] tablets as a higher proportion of the dose will dissolve in available water.

In the NDA, *in vitro* dissolution conditions and specifications as well as most data are redacted. However based on unredacted data, Aleve[®] tablets achieve 95 % dissolution in 15 min and 101 % in 30 min. Dissolution from the capsules is slower under the same conditions, reaching 59 %, 77 %, 88 % and 92 % at 15, 30, 45 and 60 minutes respectively. These differences under test conditions that favour dissolution to a greater extent than those used by Imaginot are reflected in reported PK data.

3.4 Pharmacodynamics (PD)

In considering the impact of the slower absorption of the liquid filled capsule, it was noted that 15,000 ng/mL is the effective plasma concentration of naproxen for meaningful pain relief²⁹. Allowing for the use of 440 mg sodium naproxen in the PK study, such levels were achieved in around 30 minutes for each product so the slower absorption was not considered to be clinically significant. While this might be so in the fasted state where C_{max} values were around 3 - 4 times the effective level, the margin for efficacy is much lower in the fed state where C_{max} values are only around 30 % higher.

Most PD studies published to date report clinical efficacy of sodium naproxen compared with placebo rather than other forms of naproxen. The NNT for oral naproxen sodium 550 mg in post surgical pain with at least 50 % pain relief over 4 – 6 h is ~ 2.6 and in dysmenorrhoea ~ 3 for 50 % pain relief at 6, 8 and 12 h post dose.

Although no NNT data have been found for earlier relief end points, onset of action has been reported as early as 30 minutes, generally within the range 0.5 – 2 hours which is consistent with absorption profiles:

- In migraine, 8 % of patients reported relief at 30 min, 27 % at 1 h and 46 % at 2 h following oral administration of 550 mg naproxen sodium,

²⁹ NDA #21-920 Naproxen sodium soft gelatine capsules, Banner Pharm Inc

- Pain relief from 550 mg sodium naproxen was superior to placebo by 1 h and remained at the 12 h test point in primary dysmenorrhoea
- In moderate to severe acute pain associated with surgical dental extractions, the median time to onset of analgesia was ~ 30 min for naproxen sodium 550 mg compared with > 4 h for placebo. The median time of 20.8 h to rescue medication was consistent with the long mean plasma elimination half-life ($t_{1/2}$) of 14 - 15 h which is highly variable (10 – 30 h).
- After hip or knee replacement surgery, the median time to onset of analgesia was 1.4 h for 1100 mg naproxen sodium compared with > 4 h for placebo

4 Surge Dose[®] naproxen

Based on this analysis of the physicochemical properties and published PK and PD data, naproxen appears to be a good candidate for a new fast-dissolving fast-absorbed tablet formulation using Imaginot's Surge Dose[®] technology.

4.1 Clinical considerations

The wide range of T_{max} values from 0.33 – 3 h for commercial naproxen and sodium naproxen products indicates significant scope for an improved oral tablet with faster and more consistent absorption. Based on PK data in fasted subjects for Surge Dose[®] lornoxicam, another acidic NSAID, a Surge Dose[®] naproxen tablet would be expected to achieve mean and median T_{max} values in the region of 0.5 h with a correspondingly faster and more consistent onset of action. The reference lornoxicam had a mean and median T_{max} of 1 and 0.8 h respectively, similar to values reported for existing naproxen products.

More consistent faster absorption would be expected to increase C_{max} values towards the high end of the range which has the potential to allow reduce dosage for a comparable clinical effect. In the fasted state, peak plasma levels following a 440 mg dose of naproxen sodium were more than 300 % greater than effective plasma levels of 15,000 ng/mL.

The potential for gastrotoxicity of NSAIDs such as naproxen is well recognised requiring the drug to be taken with food which significantly slows absorption and reduces the AUC, reducing C_{max} values to around 40 % of those in the fasted state.

Although gastrotoxicity may still result from systemic effects on chronic dosing, Surge Dose[®] naproxen has the potential to reduce local effects on the gastric mucosa through reduced contact time. This results from faster gastric emptying of dissolved drug, a high degree of ionisation of dissolved drug at higher pH which form is less favourable to local absorption into gastric mucosal cells, and less undissolved drug that will cause local erosion.

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

Faster *in vivo* dissolution with Surge Dose[®] naproxen is likely to lead to faster absorption in the fed state as well as the fasted state which is important for naproxen taken with food to reduce gastrotoxicity. As the margin between peak plasma levels and effective plasma levels is much lower in the fed state, a Surge Dose[®] naproxen potentially offers higher and more consistent efficacy under normal conditions of use.

Thus Surge Dose[®] naproxen offers the potential for improved clinical outcomes through:

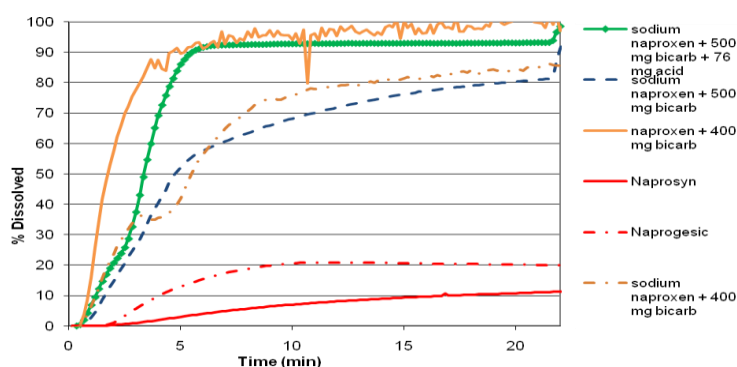
- Faster onset of action
- More consistent onset of action even after food
- Reduced gastrotoxicity

4.2 Technical considerations

Limited preliminary work conducted by Imaginot demonstrates that Surge Dose[®] technology significantly increases the rate and extent of naproxen dissolution. As no raw materials were available, commercial tablets were reformulated with sodium bicarbonate and citric acid anhydrous as pH modulating agents, microcrystalline cellulose as a direct compression aid, and croscarmellose sodium or crospovidone as disintegrants. Appendix 1 details formulations and methods. Dissolution profiles were determined in USP dissolution apparatus II using 900 mL 0.0033 M HCl at 37 °C and 30 rpm or 0 rpm.

Figure 4 shows the increase in dissolution that can be achieved with naproxen free acid or naproxen sodium by the addition of sodium bicarbonate with and without an organic acid compared with Naprosyn[®] (naproxen) and Naprogesic[®] (sodium naproxen) tablets.

Figure 4 Dissolution profiles for naproxen and sodium naproxen tablets in 900 mL 0.0033 M HCl at 30 rpm



Both commercial tablets show quite slow dissolution, with the more soluble sodium naproxen in Naprogesic[®] reaching higher levels around 20 % dissolution.

The addition of sodium bicarbonate to both forms of naproxen increases the pH of the solution to above pH 6 as well as providing effervescence that creates local agitation around

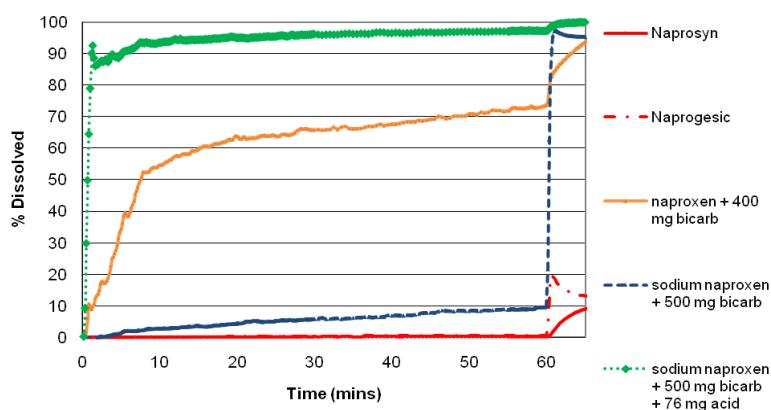
Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

the dissolving particles increasing the dissolution rate. However it is notable that dissolution of the formulation using naproxen free acid with only 400 mg sodium bicarbonate was much faster than when the more soluble sodium salt was used. Increasing the level of sodium bicarbonate to 500 mg with sodium naproxen did not produce a significant increase in dissolution despite the increased effervescence and the higher final pH (pH 6.4 versus pH 6.2). Naproxen with 400 mg sodium bicarbonate exceeded 80 % dissolution in 3 min under these test conditions compared with less than 5 % dissolution for the commercial naproxen product, and around 10 % for the more soluble faster dissolving commercial sodium naproxen tablets.

Although the addition of anhydrous citric acid enhanced the dissolution of sodium naproxen compared with sodium bicarbonate alone, the dissolution was still less than that found with the free acid naproxen and a lower level of bicarbonate.

Figure 5 shows the increase in intrinsic activated dissolution that can be achieved in the absence of any external stirring (0 rpm) highlighting and magnifying the differences seen between formulations containing the free acid or the more soluble sodium naproxen. The stirring speed was increased at 60 min to maximize dissolution.

Figure 5 Comparative dissolution profiles for naproxen and naproxen sodium tablets in 900 mL 0.0033 M HCl at 0 rpm



Both commercial products show negligible dissolution at 0 rpm, although the increased levels for Naprogesic[®] when the stirring speed increased after 60 min reflects the higher solubility of the sodium naproxen compared with the free acid. The final pH of the dissolution medium for both these products was 2.3 for Naprosyn[®] and 2.5 for Naprogesic[®].

Under no stir conditions simulating gut stasis in migraine, 500 mg sodium bicarbonate with 76 mg anhydrous citric acid formulated with sodium naproxen demonstrated the fastest dissolution exceeding 80 % in the first 3 minutes. Sodium naproxen formulated with 500 mg bicarbonate showed much slower dissolution than naproxen formulated with only 400 mg

bicarbonate. These results confirm the earlier results at 30 rpm, highlighting the importance of the reaction between the acidic drug and the sodium bicarbonate to produce intrinsic effervescence and mixing in the vicinity of the dissolving drug particles. This does not occur with the neutral sodium salt which per se will not react with the bicarbonate.

Under no stir conditions, the difference in final pH was greater for the formulation with 400 mg (pH 5.9) compared with 500 mg bicarbonate (pH 6.7) which suggests there was some undissolved bicarbonate. This further highlights the importance of the drug – bicarbonate reaction as dissolution is faster in the medium with the lower pH than in the higher pH. As naproxen solubility increases with increasing pH, higher solubility and faster dissolution would be expected at higher pH.

Overall preliminary results with naproxen suggest that the free acid dissolves faster with lower amounts of bicarbonate compared with the sodium salt, and the addition of a low level of organic acid ensures ultra-fast dissolution under no stir conditions and at high pH.

4.3 Development & manufacturing considerations

Formulation development and stability testing will be required to optimize formulations for maximum dissolution under simulated adverse physiological conditions. The direct compression formulations provided in Appendix 1 provide a good starting point. Recognising the need to keep the tablet weight as low as possible for ease of swallowing, preliminary work suggests that the free acid naproxen should be used for initial formulation optimization, with levels of 300 – 600 mg sodium bicarbonate to identify those with the fastest and most extensive dissolution. Then the effect of different amounts of an organic acid such as anhydrous citric acid should be assessed and the best combination selected. Different alkaline and acid components can then be evaluated as well as the effect of other excipients such as disintegrants and binders.

Once optimum formulation parameters have been established for naproxen free acid, the effect of using more soluble salts can be investigated as well as different particle size distributions.

If wet granulation is required to achieve satisfactory mixing and content uniformity, then alcoholic or hydro-alcoholic granulating solutions should be investigated.

Film coating of the final tablets can be conducted, optimizing conditions and components to have negligible impact of the dissolution performance and stability of the tablets.

Although formulation development can be undertaken in air-conditioned laboratories at ambient relative humidity (RH), controlled low RH around 10 - 20 % will be required for manufacture and packaging. Process development will be required to determine the

sensitivity of the formulations to manufacturing RH and moisture content of excipients and powder blends.

With appropriate manufacturing conditions and unit packaging, a minimum shelf life of 2 years should be achievable.

4.3 IP considerations

Naproxen is a weak acid exemplified in Imaginot patent WO/2007/059591 covered by the claims for acidic drugs. Dissolution limits in 900 mL 0.0033 M HCl at 37 °C are at least 50 % within 300 sec at 30 rpm and at least 5 % in 30 min at 0 rpm. Example 5 shows naproxen formulations within the scope of the claims achieved 90 % dissolution in 300 sec at 30 rpm compared with only 3 % for a commercial tablet. Example 6 for naproxen sodium shows 86 % dissolution in 300 sec compared with 13 % for a commercial tablet. Note these acidic conditions and low stirring rate are not highly favourable to dissolution, and the formulations disclosed show at least 600 % faster dissolution than the corresponding commercial product.

While a comprehensive search has not been undertaken, there are many naproxen patents, some of which target improved dissolution and absorption rates. Key patents which include the use of alkaline agents include:

- **WO 2005/041938, US 2007/0134317, EP 1684728** (Bayer Consumer Healthcare, priority 30 Oct 2003) cover non-effervescent swallow tablet formulations of specifically sodium naproxen 30 – 99 % by weight with 1 – 70 % by weight of an excipient comprising at least one basic agent such as sodium bicarbonate. Key features of these formulations are a relatively small tablet of 300 – 400 mg total weight with good compressibility given the high content of drug and fast disintegration and dissolution measured at pH 1.2 which is a more discriminating test than phosphate buffer at 7.4 where an acidic drug will readily dissolve.

Example 1 of a 316 mg tablet contains 73 % drug and 15.8 % bicarbonate equating to 50 mg tablet. Example 30 of a 400 mg tablet contains 56 % drug with 19 % bicarbonate equating to 76 mg per tablet. Imaginot Examples 5 and 6 contain lower levels of drug 26 % free acid and 24.4 % sodium naproxen than the 30 – 99 % by weight claimed by Gruber. While the levels of bicarbonate are within the claimed range of 1 – 70 %, at 42 % for the free acid and 44 % for sodium naproxen, the Imaginot tablets are much larger in the range 950 – 1126 mg, the absolute of bicarbonate used by Imaginot is much higher at 400 – 500 mg per tablet (40 – 50 % by weight of the tablet).

Therefore while the claimed Imaginot range of 25 – 75 % soluble carbonate overlaps with this prior art, Imaginot formulations are distinguished on the basis of lower levels of drug, exemplifying both free acid and sodium salt, not just the sodium salt. It is

unlikely that the sodium naproxen formulations disclosed by Gruber with the higher levels of drug and lower levels of soluble carboante will have the in vitro dissolution characteristics claimed by Imaginot.

- **US 6,165,506, WO/1998/035666, WO/2000/013672, EP 1109536** (Jain et al, Elan Pharma Int Ltd, priority 04 Sep 1998 <Jain>) covers nanoparticles of spray dried naproxen with an adsorbed surface modifier such as PVP where the drug particles are less than 600 nm in diameter.

Disclosed formulations include an alkaline agent to increase solubility and hence the dissolution rate, with the addition of an acid to produce effervescence with the release of carbon dioxide for activated dissolution. In pH 7.4 phosphate buffer at 50 rpm, which conditions favour solubility and dissolution, nanoparticle formulations achieved 64 % dissolution compared with 30 % for Aleve[®] tablets. Aleve[®] dissolution rates are faster at pH 7.4 at 50 rpm than in acid at 30 rpm highlighting the solubilising effect of alkaline conditions which increases the rate of dissolution of acidic drugs.

Formulations in Examples 3 and 4 disclose the use of 21 mg sodium bicarbonate with 4 mg citric acid, and 15 mg sodium bicarbonate with 5 mg citric acid per tablet respectively.

These levels equate to around 5 and 4 % by weight bicarbonate which is lower than the 25 – 75 % by weight taught in the Imaginot specification. Imaginot formulations are distinguished from Jain in that that they use standard grades of drug without the need for nanoparticle production with lower levels of sodium bicarbonate to achieve around 50 % faster dissolution under less favourable conditions, namely 86 % in 5 min.

Other formulation patents on naproxen tablets include:

- US 2003/0211150 (Merck GmbH, priority 26 Nov 2001) covers immediate release tablets with spray dried mannitol for improved dissolution as measured in phosphate buffer at pH 7.4 and 50 rpm. None of these formulations include alkaline agents.
- US 5,756,125, US 5,609,884, WO/1994/005277, EP 0656776 (GDSearle, filed 01 Jun 1995) cover bilayer tablets of controlled release and immediate release drug using naproxen free acid and the more soluble sodium salt
- US 4,571,333, US 4,803,079, (Syntex Pharmaceuticals International Ltd, filed 14 Jun 1983 & 20 Dec 1985 respectively) cover controlled release tablet formulations
- US 5,480,650 (Alfa Wassermann SpA, filed 01 Sep 1993) covers programmed release naproxen formulations

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

- US 5,358,717, US 5,470,580 (Syntex Pharmaceuticals International Ltd, filed 06 Jul 1994) covers direct compression formulations using spray dried naproxen and processing methods
- WO/2011/017346 (Emisphere Technologies Inc, priority 03 Aug 2009) covers naproxen with reduced gastrotoxicity using specified delivery agents
- WO/1997/018245 (Farmac Netherland BV, Penkler & Whittaker, priority 14 Nov 1995 & 14 May 1996) covers inclusion complexes of cyclodextrins with naproxen
- US 2005/0249811 (Pozen Inc, priority 16 May 2005) covers coated tablets of naproxen with ingredients such as proton pump inhibitors that will reduce gastric acidity

Other patents cover combination products containing naproxen with other actives such as the triptans, pseudoephedrine etc incorporating alkaline and acidic excipients such as bicarb and organic acid. WO 2008/124081 (Teva Pharm Ind) covering naproxen and other NSAIDs with triptans claims not less than 60 % dissolution of the triptan in 200 mL 0.01 N HCl at 40 rpm. This has later priority than the Imaginot specifications which would constitute prior art.

4.4 Competitive positioning

Since the initial introduction of naproxen, there has been a move to the use of sodium naproxen in immediate release tablets to provide faster absorption and associated faster onset of action in acute conditions. Despite this, there is still an unmet clinical need for faster absorbed, more effective oral dosage forms. The recent introduction of liquid filled soft gelatine capsules which are easy to swallow and imply fast absorption since the drug is already in solution, do not provide the necessary faster absorption compared with Aleve[®] tablets, a leading US brand. Absorption is slower from the liquid filled capsules in both fed and fasted states.

Hence the significant opportunity for Surge Dose[®] naproxen offering faster onset of action even when taken with food and reduced gastrotoxicity even when taken without food.

5 Conclusions

It can be concluded from this review that naproxen is a suitable candidate for application of the Surge Dose[®] technology will provide fast dissolving and fast absorbed tablets with a faster onset of action and reduced variability compared with existing oral dosage forms. Fast absorption is expected in both fasted and fed states so that Surge Dose[®] naproxen taken with food to reduce gastrotoxicity should reduce the delayed absorption seen in fed subjects. Tmax

Application of Surge Dose[®] ultra-fast dissolution technology to naproxen

values in the region of 0.5 h would be expected for Surge Dose[®] naproxen compared to 1 h for existing sodium naproxen tablets and 2 h for existing naproxen tablets.

Additionally faster absorption will be associated with lower gastric residence time and, combined with the high degree of ionization of dissolved drug from Surge Dose[®] formulations, these features are likely to reduce the potential for gastro-toxicity.

Preliminary work has demonstrated that Surge Dose[®] technology significantly increases the extent and rate of dissolution of both naproxen and naproxen sodium compared with the corresponding commercial tablets Naprogesic[®] and Naprosyn[®]. Dissolution data suggest that the use of the naproxen free acid provides the opportunity for enhanced dissolution through the reaction between the acidic drug and the bicarbonate. Addition acid as an excipient ensures fast dissolution in the absence of external stirring simulating gut stasis in migraine. Surge Dose[®] formulations provide micro-stirring and pH control of the in the vicinity of the dissolving drug particles. This increases the rate of dissolution even under low acid or neutral conditions which are typically experienced *in vivo* especially in the fed or partial prandial states, and where there is suppressed or impaired gastric function.

Appendix 1 Surge Dose[®] naproxen formulations

A1.1 Naproxen sodium tablets

Naprogesic[®] film coated tablets (Roche Products Pty Ltd, Australia Lot D06598) contained 275 mg naproxen sodium, microcrystalline cellulose, povidone, talc, magnesium stearate

Ingredient / mg per tablet	0520811 0520812	0521410 0521610	0521411	Naprogesic [®]
Powdered Naprogesic [®] tablets equivalent to 275 mg naproxen sodium	400	400	400	400
Sodium bicarbonate, fine	400	500	500	0
Microcrystalline cellulose	100	100	100	√
Crospovidone	50	50	50	0
Citric acid anhydrous	0	76	0	0
Total tablet weight	950	1126	1050	400
Hardness (Kp)	~ 8 / 5 - 6	~ 5	~ 7	-
Disintegration time in 0.0033 M HCl (sec)	100 / 60	30	50	-
% w/w drug	29	24	26	69
% w/w sodium bicarbonate	42	44	48	0

√ = present in the same quantity as in the commercial product

A1.2 Naproxen tablets

Naprosyn[®] tablets (Roche Products Pty Ltd, Australia Lot E6053) contained 250 mg naproxen, povidone K-90, croscarmellose sodium, yellow iron oxide, magnesium stearate

Material / mg per tablet	0520910 0520911	Naprosyn [®]
Powdered Naprosyn [®] tablets equivalent to 250 mg naproxen	268	268
Sodium bicarbonate, fine	400	0
Citric acid anhydrous	0	0
Microcrystalline cellulose	242	0
Croscarmellose sodium	40	√
Total tablet weight	950	268
Hardness (Kp)	6	-
Disintegration time in 0.0033 M HCl (sec)	47	-
% drug	26	93
% bicarbonate	42	0

√ = present in the same quantity as in the commercial product

A1.3 Methods

A quantity of commercial tablets was ground using a mortar and pestle, and the resultant powder passed through a 280 µm screen to remove fragments of film coating. Batch quantities were calculated on the basis of the label claim drug content. All excipients were

passed through a 280 µm screen prior to blending and with the exception of magnesium stearate were mixed together for 5 min. Magnesium stearate was added last, mixing for 1 min only.

The resultant powder blend was compressed on a Cadmach CMD₃ B-16 rotary press at the theoretical tablet weight. A single set of 19 mm x 9 mm oval shallow concave tooling with a break bar on one face was used.

Tablets were compressed at the maximum hardness that achieved a disintegration time at 37 °C in 0.0033 M HCl around 1 – 2 minutes.

Tablets were stored in HDPE screw cap bottles with a pressure sensitive wad and silica gel desiccant sachets.