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

Imaginot Pty Ltd

ABN 34 089 023 352

Ground floor

100, Ipswich Rd

Woolloongabba

Qld 4102 Australia

Phone

+617 3392 3811

Contacts

Managing Director, Garth MacDonald

gmacdonald@imaginot.com.au

R&D Director, Geraldine Elliott

gelliott@imaginot.com.au

Reviewers Dr Michael Robertson, Consultant Independent Forensic Consulting

Dr Geraldine Elliott, R & D Director Imaginot Pty Ltd

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EXECUTIVE SUMMARY

This review considers roflumilast, a selective phosphodiesterase inhibitor (PDE-4I) currently approved for the treatment of Chronic Obstructive Pulmonary Disease (COPD) as a candidate for the application of Imaginot's Surge Dose® ultra-fast activated dissolution drug delivery technology. Roflumilast is also under evaluation in a number of other inflammatory indications including asthma. A Surge Dose® roflumilast tablet would increase this drug's rate of *in vivo* dissolution, reduce absorption variability and improve efficacy with:

- shorter times to onset and peak anti-inflammatory effect and
- the potential for use of lower doses such that centrally mediated side effects can be reduced without compromising efficacy.

Although roflumilast is well absorbed orally with bioavailability around 80 % and T_{max} around 1 h in fasted subjects, there is evidence of solubility and dissolution rate limited absorption with gastric emptying contributing to the high inter- and intra-subject variability of 45 % and 20 % respectively. Some subjects achieve T_{max} within 30 minutes whereas others do not achieve T_{max} until 3 hours with correspondingly lower C_{max} values that may result in lack of efficacy. This is consistent with roflumilast being an acidic drug with a pKa at 8.74. Solubility is pH dependent with lower solubility at low pH which means that the drug must reach the more alkaline environment of the small intestine before significant dissolution occurs and dissolved drug can be absorbed. A Surge Dose® roflumilast should achieve more faster T_{max} values around 30 min with higher C_{max} values which should result in improved efficacy compared with existing tablets.

The low, pH dependent solubility of roflumilast is clearly recognized and a number of approaches have been patented to increase its solubility and hence improve its bioavailability and subsequent efficacy. These include the use of alkoxylated fats and high pH to solubilise the drug in injectable formulations as well as the use of micronized drug and solubilized forms of the drug in solid dosage forms. The marketed product uses PVP as a binder and alkaline excipients described in patents based on the improved bioavailability observed with such formulations. However, the information available suggests that these formulations have not been optimized to maximize *in vivo* dissolution as would be achieved using the Surge Dose® technology. Roflumilast is covered by the broad platform claims in Imaginot's patent WO/2007/059591 on acidic drugs and there is

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the potential for drug specific formulation patents to be filed based on unexpected findings in any Surge Dose[®] development program.

Roflumilast is lipophilic which facilitates distribution from the plasma to the peripheral sites of action in the lungs and also into the CNS. It is significant that the major side effects of nausea, headache and insomnia which sometimes lead to treatment withdrawal are thought to be mediated centrally. As a consequence, other PDE4Is are being evaluated by the inhalation route which, although it may reduce side effects and improve efficacy by local administration, is less preferred by patients than a once-daily tablet.

The Surge Dose[®] technology could also be applied to combination products containing roflumilast with other actives such as glucocorticosteroids or bronchodilators. Such formulations would be optimized to achieve fast dissolution and fast absorption of both actives. In addition to WO/2007/059591 covering acidic and unionized drugs, combinations with basic and amphoteric drugs would be covered by WO/2005/115345.

Imaginot's Surge Dose[®] technology was developed based on *in vivo* PK studies with paracetamol which is a known marker for liquids gastric emptying. Significant improvements have been demonstrated in fasted healthy subjects for both paracetamol and two acidic NSAIDs (non-steroidal anti-inflammatory drugs) lornoxicam and diclofenac. Surge Dose[®] has significantly increased the rate and extent of *in vitro* dissolution for more than 30 drugs of different chemical classes predicted to increase the rate and consistency of absorption of these drugs with improved clinical outcomes.

For the fast release paracetamol product (Tylenol[®] Extra Strength Rapid Release Gels), median T_{max} was 45 min but 16 % of subjects never reached the minimum therapeutic level of 10 µg/mL. In contrast, Surge Dose[®] formulations achieved median T_{max} values of 17 and 25 min where > 70 % subjects exceeded 10 µg/mL in the first 15 min compared with only 20 % for Tylenol[®]. Based on these results, PK-PD modelling predicts that Surge Dose[®] paracetamol will demonstrate a significantly faster onset of action and improved clinical efficacy with 20% more patients achieving target end points than Tylenol[®]. This is consistent with fewer sub-therapeutic absorption profiles for Surge Dose[®] formulations and confirmed by the lower predicted NNT (Number Needed to Treat) of 2.8 for Surge Dose[®] compared with 4.2 for Tylenol[®].

An optimised film coated Surge Dose[®] lornoxicam achieved significantly faster T_{max} and higher C_{max} as a result of faster and more consistent absorption compared with a leading commercial tablet. 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 indicating a

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reduction in the number of slow absorption cases. There was more consistent fast absorption with T_{max} ranging from 0.3 to 1 h and 75 % subjects achieving T_{max} within the first 0.5 h. The reference product had a mean T_{max} of 1.06 h and median 0.83 h ranging from 0.5 to 2.3 h with only 8 % subjects achieving T_{max} within the first 0.5 h. Surge Dose® lornoxicam achieved around 40 % higher mean C_{max} of 1098 ng/mL (CV 18.71 %) compared with only 788 ng/mL (CV 18.69 %) for the reference tablet. Absorption of Surge Dose® lornoxicam was similar to that published for IM lornoxicam which achieves faster onset of analgesia and improved efficacy relative to standard lornoxicam tablets.

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

Surge Dose® increases the probability of rapid absorption by controlling the pH of the dissolution reaction for maximum solubility and by creating a mechanism for active dissolution *in vivo*. This ensures that Surge Dose® formulations demonstrate fast dissolution even in limited volumes of fluid available in the stomach and independent of pH and gastric motility. **Gastric pH** varies 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).

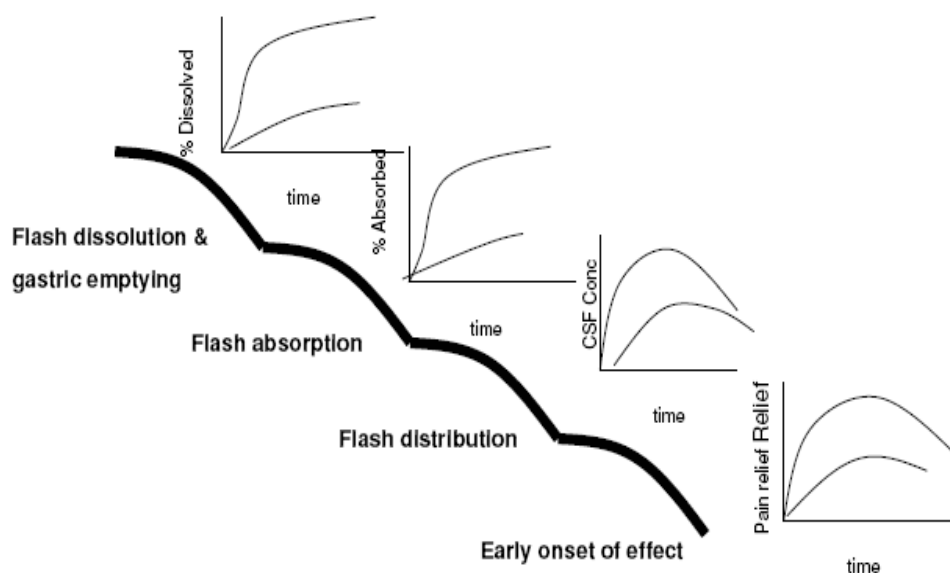
The Surge Dose® cascade is based on higher concentrations of dissolved drug achieving higher plasma concentrations which drive faster distribution to the site of action:

- The drug undergoes ultra-fast activated dissolution in co-administered water and available gastric contents

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- The resultant solution empties rapidly and passively from the stomach in both fed and fasted states i.e. the drug empties as fast as if it had been taken as a solution
- The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption
- Fast absorption quickly saturates any protein binding sites and other saturable metabolic pathways leading to short T_{max} and high C_{max} with reduced intra- and inter-subject variability
- High plasma concentrations drive rapid distribution to the effect compartment resulting in rapid onset of action and rapid peak effect



Surge Dose[®] formulations are optimized to maximise *in vitro* dissolution under specified test conditions using approved GRAS excipients. No major issues would be expected in achieving successful registration. Conventional tablet manufacturing equipment is used at controlled low relative humidity (RH) conditions and unit packaging in moisture-impervious laminates is required for maximum stability. To date Surge Dose[®] formulations of a basic drug and two acidic drugs have been successfully scaled-up for commercial manufacture using direct compression and wet granulation processing and standard film coating techniques. The first Surge Dose[®] product was launched in India in 2011, Lorsaid[®] SD containing 4 and 8 mg lornoxicam. A second product launch is planned for late 2012.

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This review concludes that there is a technically supportable opportunity to develop and register an improved Surge Dose[®] roflumilast that will offer:

- clinical benefits over the current tablets with faster and more consistent absorption which will improve efficacy
- the potential to reduce dosage and reduce side effects without compromising efficacy in existing and new indications
- the opportunity for more compelling clinical efficacy evidence to achieve successful registration in new indications including acute conditions such as perennial rhinitis
- market exclusivity associated with registering a new formulation
- extended patent protection of improved formulations

There is also the potential for developing a combination product of roflumilast with an additional therapeutic agent such as an anti-inflammatory glucocorticosteroids or long acting bronchodilator which could allow reduced dosage of both actives.

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1 Introduction

1.1 Surge Dose[®] drug delivery technology

The Surge Dose[®] formulation technology for fast dissolution and fast absorption of orally administered drugs has been developed by Imaginot Pty Ltd, a privately owned drug delivery company based in Queensland, Australia. Surge Dose[®] formulations provide fast and consistent absorption resulting in faster and more reliable onset of action compared with conventional tablet formulations. 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), lornoxicam and diclofenac in pharmacokinetic (PK) studies in man. Based on PK-PD (pharmacodynamic) modelling, Surge Dose[®] paracetamol is predicted to achieve improved efficacy as the variable absorption of currently marketed tablets results in frequent sub-therapeutic plasma levels with an associated lack of efficacy.

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

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

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

Surge Dose[®] provides a convenient, portable easy-to-swallow tablet that can be easily manufactured and will effectively compete with the newer second generation 'fast' formulations such as liquid filled soft capsules, ODTs and absorption enhanced tablets. In practice these do

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not deliver the desired fast and consistent onset of action required for drugs taken on demand and exhibit slower *in vivo* dissolution and absorption. Soluble formulations present major problems in relation to convenience of use and palatability. Liquid dosage forms provide faster absorption but tend to be less stable, require taste masking, flavouring and satisfactory preservation against microbial spoilage, are less convenient to use, are bulky, may require controlled storage and can be expensive to manufacture.

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 therapeutic agents claiming priority 28 Nov 2004. This has been granted in Australia and is in examination 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. This has been granted in Australia and Canada without limitation and is under examination in US, Europe, India and Japan.
- iii. PCT/AU 2005/00758 published as WO/2005/115344 covering paracetamol and paracetamol combinations has been assigned to a third party in Australia, Europe, India and Japan. The patent has been granted in Australia, Canada and US.

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

Surge Dose[®] tablet formulations are designed to maximize the rate and extent of drug dissolution in co-administered water and available liquid in the stomach. This provides a high drug concentration reaching the small intestine driving rapid absorption and resulting in 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 ultra-fast activated dissolution system as demonstrated by *in vitro* testing. The pH modulating agents have a dual role, providing effervescence which disrupts the boundary layers around dissolving drug particles independent of the gastric pH, and controlling the pH in the microenvironment of the tablets to maximize drug solubility. As solutions drain rapidly from the stomach independent of

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gastric motility (Migrating Motility Complex (MMC)), higher concentrations of dissolved drug in the first few minutes after administration mean provide higher drug concentrations in the small intestine to drive faster absorption.

In contrast, traditional tablet formulations release drug slowly into solution by passive diffusion across stagnant boundary layers around dissolving drug particles which provide a barrier to fast dissolution. Such slow dissolving tablets produce only low concentrations of dissolved drug and rely on MMC gastric emptying for drug absorption.

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

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

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

- 900 mL 0.05 M HCl at 30 rpm is frequently used in pharmacopoeial test methods, where pH 1.2 is similar to that in the fasted stomach, but with a higher volume and higher total amount of acid than found *in vivo*
- 900 mL 0.0033 M HCl at 30 rpm, pH 2.2, contains the finite amount of acid (3 mmoles) estimated to be present in the fasted stomach *in vivo*, and are the conditions used to characterise Surge Dose® formulations in the Imaginot patents

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- 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, three deals have been completed involving a major international pharmaceutical company (confidential), a French drug delivery company (Ethypharm SA) and India's largest pharmaceutical company (Abbot India). Imaginot has an agreement with Piramal Healthcare Ltd. in India for the contract development and manufacture of Surge Dose[®] formulations. Piramal can undertake 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.

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 Clinical premise for Surge Dose[®]

2.1 Key sources of physiological variability affecting drug absorption

2.1.1 Gastrointestinal (GI) motility

Drug absorption following oral administration is influenced by:

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

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- iii. the rate of passive emptying of liquids, including dissolved drug, from the stomach into the small intestine which is independent of the MMC.

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

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

Independent of these MMC phases, liquids empty relatively quickly and exponentially from the stomach with a half life in the region of 20 min during Phase I, reduced by Phase II or Phase III MMC activity to 12 and 5 min respectively¹.

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

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

¹ Oberle RL, Chen T-Z, Lloyd C, Barnett JL, Owyang C, Meyer J, Amidon GL. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroent* (1990) **99**:1275-1282

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Delayed absorption and reduced variability seen in fed studies result from the fact that the underlying MMC is interrupted by the ingestion of food which generally triggers Phase I MMC².

GI motility can be influenced by other factors, and where slowing occurs this will have an impact on gastric emptying and subsequent drug absorption. Certain pathological conditions will reduce GI activity such as diabetes mellitus and also migraine where drug efficacy can be delayed by gut stasis. Opiates, where fast onset of action is required, generally reduce GI activity which will slow absorption and hence slow onset of action.

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

2.1.2 GI pH

2.1.2.1 Stomach

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

² Rees WD, Go VL, Malagelada JR. Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. *Gut* (1979) **20** (Nov):963-970

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

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

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

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

2.1.2.2 Small intestine

Conditions in the small intestine which is the primary site for absorption of most drugs, differ to those in the stomach, with a more consistent higher pH and high secretion rates of relatively alkaline intestinal fluids. Under such conditions, poorly soluble drugs which are weak bases and are more soluble under acidic conditions in the stomach may precipitate out. This will slow absorption and may be responsible for long T_{max} values seen for drugs which are weak bases. This problem is well recognized and *in vitro* methods have been developed to predict the impact of such behaviour on drug absorption^{3,4,5}.

Where a basic drug has not already completely dissolved in the stomach, the alkaline secretions will reduce solubility and hence delay dissolution and slow absorption. There is also the potential for precipitation of the less soluble form on the surface of undissolved drug which will further slow dissolution and absorption. This is demonstrated for the antifungal agent

³ Kostewicz ES, Brauns U, Becker R, Dressman JB. Forecasting the oral absorption behaviour of poorly soluble weak bases using solubility and dissolution studies in biorelevant media Pharm Res (2002) 19:345-9

⁴ Kostewicz ES, Wunderlich M, Brauns U, Becker R, Bock T, Dressman JB. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. JPP (2004) 56:43-51

⁵ Gu C-H, Rao D, Gandhi RB, Hilden J, Raghavan K. Using a novel multicompartiment dissolution system to predict the effect of gastric pH on the oral absorption of weak bases with poor intrinsic solubility. J Pharm Sci (2005) 94(1):199-208

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itraconazole, where use of hydroxypropyl methylcellulose as a precipitation inhibitor improved its oral bioavailability by some 60 % in rats⁶.

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

2.2 Clinical rationale

Drug absorption following oral administration is influenced by:

- 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
- iv. 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

⁶ Van Speybroeck M, Mols R, Mellaerts R, Thi TD, Martens JA, van Humbeeck J, Annaert P, van den Mooter G, Augustijns P. Combined use of ordered mesoporous silica and precipitation inhibitors for improved oral bioavailability of the poorly soluble weak base itraconazole. Eur J Pharm Biopharm (2010) 75:354-65

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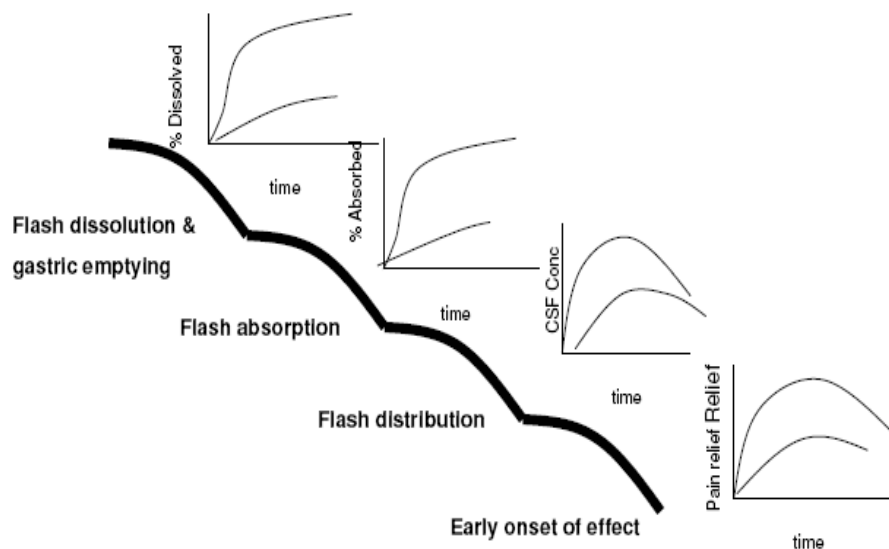
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solid dosage form into the co-administered liquid and gastric contents provides the maximum concentration to drive absorption and distribution to effect compartments by passive diffusion resulting in faster onset of action and improved efficacy.

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

Surge Dose[®] is designed to maximize the extent of drug dissolution in the stomach so that dissolved drug quickly reaches the small intestine independent of the MMC as summarized below:

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

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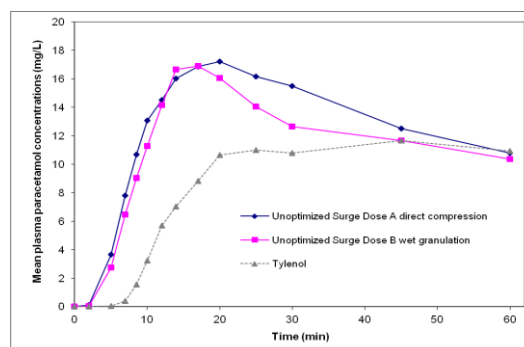
- iii. The concentrated bolus of dissolved drug reaching the small intestine sets up a high concentration gradient providing high driving forces for rapid absorption
- iv. Fast absorption quickly saturates any protein binding sites and saturable metabolic and transport processes leading to earlier achievement of therapeutic plasma concentrations with short T_{max} and high C_{max} as well as reduced intra- and inter-subject variability
- v. High plasma concentrations drive rapid distribution to effect compartments resulting in rapid onset of action and rapid peak effect

2.3 Proof of concept

2.3.1 Paracetamol

Data from a Phase I study in 25 fasted healthy subjects⁷ demonstrated significantly faster absorption with two fast dissolving Surge Dose[®] paracetamol formulations that have subsequently been improved, compared with Tylenol[®] Extra Strength Rapid Release Gels (McNeil Consumer, US) <Tylenol[®]>. Absorption was faster as shown in Figure 2.

Figure 2 Mean plasma concentration – time profiles for a 1,000 mg paracetamol dose delivered from two unoptimized Surge Dose[®] formulations paracetamol and Tylenol[®] Extra Strength Rapid Release Gels in fasted healthy subjects



- Median T_{max} values for Surge Dose[®] 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[®]

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

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- 64 and 76 % subjects receiving Surge Dose[®] paracetamol exceeded the minimum therapeutic level of 10 µg/mL in the first 15 min compared with only 20 % for 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[®] tablets⁸. Improved clinical efficacy is predicted for Surge Dose[®] formulations as a result of fewer sub-therapeutic absorption profiles with 20% more patients achieving target end points than Tylenol[®]. This is reflected in the predicted lower NNT (Number Needed to Treat) of 2.8 for Surge Dose[®] compared with 4.2 for Tylenol[®].

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

2.3.2 Lornoxicam

A PK study in 24 fasted subjects demonstrated Surge Dose[®] maximises *in vivo* lornoxicam dissolution rates and achieves faster absorption than a conventional tablet as seen in Figure 3⁹. Surge Dose[®] tablets significantly reduced T_{max} and resulted in significantly higher C_{max} levels

⁸ Green B, Chandler S, Macdonald G, Elliott G, Roberts MS. Quantifying pain relief following administration of a novel formulation of paracetamol (acetaminophen), *J. Clin. Pharmacol.* (2010) Online First doi 10.1177/0091270009359181

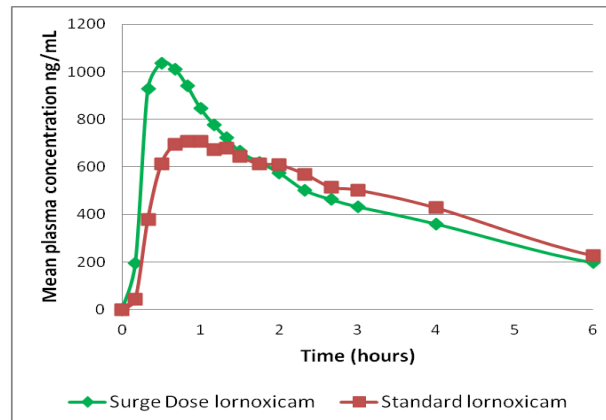
⁹ Wellquest Clinical Research. Report No CR-BE-267-LORN-2009. An open label, balanced, randomised, two-treatment, two-period, two-sequence, cross-over, single-dose bioequivalence study of Lornoxicam Rapid Release 8 mg tablets comparing with Lornoxicam 8 mg tablets in healthy adult human subjects under fasting conditions. 11 Aug 2010

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similar to parenteral administration¹⁰. Faster and more consistent absorption has the potential to improve efficacy.

Figure 3 Mean plasma concentration – time profiles for Surge Dose[®] lornoxicam 8 mg and Lorsaid[®] 8 mg tablets in fasted healthy subjects



Absorption from Surge Dose[®] lornoxicam tablets was twice as fast:

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

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

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Surge Dose[®] lornoxicam PK were similar to those published for IM lornoxicam and a quick release lornoxicam tablet which achieves faster onset of analgesia and improved efficacy relative to standard lornoxicam tablets¹¹.

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^{12,13} or IM^{14,15} administration whereas those for Voveran[®]-D were lower than $1,340 \pm 627$ ng/mL reported for standard tablets¹⁶.

¹¹ Moller PL & Norholt SE. Analgesic efficacy of quick release versus standard lornoxicam for pain after third molar surgery. Clin Drug Invest (2008) 28 (12) 757-766

¹² Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Brune K, Werner U. Bioavailability of diclofenac potassium at low doses. Br J Clin Pharmacol (2005) 59(1):80-84

¹³ Willis JV, Kendall MJ, Flinn RM, Thornhill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. Eur J Clin Pharmacol (1979) 16:405-10

¹⁴ Auler JO, Espada EB, Crivelli E, Quintavalle TBG, Kurata A, Stolf NAG, Issy AM, Paschoa OED, Danhof M, Breimer DD, Chamone DAF, Santos SRCJ. Diclofenac plasma protein binding: PK-PD modelling in cardiac patients submitted to cardiopulmonary bypass. Braz J Med Biol Res (1997) 30:369-74

¹⁵ Derendorf H, Mullersman G, Barth J, Gruner A, Mollmann H. Pharmacokinetics of diclofenac sodium after intramuscular administration in combination with triamcinolone acetate. Eur J Clin Pharmacol (1986) 31:363-5

¹⁶ Reiner V, Reiner A, Reiner G, Conti M. Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. Arznei-Forsch/Drug Res (2001) 51(11): 885 – 890

- 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 Roflumilast

3.1 Phosphodiesterase 4 (PDE4) inhibitors

Phosphodiesterases (PDEs) are intracellular enzymes widely distributed in the body that specifically hydrolyze the cyclic nucleotides adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP). Many different isoforms are involved in physiological processes mediated at the cellular level by cAMP and cGMP, with inhibition prolonging or enhancing the effect. PDE4 is specific for cAMP and is expressed in lung smooth muscle, airways epithelial cells and inflammatory cells in the lungs. PDE4 inhibition increases intracellular cAMP and typically leads to anti-inflammatory and bronchodilator effects.

Roflumilast is a selective phosphodiesterase 4 inhibitor (PDE-4I) which has more of an anti-inflammatory effect than a bronchodilator effect as the increase in intracellular cAMP is less in smooth muscle cells and greater in inflammatory and airway epithelial cells¹⁷. Roflumilast targets systemic and pulmonary inflammation caused by PDE4A, 4B and 4D but not the PDE4C splicing variants. Roflumilast N-oxide, the major active metabolite has a similar selectivity.

The use of non-selective PDEIs such as the methylxanthine theophylline, in respiratory conditions such as asthma and COPD (chronic obstructive pulmonary disease) has been limited by side effects and the relatively narrow therapeutic index. With evaluation of the newer specific PDE4Is, the side effects of nausea and headache seen with PDE4Is and theophylline are now known to be caused by central PDE4 inhibition in the area postrema (CTZ) resulting in increased cAMP levels which trigger emesis.

Other drugs in this category include:

- cilomilast (GSK), the first drug in this class, which was rejected by the FDA in 2003 citing lack of substantial efficacy based on improved lung function (FEV1) in COPD

¹⁷ Antoniu SA. New therapeutic options in the management of COPD – focus on roflumilast. Int J COPD (2011) 6:147-55

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- the quinoline carboxamide GSK256066 administered by inhalation in an attempt to reduce systemic side effects has completed phase II studies in asthma, COPD and allergic rhinitis¹⁸ and is more potent *in vitro* than roflumilast¹⁹
- Oglemilast (GRC-3886, Glenmark/Forest/Teijin) is currently in Phase IIb clinical trials for asthma and COPD
- OX914 (BLX-028914, Orexo) discovered by Inflazyme (IPL-455,903) and developed by Helicon for learning and memory disorders, is in Phase II trials for asthma and COPD²⁰
- Merck, Elbion and Celgene also have PDE-4I drugs in early stages of development²¹

3.2 Therapeutic indications

Chronic lower respiratory disease including asthma, COPD, chronic bronchitis and emphysema is the fourth leading cause of mortality (5.3 %) in the US responsible for 128,000 deaths each year the majority attributable to COPD²². Asthma prevalence is increasing affecting around 1 in 10 children and 1 in 20 adults while COPD affects around 1 in 25 of the adult US population.

COPD is an inflammatory disease of the airways related to smoking associated with air flow limitation. Chronic airways inflammation leads to progressive obstruction, lung damage, mucous hyper secretion, abnormalities in gas exchange and ultimately respiratory failure. Although inhaled bronchodilators and anti-inflammatory glucocorticosteroids have been the gold standard treatment for COPD and asthma, there is a clear preference for oral therapy as many patients have problems using inhaler devices²³ and are not adequately controlled with inhaled corticosteroids²⁴. Roflumilast meets that need for a once daily oral administration and to date

¹⁸ Higgs G. Is PDE4 too difficult a drug target? *Current Opinion in Investigational Drugs* (2010) **11**(5):495-498

¹⁹ Tralau-Stewart CJ, Williamson RA, Nials AT, Gasgoigne M, Dawson J, Hart GJ, Angell AD, Solanke YE, Lucas FS, Wiseman J, Ward P, Ranshaw LE, Knowles RG. *J Pharmacol Exp Ther* (2011) **337**(1):1545-54

²⁰ Pages L, Gavalda A, Lehner M. PDE4 inhibitors: a review of current developments (2005 – 2009). *Expert Opin. Ther. Patents* (2009) **19**(11):1501-1519

²¹ Blease K, Raymon H. Small molecule inhibitors of cell signaling: Novel future therapeutics for asthma and chronic obstructive pulmonary diseases. *Current Opinion in Investigational Drugs* (2003) **4**(5):544-551

²² Centers for Disease Control and Prevention Death statistics 2007
<http://www.cdc.gov/nchs/fastats/asthma.htm>

²³ Boswell-Smith V, Page C. Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of respiratory disease. *Expert Opin. Investig. Drugs*. (2006) **15**(9):1105-1113

²⁴ Bethke T, Bohmer G, Hermann R, Hauns B, Fux R, Morike K, David M, Knoerzer D, Wurst W, Gleiter C. Dose-Proportional Intraindividual Single- and Repeated-Dose Pharmacokinetics of Roflumilast, an Oral, Once-Daily Phosphodiesterase 4 Inhibitor. *J. Clin. Pharmacol.* (2007) **47**:26-36

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been approved for COPD although an extensive clinical evaluation continues for asthma, allergic rhinitis, osteo-arthritis and rheumatoid arthritis.

There are other potential indications for roflumilast consistent with its anti-inflammatory mechanism of action including inflammatory bowel disease and psoriasis²⁵. A recent study has demonstrated that roflumilast is effective in relieving the symptoms of allergic rhinitis²⁶. It is also being evaluated in diabetes mellitus, pulmonary hypertension and for the prophylaxis or treatment of emphysema²⁷. With direct evidence reported of PDE4-dependent pathways in human rheumatoid arthritis synovial inflammatory cytokine and chemokine release, roflumilast may also have application in treating chronic autoimmune conditions like rheumatoid arthritis²⁸.

3.3 Regulatory status

Altana Pharma AG (Eu) collaborated with Pharmacia Corp (now Pfizer) in the US²⁹ and Tanabe Seiyaku Co Ltd in Japan³⁰ on the development of roflumilast. Although now approved in Europe and the US, approved indications are different based on different regulatory opinion on the efficacy data submitted³¹. This drug was first approved as Daxas[®] in the EU for the maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment (23 Apr 2010)³². In the US, Forest Pharmaceuticals took over Nycomed's submission filed for "maintenance treatment of COPD associated with chronic bronchitis in patients with risk of exacerbation" in Dec 2009³³. Forest revised the indication to "maintenance treatment to reduce exacerbation of

²⁵ Page CP & Spina D. Phosphodiesterase inhibitors in the treatment of inflammatory diseases. *Handbook Exper Pharmacol* (2011) 204:391-414

²⁶ Schmidt B, Kusma M, Feuring M, Timmer W, Neuhauser M, Bethke T, Stuck B, Hormann K, Wehling M. The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis. *J Allergy Clin Immunol* (2001) **108**(4):530-536

²⁷ Pages L, Gavalda A, Lehner M. PDE4 inhibitors: a review of current developments (2005 – 2009). *Expert Opin. Ther. Patents* (2009) **19**(11):1501-1519

²⁸ Crilly A, Robertson SE, Reilly JH, Gracie LA, Lai WQ, Leung BP, Life PF, McInnes IB. Phosphodiesterase 4 (PDE4) regulation of proinflammatory cytokine and chemokine release from the rheumatoid synovial membrane. *Ann Rheum Dis* (2011) **70**(6):1130-7

²⁹ Reid. P. Roflumilast. *Current Opinion in Investigational Drugs* (2002) **3**(8):1165-1170

³⁰ Roflumilast. *Drugs*. (2004) **5**(3):176-181

³¹ Cazzola M. The divergent opinions of regulatory authorities on roflumilast are puzzling but we need new drugs for treating chronic obstructive pulmonary disease. *Ther Adv Respir Dis* (2010) **4**(4):195-8

³² European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001179/human_med_001363.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124

³³ NDA 022-522

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COPD associated with chronic bronchitis in patients at risk of exacerbation” and in Feb 2011, Daliresp[®] was approved as “a once daily treatment to reduce exacerbation of COPD associated with chronic bronchitis in patients at risk of exacerbation”. Forest highlighted safety concerns based on psychiatric adverse reactions including suicidality risks with a product label warning.

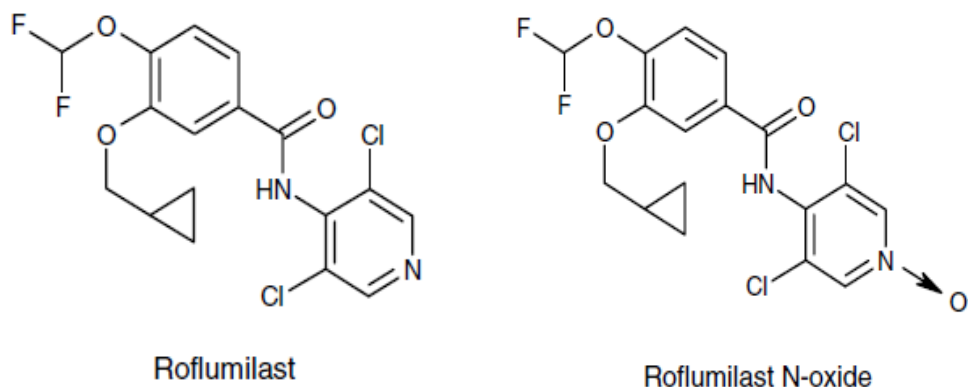
Daliresp[®] and Daxas[®] tablets contain 500 µg roflumilast with lactose monohydrate, corn starch, povidone (PVP) and magnesium stearate^{34,35}. Daliresp[®] tablets are uncoated, and Daxas[®] tablets are yellow film-coated.

3.4 Physicochemical properties

3.4.1 Structure

Roflumilast [3-cyclopropylmethoxy-4-difluoromethoxy-*N*-(3,5-dichloropyrid-4-yl)-benzamide] has the empirical formula C₁₇H₁₄Cl₂F₂N₂O₃, molecular weight 403.2^{36,37} and structure shown in Figure 4 compared with its active N-oxide metabolite. Roflumilast exists as single polymorph.

Figure 4 Chemical structures of roflumilast and its active N-oxide metabolite³⁸.



³⁴ NDA 022 522 Roflumilast Chemistry review: p 2

³⁵ CHMP assessment report EMA/464905/2010 Page 6/46

³⁶ Boswell-Smith V, Page C. Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of respiratory disease. *Expert Opin. Investig. Drugs*. (2006) **15**(9):1105-1113

³⁷ Cazzola M, Picciolo S, Matera M. Roflumilast in chronic obstructive pulmonary disease: evidence from large trials. *Expert Opin. Pharmacother*. (2010) **11**(3):441-449

³⁸ Antoniu S. Roflumilast for the treatment of chronic obstructive pulmonary disease. *Current Opinion in Investigational Drugs* (2006) **7**(5):412-417

3.4.2 Solubility

Roflumilast is a weak acid with a pKa of 8.74 and pH dependent solubility. Its solubility in water is 0.52 – 0.56 µg/mL at 22°C³⁹ so that a dose of 500 µg needs around 1,000 mL water for complete dissolution. Its solubility increases from about 0.8 µg/mL in neutral conditions to about 35.8 µg/mL at pH 10. Although micronized roflumilast is used in pharmaceutical formulations to provide an increased surface area to facilitate dissolution, clear solutions have been produced by the use of alkoxylated fats at pH 7.0 – 7.4⁴⁰, and by increasing solution pH to 10 – 13⁴¹.

3.4.3 Permeability

Roflumilast is highly lipophilic with a logP at pH 7.4 of 3.99 which favours absorption across the intestinal mucosa and distribution into the tissues and CNS⁴². The higher the concentration of drug in solution reaching the small intestine, the higher will be driving force for absorption and distribution. While pH will influence roflumilast solubility, it will have little effect on absorption as with a pKa of 8.74, the drug will be mostly unionized over the physiological range of pH 1 – 7.

3.4.4 BCS classification and IVIVC

Roflumilast is classified as a BCS class 2 based on its low solubility and high permeability⁴³. As such it would be expected to show an *in vitro in vivo* correlation (IVIVC) with the rate of absorption being dependent on the rate of dissolution.

Dissolution in acidic fasted conditions is likely to be solubility limited, with most dissolution occurring when the drug reaches the more alkaline intestinal environment. Variability would be expected to result from changes in gastric pH and motility which vary significantly during the day and are affected by age, disease state and concurrent medications. Higher less acidic pH will occur in the fed state and in patients taking antacids or histamine H₂-receptor antagonists.

Although dissolution specifications and test conditions are not published in the regulatory reviews, it is noted that particle size is directly correlated with dissolution and needs to be

³⁹ CHMP assessment report EMA/464905/2010 Page 6/46

⁴⁰ EP 1 796 668 Aqueous pharmaceutical preparation comprising roflumilast. Nycomed GmbH

⁴¹ WO/2006/032676 Pharmaceutical compositions comprising roflumilast or the N-oxide of roflumilast. Altana Pharma

⁴² CHMP assessment report EMA/464905/2010 Page 6/46

⁴³ NDA 022522 Roflumilast Medical review: p 5 of 34

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controlled^{44,45}. Micronized drug is used in the approved formulations so that the smaller particle size and larger surface area will facilitate dissolution.

Surge Dose[®] roflumilast will leverage pH effects on solubility to increase the extent and rate of dissolution for faster delivery of a higher concentration into the small intestine, driving faster absorption and distribution across a wide range of physiological conditions

3.5 Pharmacokinetics (PK)

3.5.1 ADME

After IV administration, roflumilast has a clearance of 0.14 l/h/kg, volume of distribution 2.92 l/kg and terminal elimination half life ($t_{1/2}$) 14.8 h⁴⁶. It is well absorbed after oral administration, with mean absolute bioavailability around 80 % as a result of hepatic metabolism to the active metabolite, roflumilast-N-oxide by CYP3A and CYP1A2 enzymes which is subsequently dealkylated by CYP3A4 and glucuronidated^{47,48}.

Both parent drug and metabolite have high plasma protein binding of 99 % and 97 % respectively⁴⁹ which is non-saturable in the clinical range. Reported $t_{1/2}$ for roflumilast and roflumilast N-oxide are around 17 hours and 27 hours respectively⁵⁰ with approximately 70% excreted via the urine and 20% in the feces⁵¹. Steady state levels of roflumilast and its metabolite are achieved in 4 and 6 days respectively.

⁴⁴ NDA 022522 Roflumilast Chemistry review: p 1-3

⁴⁵ CHMP assessment report EMA/464905/2010 Page 8/46

⁴⁶ Bethke TD & Lahu G. High absolute bioavailability of the new oral phosphodiesterase-4 inhibitor roflumilast. *Int J Clin Pharmacol Ther* (2011) 49(1):51-7

⁴⁷ Hermann R, Nassr N, Lahu G, Peterfai E, Knoerzer D, Herzog, R, Zech K, de May C. Steady-state pharmacokinetics of Roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. *Clin Pharmacokinet* (2007); **46**(5):403-416

⁴⁸ Bohmer G, Gleiter C, Morike K, Nassr N, Walz A, Lahu G. No Dose Adjustment on Coadministration of the PDE4 Inhibitor Roflumilast With a Weak CYP3A, CYP1A2, and CYP2C19 Inhibitor: An Investigation Using Cimetidine. *J Clin Pharm OnlineFirst*, published on May 19, 2010 as doi:10.1177/0091270010368282

⁴⁹ CHMP Assessment Report, p 19

⁵⁰ Bohmer G, Gleiter C, Morike K, Nassr N, Walz A, Lahu G. No Dose Adjustment on Coadministration of the PDE4 Inhibitor Roflumilast With a Weak CYP3A, CYP1A2, and CYP2C19 Inhibitor: An Investigation Using Cimetidine. *J Clin Pharm OnlineFirst*, published on May 19, 2010 as doi:10.1177/0091270010368282

⁵¹ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 22

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Roflumilast exhibits linear PK across the therapeutic range of 250 µg - 1000 µg⁵² with a dose proportional increase in C_{max} and AUC values for the parent drug and metabolite. Oral absorption is relatively fast reaching T_{max} within around 1 h for roflumilast and around 11 – 12 h for the metabolite as shown in Figure 5 and Table 1⁵³. 250 µg and 500 µg tablets were taken with 240 mL water by 19 healthy fasting subjects with the first two sampling points at 30 minutes and 1 hour post-dose.

Figure 5 Mean (\pm SD) plasma concentration-time profiles for (a) roflumilast and (b) roflumilast N-oxide after single oral doses of 250 and 500 µg roflumilast (from Bethke et al 2007)

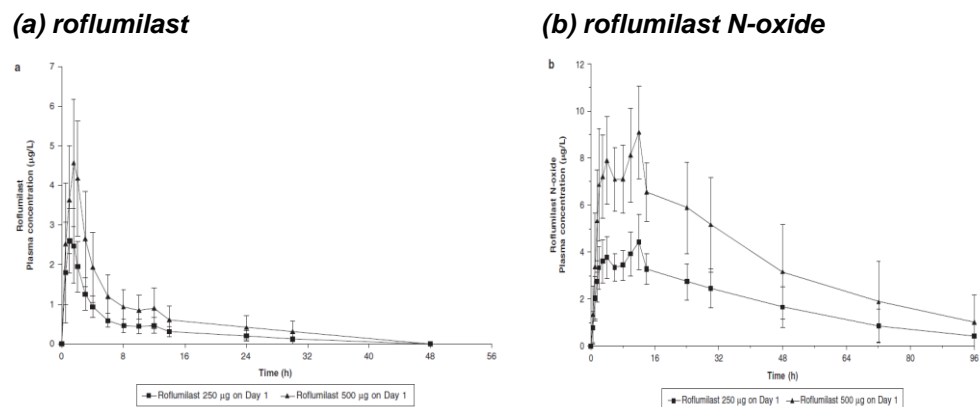


Table 1 Summary of single-dose PK parameters of roflumilast and roflumilast N-oxide following single dose of 250 µg and 500 µg (from Bethke et al 2007)

	Roflumilast		Roflumilast N-oxide	
	Roflumilast 250 µg SD	Roflumilast 500 µg SD	Roflumilast 250 µg SD	Roflumilast 500 µg SD
$AUC_{0-\infty}$, µg·h/L (68% range)	18.1 (11.1, 29.7)	35.0 (20.5, 59.8)	178.6 (115.8, 275.2)	351.3 (235.5, 524.0)
C_{max} , µg/L (68% range)	2.92 (2.0, 4.25)	5.27 (4.19, 6.63)	4.50 (3.50, 5.79)	9.39 (7.48, 11.78)
t_{max} , h (min, max)	1.00 (0.50, 2.00)	1.25 (0.50, 2.00)	12.00 (2.00, 12.00)	11.00 (2.00, 12.00)
$t_{1/2}$, h (68% range)	13.56 (7.26, 25.31)	14.47 (7.86, 26.63)	22.13 (14.58, 33.58)	23.16 (14.24, 37.66)

Data are presented as geometric means with 68% ranges; for t_{max} , median (min, max) values are given.

⁵² NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 3

⁵³ Bethke T, Bohmer G, Hermann R, Hauns B, Fux R, Morike K, David M, Knoerzer D, Wurst W, Gleiter C. Dose-Proportional Intraindividual Single- and Repeated-Dose Pharmacokinetics of Roflumilast, an Oral, Once-Daily Phosphodiesterase 4 Inhibitor. *J. Clin. Pharmacol.* (2007) **47**:26-36

Table 1 shows some evidence of solubility/dissolution rate limited absorption with a trend to longer T_{\max} values as the dose increases. Where the volume of fluids available for dissolution in acidic fasted gastric conditions is the same for all doses, higher doses will demonstrate slower dissolution and complete dissolution may not be achieved. The shorter median T_{\max} of 0.75 h for a lower dose of 125 µg, with a narrower range of 0.5 – 1.0 h, compared with 250 and 500 µg doses is consistent with dissolution rate limited absorption⁵⁴.

High lipid solubility enables rapid distribution from the plasma consistent with its relatively high volume of distribution 2.9 L/kg⁵⁵.

Similar PK have been demonstrated in children from 6 to 16 years of age and in older adolescents and adults⁵⁶. However older patients 45 – 60 years showed an increase in AUC (+27 %) and C_{\max} (+16 %) with smaller increases for the N-oxide metabolite attributable to reduced metabolism. Women tend to show greater exposure to the drug compared with males. Roflumilast shows significantly slower clearance in COPD patients compared with healthy volunteers with 65 % higher exposure as a result of reduced metabolism. Renal impairment has little impact of roflumilast PK⁵⁷ but hepatic impairment significantly increases exposure due to reduced hepatic metabolism.

Some racial differences are evident which may be attributable to polymorphic variability in CYP enzymes involved in roflumilast metabolism. Hispanics show the greatest increase in AUC (+47 %) followed by African Americans (+ 25 %) and then Japanese (+ 16 %) relative to Caucasians.

3.5.2 Absorption variability

Although T_{\max} after 150 µg IV is reproducible $0.22 \text{ h} \pm 0.1 \text{ h}$ ⁵⁸, T_{\max} after oral administration is highly variable with individual subject values ranging from 0.5 to 3 h and median values from 1 –

⁵⁴ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 17

⁵⁵ CHMP Assessment Report, p 19

⁵⁶ Neville K, Szeffler S, Abdel-Rahman S, Lahu G, Zech K, Herzog R, Bethke T, Gleason M, Kearns G. Single-Dose Pharmacokinetics of Roflumilast in Children and Adolescents. *J. Clin. Pharmacol.* (2008) **48**: 978-985

⁵⁷ Bethke TD, Hartmann M, Hunnemeyer A, Lahu G, Gleiter CH. Influence of renal impairment on the pharmacokinetics of oral roflumilast: an open-label, parallel-group, single-centre study. *Int J Clin Pharmacol Ther* (2011) **49**(8):491-9

⁵⁸ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 20

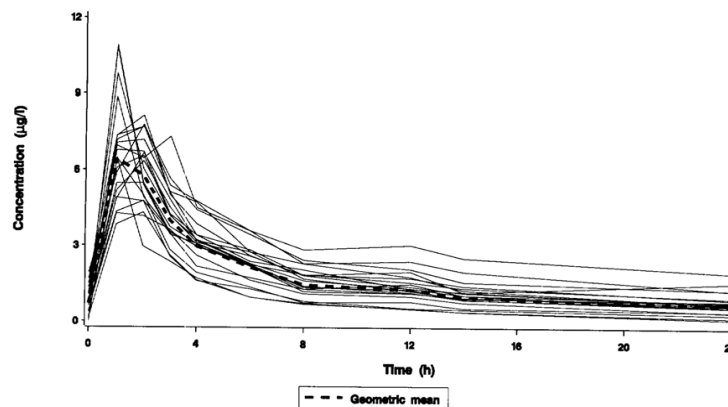
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1.5 hours^{59,60}. Gastric emptying is likely to be a major contributor to the high intersubject variability of around 45 % and intrasubject variability around 20 %.

There is a wide range of individual subject T_{max} values from 30 min to 3.5 h as shown in Figure 6 compared with the geometric median curve after 7 days of dosing with 500 µg roflumilast in 21 fasted healthy subjects⁶¹. Fast absorption occasions with T_{max} at the first or second sampling point less than 1 h associated with high C_{max} values are consistent with Phase III MMC gastric emptying.

Figure 6 Individual absorption profiles with geometric mean after 7 days dosing with 500 µg roflumilast daily in 21 fasted healthy male subjects (from Bethke et al 2007)



Low C_{max} values will result from slow *in vivo* dissolution, where the concentration of dissolved drug reaching the small intestine is low. Low concentrations provide a low driving force for absorption across the gastrointestinal wall. Overall slow *in vivo* dissolution will lead to slow absorption and lower C_{max} values which in some subjects may be sub-therapeutic.

T_{max} values for the N-oxide metabolite were much longer, around 11 – 12 hours ranging from 2 – 12 hours. Secondary peaks in the plasma concentration - time curves of the metabolite when subjects took their meals was attributed to enterohepatic recirculation but could also result from increased hepatic conversion of roflumilast to the N-oxide due to increased blood flow caused by food.

⁵⁹ Bethke T, Bohmer G, Hermann R, Hauns B, Fux R, Morike K, David M, Knoerzer D, Wurst W, Gleiter C. Dose-Proportional Intraindividual Single- and Repeated-Dose Pharmacokinetics of Roflumilast, an Oral, Once-Daily Phosphodiesterase 4 Inhibitor. *J. Clin. Pharmacol.* (2007) **47**:26-36

⁶⁰ Lahu G, Huennemeyer A, Herzog R, McCracken N, Hermann R, Elmlinger M, Zech K. Effect of repeated doses of erythromycin on the pharmacokinetics of roflumilast and roflumilast-N-oxide. *Int J Clin Pharmacol Ther* (2009) **47**(4):236-245

⁶¹ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 210

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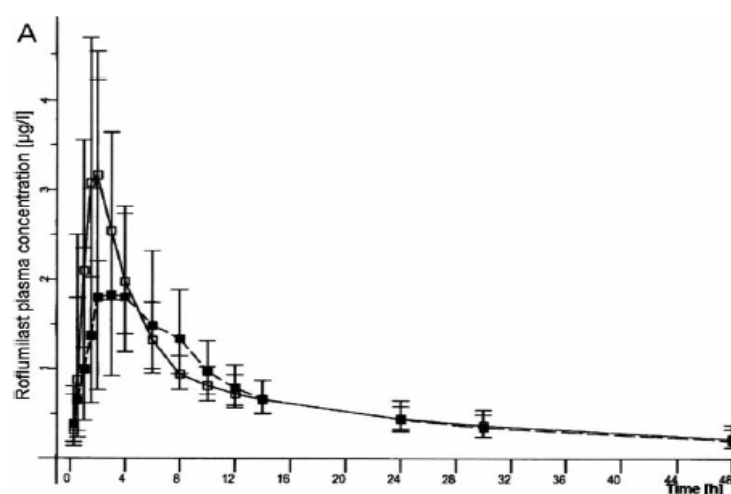
Individual subject data are published for a 500 µg dose of roflumilast taken in the morning 7 am and evening 7 pm 30 minutes after a standard breakfast or dinner⁶². While it was concluded that the differences were not of clinical significance, the results in Table 2 and Figures 7 and 8 are consistent with the effects of variable gastric motility on absorption. Median T_{max} for the morning dose was 1.5 h and for the evening dose 2.0 h. At both times some subjects experienced short T_{max} values of 30 min which was the second sampling point. In the morning, the longest T_{max} was 4 h and in the evening 8 h which may result from a greater food effect and reduced gastric activity in the evening and at night.

Table 2 Summary of PK parameters for 500 µg roflumilast dosed 30 minutes after food at 7 am [○] and 7 pm [●](from Bethke et al 2010)

Pharmacokinetic parameter	Geometric means (68% range)	
	Roflumilast	
	Morning	Evening
AUC_{0-inf} (µg/L·h)	40.6 (29.2, 56.4)	38.9 (29.0, 52.2)
C_{max} (µg/L)	3.79 (2.71, 5.32)	3.06 (2.15, 4.34)
t_{max}^* (h)	1.50 (0.50, 4.00)	2.00 (0.50, 8.00)
$t_{1/2}$ (h)	20.09 (14.28, 28.26)	20.03 (13.45, 29.85)

*Median (min, max).

Figure 7 Mean absorption profiles for 500 µg roflumilast dosed 30 minutes after food at 7 am [○] and 7 pm [●](from Bethke et al 2010)

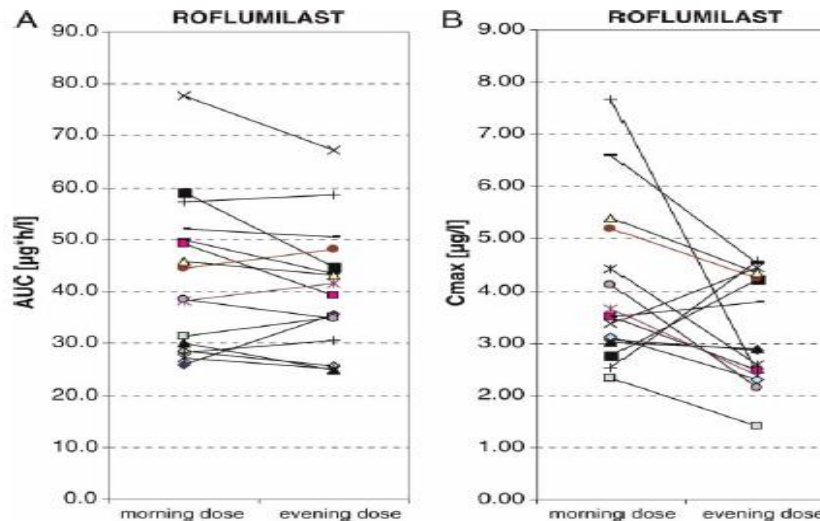


⁶² Bethke TD, Huennemeyer A, Lahu G, Lemmer B. Chronopharmacology of roflumilast: a comparative pharmacokinetic study of morning versus evening administration in healthy adults. Chronobiol Int (2010) 27(9-10):1843-53

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Figure 8 Individual PK parameters for 500 µg roflumilast dosed 30 minutes after food at 7 am [○] and 7 pm [●](from Bethke et al 2010)



Individual AUC values show little effect but the C_{max} values more consistently show lower values at 7 pm associated with the slower absorption which could have clinical implications.

3.5.3 Effect of food

Food delays absorption of a roflumilast tablet administered with 200 mL water, consistent with the effect of food, triggering Phase 1 MMC and delaying gastric emptying as shown in Table 3 and Figure 9⁶³.

Table 3 PK characteristics of roflumilast and roflumilast n-oxide in fed and fasted subjects (from Hauns et al 2006)

Pharmacokinetic Characteristics	Fed		Fasted	
	Roflumilast	Roflumilast N-oxide	Roflumilast	Roflumilast N-oxide
AUC _{0-last} , µg·h/L	30.1 (23.2-38.8)	267.0 (232.4-306.7)	28.9 (22.9-36.3)	271.1 (217.3-338.1)
AUC _{0-∞} , µg·h/L	34.9 ^a (29.6-41.1)	304.6 ^b (255.8-362.7)	31.3 (24.7-39.5)	350.9 ^a (283.1-434.8)
C _{max} , µg/L	3.9 (3.0-4.9)	8.4 (7.0-10.1)	6.5 (5.0-8.5)	8.8 (7.1-11.0)
t _{1/2} , h	11.1 (7.3-17.0)	20.6 (13.5-31.5)	10.3 (6.4-16.4)	19.6 (13.7-28.1)
t _{max} , h	2.0 ± 0.4	12.1 ± 0.8	1.0 ± 0.2	12.3 ± 0.8

Results are shown as geometric means with a 68% range (except for t_{max}, which is given as a mean ± SEM). Data excluded from subjects with extrapolated area for AUC_{0-∞} > 30%. AUC_{0-last}, area under the concentration-time curve from zero up to the last sampling time; AUC_{0-∞}, AUC from zero to infinity; C_{max}, peak plasma concentration; t_{1/2}, half-life; t_{max}, time to maximum observed concentration.

a. n = 11.

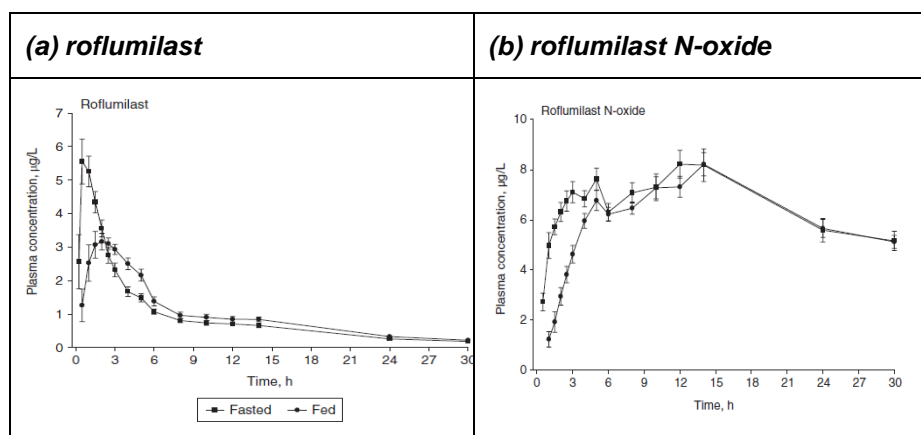
b. n = 9.

⁶³ Hauns B, Hermann R, Hunnemeyer A, Herzog R, Hauschke D, Zech K, Bethke T. Investigation of a Potential Food Effect on the Pharmacokinetics of Roflumilast, an Oral, Once-Daily Phosphodiesterase 4 Inhibitor, in Healthy Subjects. *J Clin Pharmacol* (2006)**46**:1146-1153

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Figure 9 Mean plasma concentration - time profiles (\pm SEM) of (a) roflumilast and (b) roflumilast N-oxide with food (solid circles) and without food (solid squares) (from Hauns et al 2006)



A high-fat meal delayed mean T_{max} from a fasted value of 1.0 ± 0.2 h to 2.0 ± 0.4 h. Slower absorption was associated with significantly reduced C_{max} values decreased by 40% from a mean of $6.5 \mu\text{g/L}$ to $3.9 \mu\text{g/L}$. C_{max} and T_{max} values for roflumilast N-oxide were unaffected being a function of metabolism rather than absorption independent of gastric emptying. This delayed absorption caused by food will be associated with slower onset and potentially reduced clinical efficacy if therapeutic plasma levels are not achieved.

3.5.4 Drug interactions

Minimal interactions occur with drugs prescribed for the treatment of asthma and COPD, such as β_2 -agonists and inhaled corticosteroids⁶⁴; ketoconazole⁶⁵ and enoxacin⁶⁶ as neither roflumilast nor its N-oxide are substrates of P-glycoprotein⁶⁷.

Despite the higher solubility of roflumilast under alkaline conditions, a magnesium hydroxide/aluminium hydroxide antacid did not change the rate or extent of absorption when administered together or 2 h after the roflumilast as shown in Table 4⁶⁸.

⁶⁴ Karish S, Gagnon J. The Potential Role of Roflumilast: The New Phosphodiesterase-4 Inhibitor. *Ann Pharmacother* (2006) **40**:1096-1104

⁶⁵ Lahu G, Huennemeyer A, von Richter O, Hermann R, Herzog R, McCracken N, Zech K. Effect of Single and Repeated Doses of Ketoconazole on the Pharmacokinetics of Roflumilast and Roflumilast N-Oxide. *J Clin Pharmacol* (2008) **48**:1339-1349

⁶⁶ Lahu G, Nassr N, Herzog R, Elmlinger M, Ruth P, Hinder M, Huennemeyer A. Effect of Steady-State Enoxacin on Single-Dose Pharmacokinetics of Roflumilast and Roflumilast N-Oxide. *J Clin Pharm OnlineFirst*, published on May 13, 2010 as doi:10.1177/0091270010370590

⁶⁷ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 3

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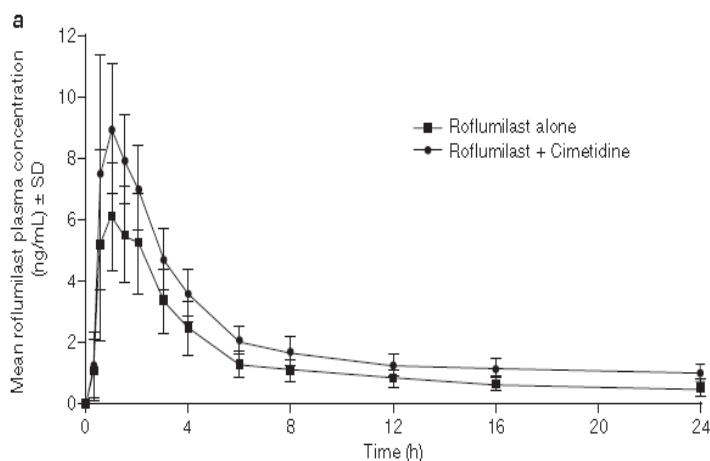
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Table 4 Effect of concurrent and 2 h later administration of antacid on roflumilast 500 µg absorption (from Nassr et al 2007)

Parameter	Roflumilast				
	Roflumilast _{alone} (Reference) n = 28	Roflumilast + Antacid (Test 1) n = 30	Test 1/ Reference Ratio ^a	Roflumilast + Antacid 2 h (Test 2) n = 29	Test 2/ Reference Ratio ^a
C _{max} , µg/L	7.37	6.55	0.89 (0.80-0.98)	7.21	0.98 (0.89-1.08)
AUC _{last} , µg · h/L	52.4	54.5 ^b	1.04 (1.00-1.08)	54.6	1.04 (1.00-1.08)
AUC _∞ , µg · h/L	55.6	58.0 ^b	1.04 (1.00-1.09)	58.2	1.05 (1.00-1.09)
t _{max} , h	1.50	1.50	NA	1.50	NA
t _{1/2} , h	28.4	28.5 ^b	NA	30.3	NA

However when roflumilast was administered to patients on steady state therapy with the histamine 2-agonist cimetidine, there was a significant increase in mean C_{max} from 6.84 to 9.99 ng/mL and AUC from 43.35 to 80.06 ng.h/mL as shown in Figure 10⁶⁹. T_{max} was unchanged with a median value of 1 h (0.5 – 2.0 h). This increase was attributed to the effects of cimetidine on roflumilast metabolism being a weak inhibitor of CYP3A, CYP1A2 and CYP2C10 enzymes rather than an effect of gastric pH on drug solubility. The increase was considered insufficient to warrant dose adjustment.

Figure 10 Effect of steady state cimetidine on roflumilast 500 µg absorption (from Bohmer et al 2010)



- ⁶⁸ Nassr N, Lahu G, Hunnemeyer A, von Richter O, Knoerzer D, Reutter F, Zech K, Hermann R. Magnesium Hydroxide/Aluminium Hydroxide-Containing Antacid Does Not Affect the Pharmacokinetics of the Targeted Phosphodiesterase 4 Inhibitor Roflumilast. *J Clin Pharmacol* (2007)**47**:660-666
- ⁶⁹ Bohmer G, Gleiter C, Morike K, Nassr N, Walz A, Lahu G. No Dose Adjustment on Coadministration of the PDE4 Inhibitor Roflumilast With a Weak CYP3A, CYP1A2, and CYP2C19 Inhibitor: An Investigation Using Cimetidine. *J Clin Pharm OnlineFirst*, published on May 19, 2010 as doi:10.1177/0091270010368282

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Co-administration with erythromycin, a moderate CYP3A4 inhibitor, reduces roflumilast metabolism, increasing AUC and C_{max} by 70 and 40 % respectively, and reducing apparent clearance from 8.2 L/h to 4.8 L/h with no increase in clinical relevant adverse events⁷⁰. The half-life of roflumilast was prolonged, there was no change in T_{max} consistent with reduced metabolism. The AUC ratio of the N-oxide metabolite to parent drug reduces from 10.6 to 6.4 with 34 % lower C_{max} .

Co-administration with rifampicin, a potent cytochrome P450 inducer, reduced total PDE-4I activity by about 58% through increased metabolism of the N-oxide metabolite reducing the therapeutic efficacy⁷¹.

Studies on the CYP3A substrate midazolam and CYP1A2 substrate caffeine show that while roflumilast does not inhibit or induce these P450 enzymes, they influence roflumilast PK⁷².

3.6 Pharmacodynamics (PD)

3.6.1 Dose response

Roflumilast is primarily a non steroidal anti-inflammatory agent without significant bronchodilator activity consistent with its superior improvement in late asthmatic response (LAR) compared with early asthmatic response (EAR) in allergen tests⁷³. Oral roflumilast in single daily doses of 500 µg provides a steroid-free anti-inflammatory option with an improved tolerability and safety profile⁷⁴. Whilst no relationship has been established between plasma levels and the onset of action or duration of anti-inflammatory activity, daily dosing with 500 µg roflumilast generally achieves plasma levels in the range 5 – 10 µg/L of the parent drug and 22 – 43 µg/L of its active N-oxide metabolite. Roflumilast-N-oxide has a PDE-4 selectivity profile and *in vivo* potency

⁷⁰ Lahu G, Huennemeyer A, Herzog R, McCracken N, Hermann R, Elmlinger M, Zech K. Effect of repeated doses of erythromycin on the pharmacokinetics of roflumilast and roflumilast-N-oxide. *Int J Clin Pharmacol Ther* (2009) **47**(4):236-245

⁷¹ Nassr N, Huennemeyer A, Herzog R, von Richter O, Hermann R, Koch M, Duffy K, Zech K, Lahu G. Effects of rifampicin on the pharmacokinetics of roflumilast and roflumilast N-oxide in healthy subjects. *Br J Pharmacol* (2009) **68**(4):580-587

⁷² Bohmer G, Nassr N, Wenger M, Hunnemeyer A, Lahu G, Templin S, Gleiter C, Hermann R. The Targeted Oral, Once-Daily Phosphodiesterase 4 Inhibitor Roflumilast and the Leukotriene Receptor Antagonist Montelukast Do Not Exhibit Significant Pharmacokinetic Interactions. *J. Clin. Pharmacol.* (2009) **49**: 389-397

⁷³ Boswell-Smith V, Page C. Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of respiratory disease. *Expert Opin. Investig. Drugs.* (2006) **15**(9):1105-1113

⁷⁴ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 41

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similar to the parent drug⁷⁵, estimated to account for about 90% of roflumilast's overall clinical efficacy⁷⁶.

Given the variability in efficacy reported in clinical trials on both COPD and asthma at steady state, it is possible that variable absorption as demonstrated here may be a contributing factor.

3.6.2 Efficacy

Clinical trials in broad patient populations with COPD have been associated with inconsistent efficacy results such that patient populations and efficacy measures have been progressively narrowed resulting in the currently approved indication to reduce exacerbations in COPD in the US. No improvement in the St George's Respiratory Questionnaire (SGRQ) score was found for roflumilast relative to placebo. Although roflumilast offers a benefit of 39 – 80 mL in improved FEV1 (mean 50 mL), it is primarily an anti-inflammatory agent not a bronchodilator and so is not superior to bronchodilators such as β 2-adrenoceptor agonists and anticholinergics. However given the highly variable absorption, it is possible that some lack of efficacy may result from doses achieving sub-therapeutic plasma levels.

Although not yet approved for the treatment of asthma, once-daily roflumilast 500 μ g is an effective anti-inflammatory therapy for asthma⁷⁷ comparable with cornerstone asthma therapies in improving forced expiratory volume (FEV1), forced vital capacity (FVC), and respiratory symptoms as summarized in Table 5⁷⁸. Comparable efficacy to inhaled beclomethasone dipropionate with a relatively low incidence of mild to moderate, transient side effects raises the possibility that roflumilast could be an effective alternative to glucocorticosteroids⁷⁹.

⁷⁵ Bethke T, Bohmer G, Hermann R, Hauns B, Fux R, Morike K, David M, Knoerzer D, Wurst W, Gleiter C. Dose-Proportional Intraindividual Single- and Repeated-Dose Pharmacokinetics of Roflumilast, an Oral, Once-Daily Phosphodiesterase 4 Inhibitor. *J. Clin. Pharmacol.* (2007) **47**:26-36

⁷⁶ CHMP Assessment Report, p 18

⁷⁷ Bousquet J, Aubier M, Sastre J, Izquierdo J, Adler L, Hofbauer P, Rost K, Harnest U, Kroemer B, Albrecht A, Bredenbroker D. Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma. *Allergy* (2006)**61**:72-78

⁷⁸ Karish S, Gagnon J. The Potential Role of Roflumilast: The New Phosphodiesterase-4 Inhibitor. *Ann Pharmacother* (2006) **40**:1096-1104

⁷⁹ Boswell Smith V, Spina D. Selective phosphodiesterase 4 inhibitors in the treatment of allergy and inflammation. *Current Opinion in Investigational Drugs* (2005) **6**(11):1136-1141.

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Table 5 Summary of asthma clinical trials for safety and efficacy of roflumilast (taken from Karish et al 2006)

Reference	Design	Pts. (N)	Age (y)	Severity	Dosage	Duration	Efficacy	Adverse Effects
Timmer (2002) ²²	R, DB, PC, 2 period crossover	16 men	median 23 (range 20–30)	mild exercise-induced asthma	500 µg/day	28 days	41% reduction in mean percentage decrease of FEV ₁ after exercise (p = 0.021 vs placebo); 21% reduction in median TNF-α (p = 0.009 vs placebo)	headache (n = 8), diarrhea (3), disturbed sleep (3); most subsided spontaneously with continuous treatment
Leichtl (2002) ²³	R, DB, parallel-group, multicenter	690	15–70	all stages of asthma; all pts. met reversibility criteria >12% after bronchodilator	100, 250, and 500 µg/day	12 wk	improvements vs baseline in FEV ₁ of 260, 320, and 400 mL with 100, 250, and 500 µg, respectively (p < 0.0001 vs baseline for all 3 strengths; p < 0.0017 for 500 µg vs 100 µg)	NR
Albrecht (2002) ²⁴	R, DB, DD	421	12–70	all stages of asthma; all pts. met reversibility criteria >12% after bronchodilator	500 µg/day vs beclomethasone 400 µg/day	12 wk	mean changes from baseline equivalent with roflumilast and beclomethasone: FEV ₁ 0.30 and 0.37 L, FVC 0.30 and 0.36 L; morning PEF 22 and 27 L/min for roflumilast and beclomethasone, respectively (p < 0.001); decrease in use of rescue inhaler per day with both treatment groups vs baseline (–1.29 puff/day; p < 0.001)	NR

DB = double blind; DD = double dummy; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; NR = not reported; PC = placebo-controlled; PEF = peak expiratory flow; R = randomized; TNF = tumor necrosis factor.

3.6.3 Adverse events

Although roflumilast is generally well tolerated, nausea, diarrhea, weight loss and headache are the most significant dose related side effects which in some cases lead to discontinuation of treatment⁸⁰.

Weight loss occurred in 62.4 % of patients compared with 37.7 % in the placebo group although this was only reported as an adverse event by 10.3 % and 2.8 % in the two groups respectively. Diarrhea was reported by 10.1 % subjects compared with 2.6 % on placebo, and nausea by 5.2 % compared with 1.4 %. Of these GI adverse events, 90 % were classified as mild to moderate and 10 % as severe.

While the carcinogenic metabolite ADCP N-oxide is detected in human plasma and urine, no definitive link was established between the use of roflumilast and the increase in incidence of cancers in this group compared with placebo.

The incidence of psychiatric adverse events is low but significantly higher than placebo, with insomnia 3 % compared with 1.1 % for placebo, anxiety 1.4 % compared with 0.8 % and depression 1.4 % compared with 0.8 %. Increased risks of suicidality based on 5 cases out of 12,054 patients receiving roflumilast are not a major concern. Of these, 2 attempted cases had prior psychiatric histories and 2 of the 3 suicides occurred 3 weeks after cessation of treatment.

⁸⁰ NDA 022522 Roflumilast Clinical pharmacology and biopharmaceutics review: p 42

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There is a significant potential to reduce the dose-limiting adverse effects of roflumilast by combination with glucocorticosteroids allowing the dose of both agents to be reduced⁸¹ and therefore reduce the dose-related adverse effects of both agents.

4 Surge Dose[®] roflumilast

4.1 Clinical considerations

Roflumilast appears to be a suitable candidate for Imaginot's ultra-fast activated dissolution Surge Dose[®] technology based on:

- its use for the treatment of chronic conditions where consistent absorption is a clinical pre-requisite to maintain therapeutic plasma levels
- ready absorption by passive diffusion across the intestinal mucosa where high concentrations of dissolved drug will drive fast absorption and distribution
- evidence that absorption is dissolution rate limited based on the wide range of individual T_{max} values from 30 min to 3 h for existing formulations with long T_{max} values associated with low C_{max} values that could be sub-therapeutic
- highly variable absorption with intersubject variability of 45 % and intrasubject variability of 20 % consistent with variable gastric emptying
- inconsistent efficacy that may be the result of sub-therapeutic plasma levels associated with delayed and reduced absorption
- centrally mediated adverse events that could be reduced by using lower doses without compromising efficacy
- potential for reduced dosage without compromising efficacy by more consistent absorption to reduce the overlap of C_{max} and AUC values at 250 and 500 µg doses
- pH-dependent solubility which is lower in acidic gastric conditions compared with the higher pH of the small intestine which can be leveraged using Surge Dose[®]
- rapid conversion to an active metabolite so that the earlier absorption occurs, the earlier peak concentrations of both active entities can be achieved

⁸¹ Boswell-Smith V, Page C. Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of respiratory disease. *Expert Opin. Investig. Drugs*. (2006) **15**(9):1105-1113

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- delayed absorption by food consistent with gastric emptying effects that can be minimized using Surge Dose[®]

4.2 Technical considerations

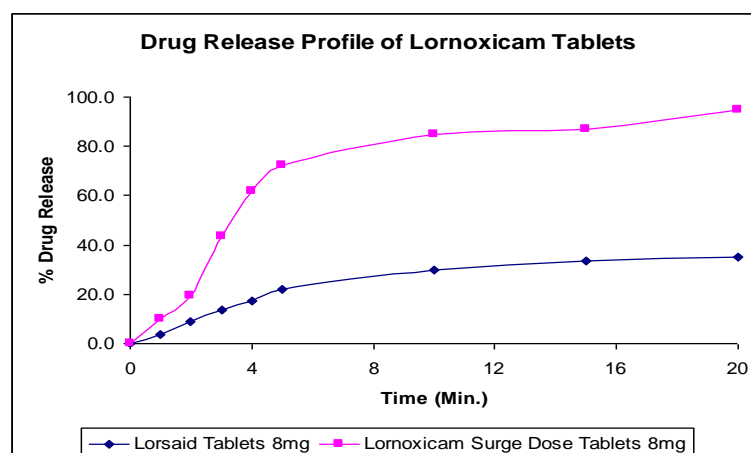
Although no data are available on roflumilast, the Surge Dose[®] technology has been shown to significantly increase the rate and extent of *in vitro* dissolution of a number of weakly acidic drugs. The physicochemical properties of these drugs are compared in Table 6. Lornoxicam shows pH-dependent solubility similar to roflumilast.

Table 6 Comparative physicochemical data for roflumilast, paracetamol and lornoxicam

Parameter	Roflumilast	Paracetamol	Lornoxicam
Dosage	500 µg	1,000 mg	8 mg
Solubility in water	0.5 µg/mL	15 mg/mL	0.01 mg/mL
Vol water to dissolve dose	~1,000 mL	~ 70 mL	~ 800 mL
pKa	8.74	9.5	4.7
Effect of increasing pH	Increased solubility	No change	Increased solubility

Fast dissolving Surge Dose[®] formulations of the weak acids paracetamol and lornoxicam provided significantly faster *in vivo* absorption compared with conventional formulations which was correlated with the faster *in vitro* dissolution as shown in Figure 11 for lornoxicam.

Figure 11 Comparative *in vitro* dissolution profiles for Surge Dose[®] lornoxicam 8 mg and Lorsaid[®] 8 mg tablets in 900 mL 0.0033 M HCl in USP dissolution apparatus 2 with paddles rotating at 30 rpm and 37 °C



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As an acidic drug, an optimized Surge Dose[®] roflumilast tablet would be expected to contain 400 – 600 mg bicarbonate with up to 100 mg of a pharmaceutically acceptable organic acid. Such a formulation will be optimized with water uptake agents to achieve at least 70 % dissolution in the first 5 min in both stirred and unstirred conditions. This would translate to faster *in vivo* dissolution under both favorable and unfavorable GI conditions, resulting in faster delivery to the small intestine and subsequently faster absorption relative to the current approved product.

A higher frequency of individual subject T_{max} values would be seen at 30 min with lower mean and median values which would be closer indicative of a more normal distribution of these values. Reduced food effects would also be expected as a result of the faster dissolution independent of gastric pH and gastric motility. As roflumilast is already formulated with alkaline excipients, it is anticipated that these higher levels will not present a chemical stability issue.

Clinical efficacy data suggests that there are opportunities for a number of combination products of other drugs with roflumilast. These include bronchodilators and also anti-inflammatory glucocorticosteroids using a lower dose of both actives in order to reduce adverse events whilst maintaining efficacy. A Surge Dose[®] formulation would be optimised to achieve fast *in vitro* dissolution for both components. Glucocorticosteroids have typically low solubility and exhibit slow dissolution which can be significantly increased by using a Surge Dose[®] formulation.

4.3 IP considerations

Roflumilast is covered by US 5,712,298 granted an extension to 27 Jan 2015 and equivalent patents in other territories including Europe and Japan with a priority of 02 Jul 1993⁸². This patent is Orange Book listed against this product with NCE data exclusivity until 28 Feb 2016.

Although not Orange Book listed, US 2005/0159492, US 2006/0269600 and WO/2003/070279 (Altana, priority 20 Feb 2002) cover tablet formulations containing PVP as a binder providing faster absorption and improved bioavailability. These would appear to cover the existing registered product which contains povidone (PVP). This patent lists the alkaline agents calcium and sodium carbonates as acceptable fillers, but these are not exemplified and there are no teachings that they are an essential feature of these formulations

Other formulation patents include:

- EP 1796668, WO/2006/032675, US 2007/0259009 for roflumilast solubilised with alkoxyated fats in solutions adjusted to pH 7.0 – 7.4 (Nycomed, priority 22 Sep 2004)

⁸² Roflumilast. *Drugs*. (2004) 5(3):176-181

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- WO/2006/032676, US 2008/0045572 for roflumilast in aqueous solutions adjusted to pH 10 – 13 (Altana, priority 22 Sep 2004)
- WO/2006/097456 for one step coating for taste masking (Altana, priority 16 Mar 2005)

There are many other patents covering the use of roflumilast, its active metabolite roflumilast-N-oxide and their salts including:

- US 2009/0215836, WO/2006/0111495 for the treatment of pulmonary hypertension (Nycomed, priority 19 Apr 2005)
- US 2008/0214625, WO/2006/094933 for treating diabetes mellitus (Koninklijke Hilips Electronics NV, priority 07 Mar 2005)
- US 2007/0254928 for the treatment of emphysema (Altana, priority 14 May 2004)
- US 2006/0142308, WO/2004/047828, WO/2004/047829, EP 1567139 for synergistic combinations with the bronchodilator formoterol (Altana, priority 27 Nov 2002)
- US 6624181, US 7.056,936 covering the synergistic combination of PDE4Is with β_2 adrenoceptor agonists (Altana, priority 28 Feb 1997)
- US 2010/0048615, US 2010/0048616, EP 1891973, EP 1891974, EP 2210613. EP 2210614, US 2009/0099148, WO/2005/115462, WO/2005/115465 covering the use of PDE4Is with M3 muscarinic receptor antagonists (Almirall, priority 31 May 2004)
- WO/2010/097332 covering use of PDE4Is with NSAIDs (BI, priority 27 Feb 2009)
- US 2004/0242597, US 2008/0255209 for combination of PDE4Is with NSAIDs with reduced gastrointestinal toxicity (Nycomed, priority 19 Sep 2001)

Although roflumilast is not specifically claimed in the Imaginot patents, an improved Surge Dose[®] IR roflumilast would be covered by the general claims for acidic drugs in Imaginot patent WO/2007/059591. Similarly an IR combination product containing roflumilast with a bronchodilator would be covered by the same patent, as well as the patent appropriate to the additional drug. Additionally there is the opportunity for drug specific patents to be filed on optimized formulations identified during development.

5 Conclusions

While roflumilast is currently only approved for limited chronic use in COPD, the clinical program is continuing and there appears to be significant potential for this drug in other chronic and also acute indications particularly in asthma and allergic rhinitis. A Surge Dose[®] reformulation of

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

roflumilast would be expected to provide faster and more consistent absorption of the drug with higher C_{\max} that will increase its potential for use in acute conditions such as allergic rhinitis where speed of onset is more important than with chronic indications.

The wide range of patents filed on this compound suggests that the solubility limitations are recognized and there is a need for formulations with improved and more consistent absorption. Fast and consistent absorption with Surge Dose[®] provides a clinical benefit for both chronic and acute usage, and will be important if roflumilast is to achieve its full clinical potential as an anti-inflammatory agent.