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

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1 Executive Summary

Imaginot Pty Ltd <Imaginot> has a portfolio of patents covering its Surge Dose[®] technology providing fast dissolution with subsequent fast absorption of drugs from swallow tablets. Surge Dose[®] formulations achieve ultra-fast activated dissolution under a wide range of *in vitro* test conditions reflecting both favourable and unfavourable physiological conditions which exist within the general population. These include gut stasis in migraine and neutral gastric conditions such as in patients with impaired gastric function or those taking proton pump inhibitors or antacids.

Surge Dose[®] formulations of lornoxicam, diclofenac and paracetamol demonstrate significantly faster *in vitro* dissolution with faster and more consistent *in vivo* absorption than conventional products. This leads to faster onset of action and potentially improved efficacy based on PK-PD (pharmacokinetic – pharmacodynamic) modeling. *In vitro*, the Surge Dose[®] technology has been exemplified with more than 30 drugs with a wide range of different chemistries including acidic, basic, amphoteric and unionized molecules.

As part of its ongoing commercialization activities, Imaginot has reviewed a number of drugs as potential Surge Dose[®] candidates. Published data can provide evidence to assess if faster dissolution *in vitro* is likely to result in faster absorption *in vivo* with faster onset of action. Faster *in vivo* dissolution particularly under less favourable conditions should reduce inter- and intra-patient variability in absorption seen with many drugs that can result in some sub-therapeutic peak plasma concentrations. Reduced variability can potentially result in increased efficacy, or a reduction in dosage to achieve the same efficacy with an improved side effect profile.

This report considers the potential for applying the Surge Dose[®] technology to dabigatran, which is covered by the general claims in the Imaginot patents relating to basic molecules. Dabigatran is one of a new therapeutic class of direct thrombin inhibitors with anticoagulant activity. As dabigatran is not absorbed orally, it is administered orally as the pro-drug dabigatran etexilate which per se has no anti-coagulant activity. Dabigatran etexilate mesylate is marketed as Pradaxa[®], Pradax[®] and Rendix[®] by Boehringer Ingelheim GmbH. This drug was approved by the FDA in Oct 2010 for the prevention of strokes in patients with non-valvular atrial fibrillation and in Europe since Mar 2008 for short term use in hip and knee replacement surgery.

Although the vitamin K antagonist warfarin is the most widely used oral anticoagulant, there is still a significant unmet clinical need for an agent which overcomes many of the issues associated with warfarin treatment. These include unpredictable pharmacokinetics and anti-clotting effects, a narrow therapeutic window with significant risks of major bleeds, a

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high incidence of drug and food interactions and the need for routine monitoring for dosage adjustment if necessary to keep INR in the range 2.0 – 3.0. Dabigatran has the potential to become a safe and effective replacement for warfarin in those subjects at risk of excessive bleeding based on its different mechanism of action directly inhibiting thrombin, its predictable PK and PD effects, and reduced potential for drug and food interactions.

Dabigatran etexilate is a zwitter ion with pKa at 4.0 and 6.7 and exhibits pH dependent solubility which is highest under acidic conditions. At 0.1 N HCl, the solubility of > 50 mg/mL means that the highest dose of 300 mg requires only 6 mL acid for complete dissolution. Although the prodrug is readily absorbed, it has low oral bioavailability around 6 – 7 % as a result of bio conversion by non-specific esterases in the plasma and liver to the active agent dabigatran. Dabigatran is eliminated primarily by the kidneys where it is converted to active glucuronides with a slow elimination half life of 12 – 17 h. As the bioconversion and metabolism do not involve CYP450 isoenzymes, dabigatran PK are unaffected by different genetic phenotypes. While hepatic impairment does not affect the PK, renally impaired patients need to be closely monitored and doses adjusted accordingly.

Although inter-subject variability is claimed to be low and the relatively predictable PK-PD profile of dabigatran allows for fixed dose regimens compared with warfarin, there is still significant variability in C_{max} (peak plasma concentration) and T_{max} (time to C_{max}) values. While the median T_{max} is around 1.5 – 2 h and peak anti-clotting effects occur around 2 h after oral dosing, T_{max} can be highly variable ranging from 0.5 – 6 h with a clear tail of slow absorption profiles. As plasma concentrations and anti-clotting effects are dose dependent, slow absorption will be associated with lower C_{max} and hence a reduced effect. While this may reduce efficacy, it will also reduce the risk of bleeds. In contrast, fast absorption occasions will result in higher C_{max} with greater efficacy and bleeding risks.

In clinical trials, dabigatran shows a fine balance between efficacy and bleeding risk as both are dose dependent. Doses of 110 mg twice daily are non-superior compared with warfarin on efficacy but have a reduced bleeding risk, while 150 mg twice daily is superior to warfarin on efficacy but have a similar bleeding risk. This highlights an opportunity to improve current formulations of dabigatran to provide more consistent absorption so that efficacy can be achieved with a lower dose of drug and an associated reduced risk of bleeding. Surge Dose[®] dabigatran would provide such an improved PK and PD profile maximizing the extent and rate of *in vivo* dissolution independent of the prevailing gastrointestinal conditions, leading to faster delivery of the drug in solution into the small intestine whence absorption occurs by passive diffusion.

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Such an immediate release formulation differs from the current patented Pradaxa[®] dabigatran etexilate capsule which contains pellets of drug and tartaric acid in a 1 : 1 weight ratio to facilitate dissolution of this basic drug. Given the processing method, drug dissolution is unlikely to be fast and absorption would be expected to be dissolution rate limited despite the levels of tartaric acid to enhance solubility. No *in vitro* or *in vivo* release kinetics are given for the resultant pelletized formulation which has been used for all the PK and clinical studies.

Of significance is the fact that if the pellets are removed from the outer capsule before administration, the bioavailability of the drug is significantly increased by 75 %, up to around 12 %, possibly as a result of acidic solubilization of the drug in the stomach. This provides supporting evidence for the proposition that a Surge Dose dabigatran could allow the use of a lower dose within the current therapeutic range as a result of improved availability which would reduce the risks associated with major bleeds without compromising efficacy.

This review suggests that dabigatran is a suitable candidate for application of Imaginot's Surge Dose[®] technology that would be compatible with an ever-greening strategy to switch to or introduce a lower dose immediate release product prior to patent expiry. The current patented pelletized formulation and its use for all the clinical studies submitted for registration provide an effective barrier to generic competition which is likely to require significant clinical programs to demonstrate bioequivalence to the pelletized product. Given this scenario, it appears that there is a significant opportunity for Boehringer Ingelheim to develop a new improved patented formulation prior to patent expiry which would effectively extend the period of protection. A lower dose immediate release product such as a Surge Dose[®] dabigatran tablet is likely to offer an improved safety profile with comparable efficacy and lower cost, further improving the safety profile relative to warfarin. Such a strategy with an approved lower dose improved product would make it difficult to market higher dose generic products.

2 Introduction

2.1 Technology overview

The Surge Dose[®] formulation technology providing ultra-fast activated dissolution and fast absorption of oral drugs has been developed by Imaginot, a privately owned drug delivery company based in Queensland, Australia. Surge Dose[®] tablets are designed to provide superior performance after oral administration even under unfavourable physiological conditions so that fast and consistent absorption and efficacy can be achieved independent of gastrointestinal (GI) activity and pH. Surge Dose[®] maximizes the impact of

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pH dependent drug solubility to increase the rate of absorption, but is also effective for drugs where solubility is independent of pH. Although low relative humidity (RH) manufacturing and packing conditions and unit packaging are required, Surge Dose[®] tablets use conventional excipients and manufacturing processes.

Surge Dose[®] tablet formulations provide faster and more consistent drug absorption resulting in faster and more reliable onset of action. Mean and median T_{max} values are significantly reduced with Surge Dose[®] and are less variable. This has been demonstrated in human PK studies on paracetamol (acetaminophen, APAP) and two acidic NSAIDs (non-steroidal anti-inflammatory drugs) lornoxicam and diclofenac.

Based on PK-PD modelling, Surge Dose[®] paracetamol is predicted to achieve improved efficacy as variable absorption from conventional tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy.

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[®] formulations may also provide a clinical benefit for drugs taken on a regular basis, such as in the treatment of Parkinson's disease and other chronic indications, where GI conditions and resultant absorption can be highly variable.

Surge Dose[®] tablets provide a more convenient alternative to solutions and liquid formulations which are known to result in faster drug absorption than conventional solid dosage forms. Disadvantages of liquids and solutions include stability issues, the need for extensive flavouring for acceptable taste, preservation against microbial spoilage, reduced convenience for the patient unless doses are unit packed, the need for controlled storage and higher manufacturing and packaging costs.

In addition Surge Dose[®] tablets offer benefits over the new, heavily promoted second generation fast acting formulations such as liquid filled soft capsules, orally disintegrating tablets (ODTs) and absorption enhanced formulations. These do not always deliver the

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promised rapid onset of action required for drugs taken on demand for indications such as pain, migraine, allergy, nausea and erectile dysfunction.

Surge Dose[®] tablets are designed to act more like a solution or liquid formulation so that the drug will rapidly dissolve in the stomach contents after oral administration regardless of gastric pH and motility. This means that dissolved drug rapidly reach the small intestine and is available for absorption. Conventional formulations are associated with variable lag times resulting from *in vivo* capsule rupture, tablet disintegration, dispersion of capsule contents and drug dissolution which typically result in slower and more variable absorption.

2.2 Surge Dose[®] IP

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

- i. PCT/AU 2006/001798 (WO/2007/059591) covering acidic and unionized actives claiming priority from 28 Nov 2004 which has been granted in Australia without limitation and is under examination in US under the PPH and in Japan.
- ii. PCT/AU 2005/00759 (WO/2005/115345) covering basic and amphoteric actives claiming priority from 28 May 2004. Patents have been granted in Australia and Canada without limitation with examination progressing in US, Europe, India and Japan.
- iii. PCT/AU 2005/00758 (WO/2005/115344) covering paracetamol and combinations. The patent has been granted in Australia, Canada and US and has been 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 with *in vitro* dissolution data for more than 30 other drugs described by chemical class as acidic, basic, amphoteric and unionized. Drugs not exemplified are covered by broad platform claims.

2.3 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), 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.

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Surge Dose[®] formulations demonstrate satisfactory stability and have been successfully scaled up to commercial manufacture under low RH conditions. The first Surge Dose[®] product was launched in 2011 with the second planned for 2012. Other drugs are under development in optimized Surge Dose[®] formulations.

2.4 Dabigatran

Dabigatran is one of a new therapeutic class of direct thrombin inhibitors with anticoagulant activity. As dabigatran is not absorbed orally it is administered as the pro-drug dabigatran etexilate which per se has no anti-coagulant activity. Dabigatran etexilate mesylate was developed by Boehringer Ingelheim GmbH as BIBR-1048 and is marketed as Pradaxa[®], Pradax[®] and Rendix[®]. This drug was approved by the FDA in Oct 2010 for the prevention of strokes in patients with non-valvular atrial fibrillation and in Europe since Mar 2008 for short term use in hip and knee replacement surgery. In Europe, 75 and 110 mg strengths are approved with a normal dose of 220 mg four times daily reduced to 150 mg for patients older than 75 mg with moderate renal impairment. In the US, dosage is 75 or 150 mg twice daily depending on the patient's creatinine clearance.

The hard gelatin capsules contain the equivalent of 75, 110 and 150 mg dabigatran etexilate formulated as pellets with acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc and tartaric acid¹. As oral bioavailability is increased by 75 % when the pellets are administered without the shell, the capsules must be taken intact.

While warfarin is the most widely used oral anti-coagulant, it has a number of disadvantages with the necessity for regular monitoring and dose adjustment and a high potential for dietary and drug interactions. Despite its early promise as a warfarin replacement, ximelagatran, the first-in-class direct thrombin inhibitor was withdrawn as a result of hepatotoxicity and also variable efficacy. Based on results from extensive trials in the light of the ximelagatran experience, dabigatran now seems to be a safe and effective replacement for warfarin in those subjects at risk of excessive bleeding, without evidence of any hepatotoxicity.

This report considers the potential of dabigatran as a candidate for the Surge Dose[®] ultra-fast activated dissolution technology to achieve faster *in vivo* dissolution and absorption.

¹ Pradaxa label http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s004lbl.pdf

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3 Clinical premise for Surge Dose[®]

3.1 Physiological variability affecting drug absorption

3.1.1 Gastrointestinal (GI) motility

The underlying MMC (migrating motor complex) influences gastric emptying contributing to the inter- and intra-subject variability seen in PK studies with solid dosage forms and solutions administered orally. MMC effects are significant and can mask differences between formulations and other variables particularly in fasted PK studies.

In the fasted state, subjects will be cycling through the three MMC phases with the total 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, reducing to 12 and 5 min respectively in Phase II and Phase III².

Delayed absorption and reduced variability seen in fed studies result from interruption of the underlying MMC by food triggering 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 are 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. However the frequency of fast absorption occasions will be less for a slow dissolving product than for a fast dissolving product.

Well documented gastric emptying effects are responsible for the double or multiple absorption peaks often seen in individual subject PK profiles particularly with frequent sampling. Multiple gastric emptying peaks occurring during the first two hours differ from

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

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

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later peaks due to entero-hepatic recycling. They are associated with longer T_{\max} values and are 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 longer T_{\max} . When subjects are in Phase I or II, there is fast absorption of any dissolved drug that drains passively from the stomach. This is followed by a later absorption phase when remaining gastric contents are emptied by Phase III MMC. Gastric contents include 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 absorption phase and the relative sizes of these peaks will depend on its solubility and the dissolution characteristics of the dosage form.

- 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, Barbhaiya 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, Sjolund K. Absorption of enprofylline from the gastrointestinal tract in healthy subjects. *Eur J Clin Pharmacol* (1984) **27**(3):329-33

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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

3.1.2 Gastric pH

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

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

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

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

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

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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.

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

3.2 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 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.

While the physiological conditions of the patient cannot be changed by the dosage form, strategic formulation design can improve the probability of rapid absorption by modifying the pH of the dissolution reaction and creating a mechanism for activated dissolution *in vivo*. Surge Dose[®] formulations are designed to achieve ultra fast dissolution under the wide range of favourable and unfavourable conditions that occurs in the general population. This is important for drugs taken 'on demand' for immediate effect where delayed absorption often results from prevailing physiological conditions.

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

Dissolved drug will reach the small intestine quickly independent of gastric motility. The higher the drug concentration, the greater will be the driving force across the intestinal mucosa for rapid absorption and high peak plasma concentrations (C_{max}). Total dissolution of the drug from a solid dosage form into the co-administered liquid and gastric contents

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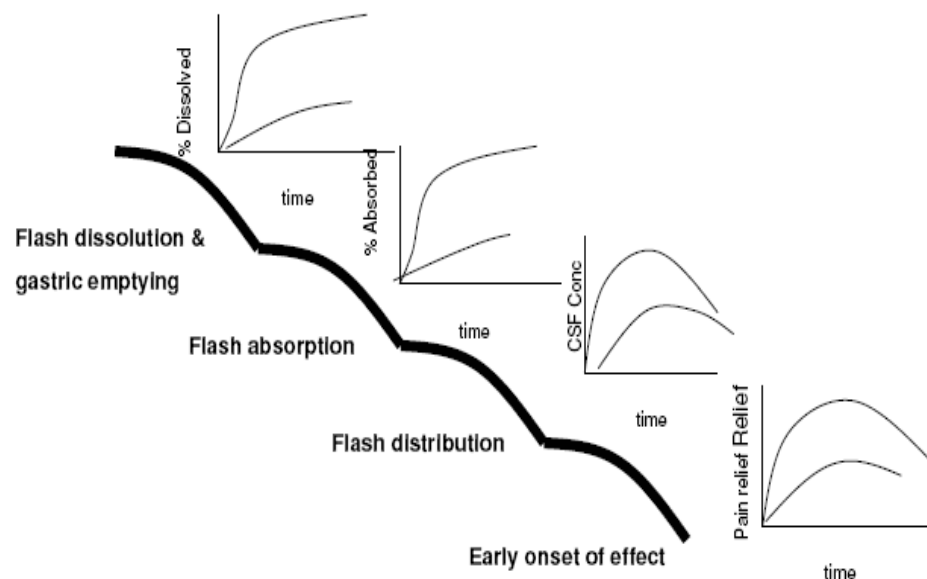
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provides the maximum concentration to drive absorption and distribution to effect compartments by passive diffusion resulting in faster onset of action and improved efficacy.

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[®] maximizes the extent of dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC as summarized in Figure 1:

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



- 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

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- iv. Fast absorption quickly saturates any protein binding sites and saturable metabolic and transport processes leading to earlier achievement of therapeutic plasma concentrations with short T_{\max} and high C_{\max} as well as reduced intra- and inter-subject variability
- v. High plasma concentrations drive rapid distribution to effect compartments resulting in rapid onset of action and rapid peak effect

3.3 Proof of concept

3.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects¹⁵ 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 µg/mL in the first 15 min compared with only 20 % subjects receiving Tylenol[®]
- 16 % subjects taking Tylenol[®] never reached 10 µg/mL indicating sub-therapeutic dosing compared with only 4 % for Surge Dose[®] formulations

This study showed good *in vitro in vivo* correlations (IVIVC). Although paracetamol absorption was variable from one dose to another reflecting MMC activity, fast *in vitro* dissolution was associated with a higher frequency of fast absorption occasions and higher C_{\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[®] tablets¹⁶. Improved clinical efficacy is predicted for Surge Dose[®] formulations

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

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

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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.

3.3.2 Lornoxicam

A PK study in 24 fasted subjects with the NSAID lornoxicam has also demonstrated the benefits of Surge Dose[®] to maximise *in vitro* drug dissolution compared with a conventional commercial tablet¹⁷. Surge Dose[®] tablets significantly reduced T_{max} and resulted in significantly higher C_{max} levels similar to parenteral administration¹⁸. 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:

- Mean and median T_{max} values for Surge Dose[®] were comparable at 0.51 and 0.50 h respectively, ranging from 0.3 to 1 h
- Median T_{max} for the commercial 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[®] achieved T_{max} within the first 0.5 h compared with only 8 % for the reference tablet
- Surge Dose[®] achieved peak plasma concentrations comparable with parenteral administration, around 40 % higher than the commercial tablet with mean C_{max} 1098 ng/mL (CV 18.71 %) compared with 788 ng/mL (CV 18.69 %)

¹⁷ 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

¹⁸ 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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- Although AUC_{0-∞} was the same for both Surge Dose[®] and commercial 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[®], respectively 3.9, 2.8 and 2.2 times higher than with the commercial tablet

3.3.3 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.

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) 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 ± 1,515 ng/mL compared with 1,042 ± 518 ng/mL for Voveran[®]-D. Surge Dose[®] C_{max} values were comparable with those obtained following IV^{19,20} or IM^{21,22} administration whereas those for Voveran[®]-D were lower than 1,340 ± 627 ng/mL reported for standard tablets²³.

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.

¹⁹ 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

²⁰ 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

²¹ 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

²² 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

²³ Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arznein-Forsch/Drug Res* (2001) 51(11): 885 – 890

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4 Technical requirements for Surge Dose[®]

Formulation optimization aims to maximize drug dissolution in available liquid in the stomach to provide a high concentration gradient for rapid absorption. Optimized levels and ratios of pH modulating agents (pHMA) and water uptake agents (WUA) for each drug or drug combination provide a pH-controlled activated dissolution system to 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 MMC. 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 absorption is more dependent on MMC gastric emptying.

For ionized drugs, the pH modulating agents are optimized to favour the proportion of drug present in the more readily absorbed unionized form. At its pKa, 50 % of a drug will be present in its unionized form in equilibrium with 50 % in the ionized form. **Basic** drugs are present predominantly unionized at pH values above their pKa, whereas **acidic** drugs are present predominantly unionized below their pKa. **Amphoteric** drugs are zwitterions which have a net neutralisation of charge at their isoelectric point.

Surge Dose[®] formulations use approved GRAS excipients and traditional manufacturing equipment for direct compression or wet granulation. 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 provide maximum stability and an acceptable shelf life of 2 years. No major capital investment is required and use of conventional ingredients should not present any regulatory hurdles. Film coatings can be selected to have minimal impact on dissolution. Small scale Surge Dose[®] batches of many drugs have been manufactured, and some successfully scaled-up.

Highly discriminating *in vitro* dissolution methods are used as a development rather than a QC tool, with standard dissolution equipment such as USP dissolution apparatus II with paddles, different media at 37 °C, different volumes and different stirring speeds to simulate *in vivo* conditions:

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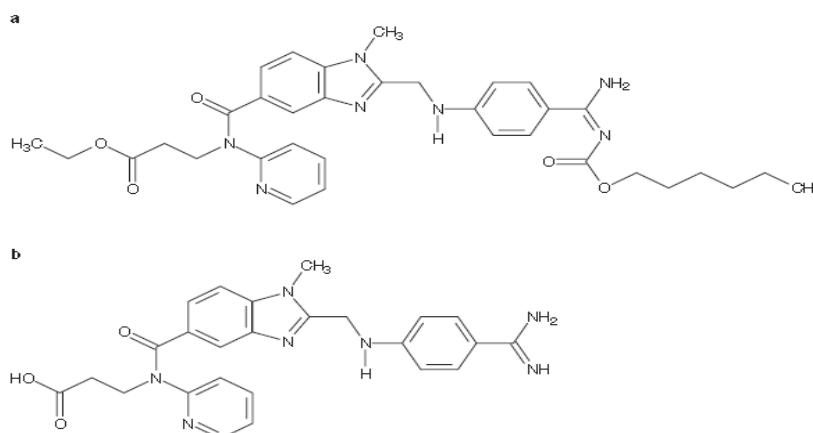
- 900 mL 0.05 M HCl at 30 rpm where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.3, contains the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo*, and is used to characterise Surge Dose[®] formulations
- 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

5 Dabigatran as a potential Surge Dose[®] candidate

5.1 Physicochemical properties and permeability

Dabigatran etexilate is the inactive pro-drug of dabigatran. Its chemical name is ethyl 3-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl](pyridin-2-yl)amino] propanoate (INN) with a molecular weight 627.73. It is used as the mesylate salt with the chemical formula $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and molecular weight 723.86 with the chemical structure shown in Figure 2²⁴.

Figure 2 Chemical structures of (a) the prodrug dabigatran etexilate and (b) the active drug substance dabigatran



²⁴ Drug Bank Dabigatran etexilate <http://www.drugbank.ca/drugs/DB06695>

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Dabigatran is a highly charged polar zwitter ion which is not absorbed through the intestinal mucosa. The prodrug etexilate has two weakly basic centres with pKa values at 4.0 and 6.7. It has a solubility in water of 1.8 mg/mL which means that the highest dose of 300 mg requires around 170 mL for complete dissolution. However this solubility is pH dependent being greater under acidic conditions, > 50 mg/mL in 0.1 N HCl where a 300 mg dose would dissolve in only 6 mL. At pH 5, solubility is 24 mg/mL, dropping to 17 mg/mL at pH 7 and pH 8.8.

The neutral form is very lipophilic with a logP of 3.8 which means that it will readily cross biological membranes and the blood brain barrier.

Dabigatran undergoes pH dependent hydrolysis which is reduced under neutral conditions.

Based on these physicochemical properties, it would be expected that a Surge Dose[®] dabigatran tablet would provide more extensive and faster dissolution through control of the pH and active effervescence in the vicinity of the dissolving drug particles. However given the acid-sensitive nature of the drug, the formulation may require protection of the acidic component to assure adequate chemical long-term stability.

5.2 Therapeutic use

Dabigatran etexilate mesylate is marketed as Pradaxa[®], Pradax[®] and Rendix[®] by Boehringer Ingelheim GmbH. This drug was approved by the FDA in Oct 2010 for the prevention of strokes in patients with non-valvular atrial fibrillation and in Europe since Mar 2008 for short term use in hip and knee replacement surgery. In Europe, 75 and 110 mg strengths are approved with a normal dose of 220 mg four times daily reduced to 150 mg for patients older than 75 mg with moderate renal impairment. In the US, dosage is 75 or 150 mg twice daily depending on the patient's creatinine clearance; the 110 mg capsule was not approved.

The hard gelatin capsules contain the equivalent of 75, 110 and 150 mg dabigatran etexilate formulated as pellets with acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc and tartaric acid²⁵. As oral bioavailability is increased by 75 % when the pellets are administered without the shell, the capsules must be taken intact.

Bulk packed capsules have a short shelf life of 30 days once opened as the drug is affected by humidity. However individual blister packed capsules do not have this limitation.

²⁵ Pradaxa label http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s004lbl.pdf

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5.3 Comparison with warfarin

Dabigatran is becoming well established as a safe and effective replacement for warfarin in those subjects at risk of excessive bleeding. Despite its narrow therapeutic window, warfarin is the most widely prescribed oral anti-coagulant with a key role in the management of patients with atrial fibrillation, deep vein thrombosis and pulmonary embolism. Warfarin a vitamin K antagonist which inhibits the vitamin K dependent biosynthesis of clotting factors II, VII, IX and X in the liver. It is used as a racemic mixture, with the S-isomer having five times the potency of R-warfarin.

Warfarin inhibits vitamin K epoxide reductase in the liver so that the resultant inactive clotting factors are no longer able to bind to the endothelial surface of blood vessels to promote clotting. Thus warfarin takes some 2 – 3 days to establish its full anticoagulant effect which occurs once endogenous levels of vitamin K and active clotting factors are depleted. During this period warfarin can promote clot formation by its effect in reducing levels of proteins C and S which are involved in the degradation of factors Va and VIIIa. After stopping warfarin treatment, it takes some days for the body to regenerate vitamin K and the clotting factors.

Limitations of warfarin are well recognized and include²⁶:

- Delayed onset and offset of action that prolong hospitalization and increase healthcare costs
- Need for regular monitoring of blood clotting to keep the INR (international normalised ratio for prothrombin time) within the range 2.0 to 3.0 particularly when initiating treatment and to individualize dosing
- Need for heparin cover for first 4 – 5 days while endogenous levels of vitamin K and functional clotting factors are depleted
- Multiple drug interactions
 - reduced efficacy with barbiturates, carbamazepine, dichloralphenazone, glutethimides, griseofulvin, nafcillin, rifampicin
 - increased anticoagulant activity with many commonly used drugs including allopurinol, amiodarone, antidepressants such as sertraline, aspirin, clarithromycin, chloramphenicol, cimetidine, clofibrate, co-trimoxazole, dextropropoxyphene, dipyridamole, erythromycin, ethylestrenol, fluconazole, gemfibrozil, glucagon, itraconazole, isoniazid, ketoconazole,

²⁶ Benmira S, Banda ZK, Bhattacharya V. Old versus new anticoagulants: focus on pharmacology. Recent Patents on Cardiovasc Drug Discovery (2010) 5(2):120-37

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metronidazole, miconazole, norethandrolone, quinidine, tamoxifen, thyroid agents, statins

- increased effects with NSAIDs that are more strongly plasma protein bound as warfarin is displaced from serum albumin, with the added risk of increased gastric bleeding
- Increased effects when used with broad spectrum antibiotics which reduce vitamin K producing gut flora
- Interactions with complementary medicines such as St John's Wort
- Variable effect of alcohol with reduced effects in regular heavy drinkers as a result of enzyme induction but increased effects where there is liver impairment
- Food interactions, particularly charbroiled foods and green vegetables containing high levels of vitamin K which reduce the anticoagulant effects
- Genetic polymorphisms:
 - in VKORC1 explaining 30 % of inter-subject variation making African Americans relatively warfarin resistant compared with Asian-Americans who are more sensitive to the anti-coagulation effects of warfarin
 - in the metabolic CYP2C9 enzyme system accounting for around 10 % of the inter-subject variability in Caucasians

Based on these issues there is a clear unmet clinical need for a safe and effective oral anti-coagulant with predictable PK and PD as an alternative to warfarin. Dabigatran provides similar or better efficacy without the many safety issues and so is being increasingly used as an alternative to warfarin^{27,28,29,30,31}.

5.4 Pharmacokinetics (PK)

5.4.1 Absorption, metabolism and elimination

The prodrug dabigatran etexilate mesylate has low oral bioavailability in the region of 6 – 7 % being hydrolysed to the active dabigatran by non-specific esterases in the gut wall,

²⁷ Lepic K & Crowther M. New anticoagulants for the prevention of thrombosis. *Curr Pharm Des* (2010) 16(31):3472-4.

²⁸ Bereznicki LR & Peterson GM. New anticoagulants for atrial fibrillation. *Cardiovasc Therap* (2010) 28(5):278-86

²⁹ Roberts LN & Arya R. New anticoagulants for the prevention and treatment of venous thromboembolism. *Curr Vasc Pharmacol* (2010) 8(3):373-82

³⁰ Benmira S, Banda ZK, Bhattacharya V. Old versus new anticoagulants: focus on pharmacology. *Rec Patents Cardiovasc Drug Disc* (2010) 5(2):120-37

³¹ Bauer K. New oral anticoagulants in development : potential for improved safety profiles. *Rev Neurol Dis* (2010) 71(1):1-8

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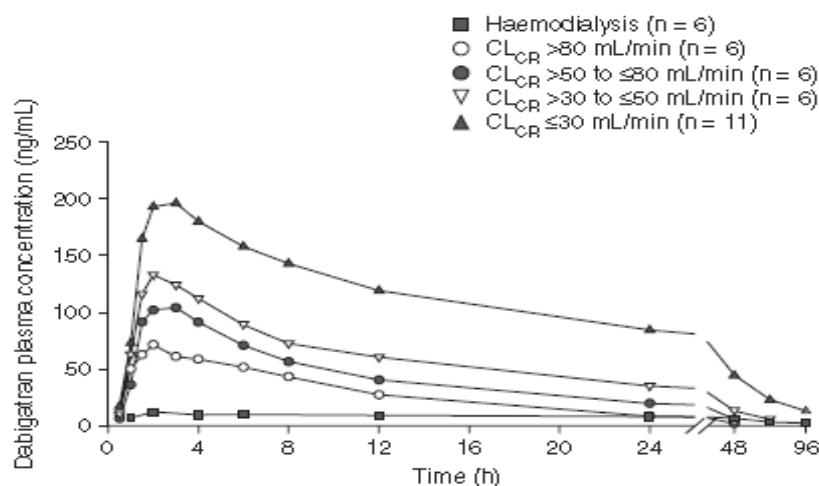
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plasma and liver. There is no metabolism by CYP450 isoenzyme systems or by oxidoreductases so drug-drug and drug-diet interactions are less likely than with warfarin.

Drug enters the portal vein as a mixture of the unconverted etexilate prodrug and the active dabigatran with bioconversion completed by esterases and microsomal carboxylesterases in the liver. 20 – 35 % dabigatran is conjugated with glucuronic acid to produce four active acylglucuronides each accounting for < 10 % plasma dabigatran. As this metabolism does not involve CYP450 isoenzymes, dabigatran PK is not affected by different genetic phenotypes. Mild hepatic impairment has little effect on this bioconversion.

Some 85 % of the drug is excreted in the urine with 6 % in the faeces with the glucuronides excreted via the biliary system. Renal elimination of unchanged drug at 100 mL/min reflects the glomerular filtration rate. Although the bioconversion is unaffected by renal impairment, it does significantly impact the PK resulting in higher plasma levels as a result of slower elimination proportional to the extent of renal impairment as shown in Figure 3³². Hence monitoring and dose reduction is necessary in renally impaired patients.

Figure 3 Effect of renal impairment on the PK of dabigatran etexilate (from Stangier et al 2010)



Dabigatran exhibits dose proportional PK over the dose range 10 – 400 mg. It has a long elimination half life ($t_{1/2}$) of 8 h after single doses in healthy subjects and 12 – 17 h at steady state after multiple doses with accumulation. Steady state is achieved after 3 days dosing. $t_{1/2}$ is longer in older subjects at 13 h and can be greater than 24 h in subjects with

³² Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. An open-label, parallel-group, single-centre study. Clin Pharmacokinet (2010) 49(4):259-68

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reduced creatinine clearance below 30 mL/min reflecting the predominant renal excretion of this drug which accounts for 80 % of each dose. Renal impairment and age increase exposure to the drug with PK modelling predicting an 11 % increase in exposure for every 10 mL/min decrease in creatinine clearance³³. Compared with healthy adults, exposure was doubled in elderly subjects with mean age 68 years receiving 150 mg of the prodrug twice daily for 6 days, and up to 6-fold in patients with severe renal impairment.

Volume of distribution is moderate at 60 – 70 L and protein binding is low around 25 - 35 % which does not limit distribution or elimination and reduces the potential for drug interactions.

PK parameters for single and multiple doses of dabigatran etexilate mesylate in healthy adult and elderly subjects and in patients are summarised in Table 1³⁴.

Table 1 Mean PK parameters for single and multiple doses of dabigatran etexilate in healthy adult and aged subjects and patients, showing the effect of food on absorption in healthy adults (from Stangier 2008)

Parameter	Healthy adult subjects			Healthy elderly subjects		Patients	
	od	bid	tid	bid, male	bid, female	od	bid
C _{max} (ng/mL)/mg	0.89					0.41 ^b	
C _{max,ss} (ng/mL)/mg		1.16	1.68	1.48	1.83		1.06
AUC _∞ (ng • h/mL)/mg	5.66					6.41 ^b	
AUC _{ss} (ng • h/mL)/mg		7.44	7.85	10.9	12.8		15.9
t _{max} (h)	1.25–1.5 ^a					6.0 ^{b,d}	
t _{max,ss} (h)		1.25–2.0 ^a		3.0 ^d	2.5 ^d		2.7 ^d
t _{1/2} (h)	8.13 ^d	11.3 ^d	13.7	12.1 ^d	13.4 ^d		
CL/F (mL/min)	2410	2828	1748	1150	981	1181 ^e	1770 ^e
C _{min,ss} (ng/mL)/mg		0.36	0.50	0.52	0.52	0.13	0.45
C _{max} (fasted/fed) [ng/mL]/mg ^f	0.74/0.71						
AUC _∞ (fasted/fed) [ng • h/mL]/mg ^f	6.03/5.97						
AUC (–P/+P) [ng • h/mL]/mg ^g	6.03/4.70			10.9/8.27	12.8/10.6		

a Values are expressed as mean unless specified otherwise.

b First oral dose after surgery.

c Range.

d Median.

e >24 hours after surgery. Typical values of CL/F for a patient with gastrin of 34.58 pmol/L and CL_{CR} of 76.16 mL/min (Troconiz et al.^[28]).

f Without/with administration of a high-fat, high-calorie breakfast.

g Without/with concomitant administration of pantoprazole (P).

AUC = area under the plasma concentration-time curve; AUC_∞ = AUC from time zero to infinity; AUC_{ss} = AUC at steady state; bid = twice daily; CL_{CR} = creatinine clearance; CL/F = apparent total oral clearance; C_{max} = peak plasma concentration; C_{max,ss} = peak plasma concentration at steady state; C_{min,ss} = minimum plasma concentration at steady state; od = once daily; t_{1/2} = terminal half-life; tid = three times daily; t_{max} = time to reach the C_{max}; t_{max,ss} = time to reach the C_{max,ss}.

³³ Samama MM. Use of low molecular weight heparins and new anticoagulants in elderly patients with renal impairment. *Drugs Aging* (2011) 28 (3): 177-193

³⁴ Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* (2008) 47(5):285-95

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Plasma concentrations and pharmacodynamic effects are dose dependent and predictable with C_{max} achieved in 0.5 – 2 h with a mean around 1.5 h³⁵. Despite this being considered predictable, it is noteworthy that range data for T_{max} in Table 2 indicate that it can be as long as 3 – 6 h with a clear tail of slow attainment of C_{max} ³⁶.

Table 2 Mean or median PK parameters for 150 mg single doses of dabigatran etexilate in healthy adult subjects and those with renal impairment, compared with 50 mg to end stage renal disease patients (ESRD) showing the range of T_{max} values (from Stangier 2010)

Parameter	Healthy subjects (n=6)	Subjects with renal impairment			
		mild (n=6)	moderate (n=6)	severe (n=11)	ESRD (n=6)
AUC_{∞} [ng•h/mL]	901 (58.6)	1580 (86.8)	2470 (10.6)	6150 (61.0)	618 (55.3)
$AUC_{\infty, norm}$ [ng•h/mL/mg]	8.0 (58.6)	14.1 (86.8)	21.9 (10.6)	54.6 (61.0)	16.5 (55.3)
C_{max} [ng/mL]	85.3 (45.3)	109 (81.9)	138 (28.5)	205 (61.3)	13.5 (53.4)
$C_{max, norm}$ [ng/mL/mg]	0.757 (45.3)	0.970 (81.9)	1.22 (28.5)	1.82 (61.3)	0.360 (53.4)
t_{max} [h]	2.0 (1.5–6.0)	2.5 (1.5–3.0)	2.0 (1.5–3.0)	2.0 (1.5–4.0)	2.0 (2.0–6.0)
$t_{1/2}$ [h]	13.8 (29.2)	16.6 (52.5)	18.7 (17.2)	27.5 (15.6)	34.1 (38.5)

Twice daily doses of 150 mg achieve C_{max} around 180 ng/mL compared with trough levels around 90 ng/mL³⁷.

Fatty food delays absorption as a result of delayed gastric emptying with food triggering Phase I MMC increasing T_{max} by around 2 h to around 3 – 4 h but not otherwise affecting the overall low oral bioavailability.

5.4.2 Drug interactions

With relatively low protein binding of 25 – 35 % and lack of involvement of CYP enzymes in the bioconversion or metabolism of dabigatran, drug interactions are fewer than with warfarin.

As the prodrug is basic with higher solubility under acidic conditions, dabigatran etexilate pellets are formulated with tartaric acid to provide an acidic environment to enhance dissolution and facilitate absorption. This is claimed to reduce the effects of variable

³⁵ Pradaxa label http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s004lbl.pdf

³⁶ Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. An open-label, parallel-group, single-centre study. Clin Pharmacokinet (2010) 49(4):259-68

³⁷ Hankey GJ & Eikelboom JW. Dabigatran etexilate: A new oral thrombin inhibitor. Circulation (2011) 123(13):436-50

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gastro-intestinal pH and the effects of co-administered proton pump inhibitors or antacids. Despite this, the bioavailability of dabigatran is reported to be reduced by pantoprazole, reducing C_{max} by 33 % and AUC by 22 %.

Although the prodrug dabigatran etexilate is a substrate for the P-glycoprotein (P-gp) efflux transporter expressed in the intestine and kidneys, the active drug is not³⁸. Therefore P-gp inhibitors and inducers affect only the absorption of the prodrug when they are competing for absorption. Quinidine a P-gp inhibitor increased C_{max} by 56 % and AUC by 53 %, with ketoconazole, amiodarone and verapamil also increasing availability. Rifampicin a P-gp inducer reduced dabigatran C_{max} by 67 % and AUC by 66 % with effects lasting 7 days.

Since P-gp affects the absorption of the prodrug only, these effects can be avoided by not giving the drugs at the same time. Administration of P-gp inhibitors such as ketoconazole and verapamil given within an hour of dabigatran etexilate increase C_{max} by 1.5 – 2.5 times as a result of reduced reabsorption into the gut lumen. However if administered 2 hours apart, no such differences are seen.

There is no interaction between the widely used cholesterol lowering agent atorvastatin and dabigatran³⁹.

5.5 Pharmacodynamics (PD)

5.5.1 Mechanism of action

Dabigatran is a rapidly acting, competitive and reversible direct thrombin inhibitor which prevents the conversion of fibrinogen to fibrin and hence disrupts the coagulation cascade to prevent clot formation. This involves prevention of positive feedback on coagulation activation, fibrin monomer cross-linking, platelet activation and fibrinolysis inhibition. Dabigatran inhibits both free and fibrin bound thrombin and thus prevents thrombin-induced platelet aggregation. It has little effect on prothrombin time or INR which targets the extrinsic coagulation pathway.

Dabigatran has a concentration dependent effect on clotting time as demonstrated by a range of measures. Prolonged clotting times are maximal at around 2 hours following oral dosage corresponding with C_{max} .

³⁸ Tran A & Cheng-Lai A. Dabigatran etexilate. The first oral anticoagulant available in the US since warfarin. *Cardiol Rev* (2011) 19:154-61

³⁹ Stangier J, Rathgen K, Stahle H, Reseski K, Kornicke T, Roth W. Coadministration of Dabigatran Etexilate and Atorvastatin. Assessment of Potential Impact on Pharmacokinetics and Pharmacodynamics. *Am J Cardiovasc Drugs* (2009) 9(1):59-68

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Unlike warfarin where vitamin K can be administered as a specific antidote for major bleeds or in the event of emergency surgery, the slow elimination of dabigatran and direct thrombin inhibition means that supportive therapy is required which may require transfusions or surgical intervention. Diuresis can be used to increase elimination and activated charcoal administered orally to remove unabsorbed drug from the GI tract

5.5.2 Therapeutic efficacy & risks

Dabigatran is now approved by the FDA as an alternative to warfarin in atrial fibrillation and is recommended as an alternative to warfarin in the prevention of stroke and systemic embolism. In patients with atrial fibrillation and previous transient ischemic attack or stroke, 150 mg dabigatran twice daily was superior reducing stroke and systemic embolism, with 110 mg daily being equivalent to warfarin⁴⁰. Results in Japanese patients were the same as the overall study group⁴¹.

Dabigatran also appears to offer some advantages compared with the low molecular weight heparin enoxaparin which is administered by sub-cutaneous injection^{42,43,44,45,46}.

However while dabigatran is clearly an effective coagulant without many of the issues associated with warfarin, the risk of major bleeding episodes remains and appears to be higher than for warfarin. With dabigatran, the frequency of bleeds is dose related, with 300 mg twice daily resulting in 23 % subjects with bleeds, 150 mg twice daily 18 % and 50

⁴⁰ Diener H-C, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, Xavier D, Di Pasquale G, Yusuf S. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial *Lancet Neurol* (2010) 9(12):1157-63

⁴¹ Hori M, Connolly SJ, Ezekowitz MD, Reilly PA, Yusuf S, Wallentin L. Efficacy and safety of dabigatran vs warfarin in patients with atrial fibrillation – sub-analysis in Japanese population in RE-LY trial. *Circ J* (2011) 75(4):800-5

⁴² Verma AK. Dabigatran etexilate: a new thrombin inhibitor. *Med J Aus* (2010) 192(7):407-12

⁴³ Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* (2009) 24(1):1-9

⁴⁴ Eriksson BI, Dahl OE, Buller HR, Hettiarachchi R, Rosencher N, Bravo ML, Ahnfelt L, Piovella F, Stangier J, Kalebo P, Reilly P. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* (2005) 3(1):103-11

⁴⁵ Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Kalebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Buller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* (2007) 5(11):2178-85

⁴⁶ Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Buller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* (2007) 370(9591):949-56

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mg twice daily 7 %. Major bleeds have been reported in patients with atrial fibrillation affecting 2.87 % on 110 mg dabigatran twice daily and 3.32 % on the 150 mg dose compared with 3.57 % on warfarin⁴⁷.

Another study showed that while 110 mg dabigatran twice daily resulted in significantly lower bleeding rates (3.11 %) than warfarin (3.54 %) and 150 mg dabigatran (3.34 %), this had intermediate rates of stroke and embolism with 150 mg dabigatran having the lowest rates of 1.15 % compared with 1.51 % for 110 mg and 1.74 % for warfarin⁴⁸. Intracranial bleeding rates were the lowest for 110 mg dabigatran (0.19 %) compared with 0.33 % for the 150 mg dose and 0.77 % for warfarin.

The major Phase III RE-LY study demonstrated similar rates of stroke and systemic embolism as warfarin but with lower risks of major bleeding, 2.71 % compared with 3.36 % for warfarin for doses of 110 mg twice daily⁴⁹. Twice daily doses of 110 and 150 mg dabigatran etexilate for stroke prevention in atrial fibrillation patients had a lower risk of intra- and extra-cranial bleeds than warfarin in patients under 75 years old. In older patients, dabigatran was associated with a lower intracranial bleed risk compared with warfarin but a similar or higher extracranial bleeding risk.

A higher dose of 150 mg twice daily showed greater reduction in stroke and systemic embolism than warfarin but similar frequency of bleeding, 3.11 % compared with 3.36 %. The risk of major bleeds was significantly higher for 150 mg dabigatran twice daily (1.51 %) than for warfarin (1.02 %). The risk of myocardial infarction is higher for dabigatran at around 0.82 % compared with 0.64 % for warfarin with no differences in mortality.

Clearly there are advantages using dabigatran compared to warfarin, but the magnitude of those advantages depends on the level of INR control in the study centre⁵⁰. Advantages are greater where there is poor INR control than good INR control maintained in the range 2.0 – 3.0.

⁴⁷ 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran) *Circulation* (2011) 123(10):1144-50

⁴⁸ Ezekowitz MD, Wallentein L, Connolly SJ, Parekh A, Chernick MR, Pogue J, Aikens TH, Wang S, Reilly PA, Lip GYH, Yusuf S. Dabigatran and warfarin in vitamin-K antagonist-naïve and -experienced cohorts with atrial fibrillation. *Circulation* (2010) 122:2246-53

⁴⁹ Eikelboom JW, Wallentein L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener H-C, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation: An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial. *Circulation* (2011) 123(21):2363-72

⁵⁰ Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* (2010) 376:975-83

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150 mg dabigatran twice daily has been shown to be a cost-effective treatment than warfarin in atrial fibrillation patients with a high risk of haemorrhage or stroke unless INR control with warfarin was excellent⁵¹.

5.5.3 Adverse events

The most commonly reported adverse events are dyspepsia and gastritis like symptoms which appear not to be dose related reported by 11.8 % patients on 110 mg and 11.3 % patients on 150 mg. These are around double those reported for warfarin 5.8 %. This could be a property of the prodrug but may also be related to the relatively high levels of tartaric acid in the pellets which would be released in the stomach and lead to slow release of the dabigatran etexilate.

There is no evidence of hepatotoxicity such as seen with ximelagatran.

5.6 Patent and regulatory considerations

Dabigatran etexilate mesylate was registered by the US FDA on 19 Oct 2010⁵² and is marketed by Boehringer Ingelheim as Pradaxa[®] capsules. This product has NCE exclusivity until 19 Oct 2015.

The following Orange book patents are listed against the US product

- US 6,087,380 expiring 18 Feb 2018 with priority from 18 Feb 1997 which covers the disubstituted bicyclic heterocyclic compounds and their use in thrombotic diseases (Boehringer Ingelheim)
- US 7,866,474 expiring 11 Aug 2027 with priority from 21 Dec 2004 which covers blister packs for capsules (Boehringer Ingelheim)
- US 7,932,273 expiring 07 Sep 2025 with priority from 29 Feb 2003 which covers dabigatran mesylate (Boehringer Ingelheim)

The pelletized formulation containing a suspension of a specific polymorphic form of dabigatran etexilate mesylate dried onto coated tartaric acid pellets in a fluidised bed process is covered by various Boehringer Ingelheim patents:

- US 2011/0123635 with priority from 13 Jul 2009

⁵¹ Shah SV & Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation (2011) 123(22):2562-70

⁵² NDA 022512 submitted by Boehringer Ingelheim
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>

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- US 2011/0129538 with priority from 28 Mar 2008
- WO 2010/007016 with priority from 14 Jul 2008
- US 2009/118322 with priority from 28 Mar 2008

This is a particularly lengthy and complex process for the pelletization of this acid sensitive drug. A smooth spherical core of tartaric acid with acacia gum is produced which is then coated with a protective coating of hydroxypropyl methylcellulose, dimethylpolysiloxane and talc suspended in ethanol to separate the drug and the tartaric acid. A suspension of drug with hydroxypropyl cellulose in isopropyl alcohol maintained below 30 °C is used to obtain the desired type 1 polymorphic form of the drug which is spray dried onto the coated tartaric acid pellets. The final dried coated pellets are then packed into capsules which have the following formulation shown in Table 3.

Table 3 Formulation of Pradaxa[®] capsules as disclosed in WO 2010/007016:

Ingredient	Mg per capsule	
Dabigatran etexilate mesylate	86.48	126.83
Acacia	4.43	6.50
Tartaric acid	88.56	129.9
Hydroxypropyl methylcellulose 2910	2.23	3.27
Dimethylpolysiloxane 350	0.04	0.06
Talc	17.16	25.16
Hydroxypropyl cellulose	17.30	25.37
Total contents	216.2	317.1

The use of dabigatran as an improved treatment for thromboses compared with warfarin at doses of 150 – 300 mg twice daily is covered by a series of Boehringer Ingelheim patents all with the same priority dates from 11 Nov 2008 and 27 Aug 2009, WO 2010/055022, WO 2010/055023, US/2010/0322869 and US/2010/0322870.

The synthesis of the drug is covered by a number of different patents including WO 2011/061080 (Boehringer Ingelheim) with priority from 18 Nov 2009, US 2011/0082299 and WO 2009/111997 with priority from 14 Mar 2008, WO 2010/045900 with priority from 24 Oct 2008.

WO 2010/086329 (Boehringer Ingelheim) covers lyophilized dabigatran etexilate mesylate as a calibrator for PD effects and assays. The drug is dissolved in acid and freeze-dried.

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A Surge Dose[®] dabigatran would be covered by the broad claims in the Imaginot PCT/AU 2005/00759 (WO/2005/115345) with priority dating from 28 May 2004. While this does not provide extended patent life beyond the patents on the current pelletized tartaric acid formulation, there is the potential for further patents that can be filed on specific formulations of dabigatran utilizing this fast dissolution technology which will have later filing and expiry dates to extend the period of protection.

6 Conclusions

Dabigatran etexilate, the prodrug of dabigatran appears to be a suitable candidate for application of Imaginot's Surge Dose[®] technology to provide a formulation with different absorption characteristics to the current pellet filled capsule. Fast dissolving Surge Dose[®] dabigatran tablets will provide improved *in vivo* dissolution which will result in faster and more consistent absorption. An optimized Surge Dose[®] dabigatran etexilate tablet would be expected to provide improved oral bioavailability through increasing the extent and rate of dissolution of the prodrug. The current capsule has an oral availability of 6 -7 % increased by 75 % (to around 12 %) if the capsule is broken and the loose pellets swallowed. This highlights a potential risk with the current formulation which may contribute to the high level of variability seen and the high level of bleeds seen with higher doses.

While dabigatran is positioned to be an improved anticoagulant to replace warfarin with predictable PK and PD effects, major bleeds remain a significant issue. In addition C_{max} and T_{max} data indicate a high level of intersubject variability with C_{max} variability around 50 % and T_{max} values ranging from 1.5 – 6 hours. Clinical data on dabigatran suggests a fine balance between efficacy and major bleeds, both of which are dose related. While 110 mg twice daily offers improved bleeding it is non-superior to warfarin. However 150 mg twice daily is superior to warfarin but has a similar risk of bleeding. The variability in absorption requires a higher dose for efficacy in those subjects experiencing slow absorption and low plasma concentrations. More consistent absorption will remove the tail of slow absorbers who are currently more likely to show an inadequate response.

An optimized Surge Dose[®] formulation will maximize the extent and rate of *in vivo* dissolution independent of physiological conditions, leading to faster delivery of the drug in solution into the small intestine whence absorption occurs by passive diffusion. Faster absorption from Surge Dose[®] formulations results in shorter and more consistent T_{max} values which drive higher C_{max} values. This provides the opportunity to allow dose reduction without compromising efficacy. Given the long elimination half-life of the drug, and the direct method of action in inhibiting thrombin, the target would be to achieve similar

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C_{max} values with lower doses of drug which would reduce the total exposure and hence reduce the risk of bleeding.

An important consideration is that all clinical studies have been based on the current pelletized tartaric acid formulation, which is covered by patents expiring in 2028 and 2029. The tartaric acid is required to facilitate dissolution of this basic drug independent of gastrointestinal pH. The complexity and variability of the manufacturing process for the pellets effectively provides a further barrier to generic competition as formulations will need to demonstrate bioequivalence and further clinical studies may be required. Conventional tablets or capsules are unlikely to offer the same PK profile.

An immediate release Surge Dose[®] formulation differs from the current patented Pradaxa[®] dabigatran etexilate capsule formulation. Based on the processing method and extensive coating of the pellets, drug dissolution is unlikely to be fast and absorption would be expected to be dissolution rate limited despite the high levels of tartaric acid to enhance solubility. No *in vitro* or *in vivo* release kinetics are given for the resultant pelletized formulation which has been used for all the PK and clinical studies.

In contrast, an optimized Surge Dose[®] formulation will maximize the dissolution rate of dabigatran etexilate across a wide range of *in vitro* conditions and provide a robust stable tablet suitable for commercial manufacture. Each tablet is likely to contain a low level of sodium bicarbonate (<200 mg) with an excess of organic acid (<500 mg) and would demonstrate faster and more extensive dissolution than the current pelletized capsule when tested in 900 mL 0.0033 M HCl at 30 rpm and 0rpm 37°C.

Of significance is the fact that if the pellets are removed from the outer capsule before administration, the bioavailability of the drug is significantly increased by 75 %, up to around 12 %, possibly as a result of acidic solubilization of the drug in the stomach. This provides supporting evidence for the proposition that a Surge Dose[®] dabigatran could allow the use of a lower dose within the current therapeutic range as a result of improved availability which would reduce the risks associated with major bleeds without compromising efficacy.

This review concludes that dabigatran is a suitable candidate for application of Imaginot's Surge Dose[®] technology which would provide an ever-greening strategy to switch to or introduce a lower dose immediate release product prior to patent expiry. The current patented pelletized formulation and its use for all the clinical studies submitted for registration provide an effective barrier to generic competition which is likely to require significant clinical programs to demonstrate bioequivalence to the pelletized product. Given this scenario, it appears that there is a significant opportunity for Boehringer Ingelheim to

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develop a new improved patented formulation prior to patent expiry which would effectively extend the period of protection. A lower dose immediate release product such as a Surge Dose[®] dabigatran tablet is likely to offer an improved safety profile with comparable efficacy and lower cost, further improving the safety profile relative to warfarin. Such a strategy with an approved lower dose improved product would make it difficult to market higher dose generic products.