MODULE 2.5

CLINICAL OVERVIEW

Marketing Authorisation Application

For

Omeprazole 1mg/ml Oral Suspension

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February 2022

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under the plasma concentration versus time curve
AUC_{0-t}	Area under the plasma concentration versus time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time zero to infinity
cBNF	Children's British National Formulary
CI	Confidence Interval
CL/F	Apparent total clearance of the drug from plasma after oral administration
C_{time}	Measured Plasma Concentration
C_{max}	Maximum Plasma Concentration
CV	Coefficient of Variation
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GER(D)	Gastro Esophageal Reflux (Disease)
ITT	Intention-To-Treat
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
PdAR	Paediatric Public Assessment Report (EU Worksharing Project)
PICS	Protection In-situ Constitution System
PPI	Proton Pump Inhibitor
RCT	Randomised Clinical Trial
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
t_{max}	Time for maximum concentration

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2.5.1 PRODUCT DEVELOPMENT RATIONALE

INTRODUCTION

The product is *Omeprazole Oral Suspension* (1mg/ml) and is a new strength (1mg/ml) for this galenical form. *Omeprazole Oral Suspension* (2mg/ml and 4mg/ml) was previously granted a Marketing Authorisation, as NL/H/4504/001-002/DC.

As a multi-dose oral liquid formulation with established bioavailability, stability, quality and efficacy, *Omeprazole Oral Suspension* represents an age-appropriate formulation of omeprazole especially suitable for paediatric patients.

The present application is a line extension application for a new strength of an existing medicinal product. This application includes bridging pharmacokinetic studies for a new strength (1mg/ml) utilising approved strengths (2mg/ml and 4mg/ml) to bridge to the reference product (*Losec capsules*). A previous application for 2mg/ml and 4mg/ml formulations compared the relevant proposed products to the reference product (*Losec capsules*), contained additional clinical data in a paediatric population and also included a review of relevant literature studies and other references relevant to the new dosage form.

The need for an age-appropriate formulation of omeprazole has been identified in lists issued by regulatory authorities, including EMA and WHO.

Omeprazole Oral Suspension 1mg/ml is a new strength especially suited to younger paediatric patients and has been specifically designed as a dosage form for the subset of children below 4.2kg in body weight who cannot be administered Omeprazole Oral Suspension 2mg/ml due to the inherent inaccuracies associated with the dosing syringe at very low volumes. An important feature of this formulation is that it is suitable for dose titration on a weight-adjusted basis, and can facilitate the accurate administration of doses less than 10mg to this extended population. In the development of the formulation, the requirements and features appropriate to this paediatric sub-set population have been taken into account, including a lower achievable dosing volume.

Infant GERD Overview – description and therapeutic needs

GERD treatment is an important medical need in children, including children younger than 1 year of age. In a UK primary care database study[1], the incidence of a GERD diagnosis in children in primary care was age-dependent and was highest among very young children and older female adolescents. Children with neurological impairments (e.g. cerebral palsy) and other comorbidities such as congenital esophageal disorders (e.g. esophageal atresia, tracheoesophageal fistula or stenosis) and cystic fibrosis[2] are at increased risk of a GERD diagnosis.

Acid exposure to the esophagus is considered to be the key feature accounting for the pathogenesis, clinical manifestations and complications of GERD. Acid reflux occurs primarily

during the esophageal motor event known as transient lower esophageal sphincter relaxation (TLESR). Studies on the pathophysiology of GERD in infants (and adults) have affirmed that TLESR is the primary pathogenetic mechanism of GERD for all patients from birth to adulthood. Acid-mediated esophagitis or erosive esophagitis, in both adults and children, is defined as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the gastroesophageal junction[2]

The clinical manifestations of GERD range from minor symptoms, such as heartburn or regurgitation, to more complicated disease, such as erosive esophagitis, esophageal stricture, or Barrett's esophagus. Acid-mediated GERD with erosive esophagitis has the same disease definition and has a similar endoscopic presentation in adults, older children, and infants. In all age groups, the treatment is targeted to normalise esophageal pH and heal acid-induced injury.

The comprehensive ESPGHAN/NASPGHAN guidelines[2] state that GERD is "present when the reflux of gastric contents causes troublesome symptoms and/or complications." Because of the unique characteristics of the infant stomach, feeding schedule, and acid production compared with older children and adults, gastric refluxate enters the esophagus much more frequently than in adults. In most infants, this does not cause distress, and is designated as gastroesophageal reflux (GER); if it causes distress, it is designated GERD. The natural history of symptomatically (non-endoscopically) diagnosed GER in infancy, particularly spitting up, is spontaneous resolution. Once a patient presents with signs of GERD (regurgitation, crying, arching back, irritability, feeding difficulties), management in primary care settings usually begins with a trial of conservative measures such as infant positioning, thickened, frequent, and smaller feeds, and frequent burping. If the infant responds favourably, conservative measures are maintained until resolution; however, if the infant does not respond, other aetiologies, such as anatomic anomalies and cow milk protein intolerance, are evaluated. In routine clinical practice, if conservative measures and a search for alternative aetiologies fail to relieve signs and symptoms, then antacids, H2 blockers, or PPIs may be initiated. The current ESPHGAN guidelines carefully address the potential need for acid suppression with PPIs. It is clear from the clinical studies that although not all infants with symptoms suggestive of GERD may need acid suppression for symptom control, a subgroup of infants with confirmed high acid exposure in the esophagus benefit from acid suppression to relieve their symptoms. The results of real world analysis indicated that PPIs are commonly prescribed to infants in the hospital setting and, to a lesser extent, in the outpatient setting. Illueca et al[3] reported that approximately 20,000 infants < 1 year were given a PPI in US hospitals each year.

Omeprazole was the first PPI used in clinical practice and was launched in 1988 as Losec in Europe, and in 1989 as Prilosec in the US. The advent of PPIs has revolutionized the approach to acid-related disorders in adults. Omeprazole itself has been used for more than 20 years in paediatrics especially in vulnerable patient groups and is considered to be an effective and safe drug in the paediatric population as well as in the adult population[4]. As in adults, these drugs are highly efficacious in children and safe for the treatment of GERD-related symptoms and signs, including the most severe degrees of reflux esophagitis.

However, available dosage forms and approved pharmacological treatments for infant GERD are limited. PPIs, while recommended in guidelines as the mainstay treatment of acid-related disorders including GERD are only presently approved for children < 1 year in Europe, as Omeprazole |Oral Suspension 2 mg/ml. For Omeprazole Oral Suspension 2 mg/ml, children from 1 month up to 12 months of age can only be accurately administered at least 2.1 ml of the Omeprazole Suspension 2 mg/ml due to the limitations of the dosing devices. Consequently only children of at least 4.2 Kg weight (corresponding to 4.2 mg of active) can be administered Omeprazole Oral Suspension 2 mg/ml.

With regard to Omeprazole Oral Suspension 1mg/ml, the aim of the product development programme and rationale for the product was to develop a stable, palatable, oral liquid, pharmaceutical formulation of omeprazole similar to that previously developed for strengths of 2mg/ml and 4mg/ml (*10mg/5ml* and *20mg/5ml*) with proven bioavailability. From a pharmaceutical perspective, omeprazole is very difficult to formulate. In particular, it is exceptionally acid labile, highly susceptible to degradation and/or transformation in acid-reacting and neutral media. It is also sensitive to heat, moisture, organic solvents, and light. After administration, an oral dosage form of omeprazole must be protected from degradation in the stomach, in order to reach the proximal part of the small intestine, where it can be absorbed. Pilbrant et al [4] reported a pilot bioavailability study in healthy, fasting volunteers, after oral administration of micronized omeprazole, 60 mg, given as a) buffered oral suspension and b) unbuffered oral suspension in a randomized, cross-over study design. Treatment a) was a suspension of micronised omeprazole, 60 mg, in sodium bicarbonate solution (pH=9). Treatment b) was a suspension of omeprazole in water (pH adjusted to 9 by sodium hydroxide), the sodium bicarbonate solution being replaced by water. For both formulations, the absorption of omeprazole proceeded rapidly and peak plasma concentrations were reached in < 30 minutes. However, the bioavailability of the suspension without buffer was ~40% of the buffered suspension, due to degradation of omeprazole in the stomach (pre-absorption degradation). The results emphasise that a conventional non-buffered, oral liquid dosage form of omeprazole would have a low systemic bioavailability owing to pre-absorption degradation of omeprazole in the stomach. The study illustrates the importance of formulating omeprazole correctly.

Due to the stability behaviour of omeprazole, the challenges in developing a formula or dosage form that would remain stable both in the body and on the shelf, and deliver the substance to the proper site of the body, are formidable.

To develop the liquid dosage form of omeprazole, the applicant previously addressed the formidable physicochemical and biopharmaceutical challenges by presenting an oral suspension using it's PICS (Protection In Situ Constitution System). [redacted] The diluent contains a bicarbonate buffer, together with additional excipients appropriate to a multi-dose oral liquid dosage form – flavouring agents, preservative etc. [redacted]. Many feeding tubes may easily become blocked by the pellets. For example, Ponrouch et al [5] evaluated the recovery of the omeprazole content of Mopral ® 10 mg Capsules (AstraZeneca) after passage through paediatric nasogastric tubes. The capsule contents (granules) were placed in a syringe barrel, water drawn in and the syringe shaken to suspend the granules. The contents of the syringe were administered through 6 Fr and 8 Fr polyurethane tubes and the tubes were flushed through with water. All of the 6 Fr tubes became blocked. Only 3.9 +/- 4.2 % of omeprazole was recovered at the tube outlet of the 8 Fr tubes.

The excipients (potassium bicarbonate and sodium bicarbonate) that contribute to the buffering activity are important to ensure effective absorption of omeprazole from the oral suspension as the buffering system protects the uncoated omeprazole from acid degradation within the

stomach. Compared to *Losec* capsules, the enteric coating system used to protect omeprazole from acid degradation is replaced by buffering agents. *Losec* capsules provides a delayed-release formulation, whereas Omeprazole Oral Suspension is an immediate release formulation.

The formulation of Omeprazole Oral Suspension has been rationally developed and evolved progressively, having due regard to the suitability of excipients for the paediatric population.

Sodium is an essential nutrient but it is important to limit sodium intake in line with guidance from WHO/EU publications[6,7,8,9]. [redacted].

In AstraZeneca's pivotal efficacy and pharmacokinetic/pharmacodynamics studies (Studies 251 and 250 respectively)[Error! Bookmark not defined.] conducted in children 0-2 years (83% of patients were < 1 year old), the patients were dosed with a suspension of omeprazole, [redacted]. The available clinical data, pharmacokinetic and pharmacodynamic data support the proposed weight-based doses for infants < 1 year.

The clinical programme for Omeprazole Oral Suspension 1mg/ml mainly focussed on establishing comparative bioavailability with the reference product (*Losec capsules*) used in AstraZeneca's pivotal efficacy/safety studies both in the adult and paediatric population and employing a biowaiver. This application includes four comparative bioavailability studies - one pivotal (376-15) and three supportive (0104-16, 375-15 and 454-14) - all conducted in healthy adults and one pharmacodynamic/efficacy study conducted in the paediatric setting (BA 04/07). Study BA 04/07 was conducted in patients aged < 3 months with diagnostically confirmed GERD and showed the effectiveness of omeprazole oral suspension in this paediatric population. The response endpoints were reflux index (i.e. time with a gastric pH below 4) and common PD biomarkers across the class of proton pump inhibitors. For omeprazole, exposure response relationships have been established for time that intragastric pH is greater than 4 for both children and adults and these relationships are comparable.

In the pivotal pharmacokinetic study (376-15), comparative bioavailability with the reference product (Losec capsules) was established in accordance with protocol requirements. Compared to the reference product, Omeprazole Oral Suspension showed equivalent exposure by AUC (primary parameter) and a higher C_{max} in study 376-15; the higher Cmax observed for Omeprazole Oral Suspension reflects the immediate-release nature of this

formulation compared to the delayed-release reference product. [redacted]

Previous regulatory assessments of omeprazole in the paediatric setting

The present application solely concerns a new strength (1mg/ml) of an existing dosage form (multi-dose oral suspension) of omeprazole. Omeprazole Oral Suspension 2 mg/ml and 4mg/ml was previously developed and authorised by the current applicant and concerned a new dosage form (multi-dose oral suspension) of omeprazole and an extension of indications to include children < 1 year in line with the characteristics of the formulation: suitability for use in children and capability to administer doses less than 10mg.

Studies 251 (efficacy and safety) and 250 (PK/PD) and 292 (retrospective efficacy study) conducted in the paediatric setting (patients 0 to 2 years) were submitted and reviewed as part of EU Worksharing Project/Paediatric Assessment Report (PdAR)Error! Bookmark not defined. and informed the current SmPC for Omeprazole Capsules/Tablets approved in Europe. These studies are directly relevant to the present application, as the clinical formulation for these studies was a buffered bicarbonate suspension. Indeed, it is notable that in the main paediatric efficacy study (Study 251), ~85% of patients were < 1 year (~59 % were < 6 months). The PdAR concluded that omeprazole was safe and efficacious for young children, but could not be recommended for children < 1 year and / or below 10 Kg as *Losec Capsules/Tablets* was not considered to be a suitable formulation due to the inability to administer doses < 10mg. The PdAR also considered a proposal that *Losec powder for solution* (IV formulation) be used to constitute a buffered solution with stability up to one hour after dilution. In principle, the diluted IV solution would be suitable for dosages < 10mg. However, the proposal was not considered to be acceptable due to lack of an *appropriate formulation* for the following reasons, *inter alia*: (i) It was not considered to be acceptable for an oral and parenteral product to have the same label due to the potential for mix-up (the proposed handling would have involved storage of a non-sterile product – labelled as a sterile product - for an extended period), (ii) stability data was not available for the re-constituted/diluted formulation and (iii) no PK study was available showing that the orally administered IV solution gave equivalent exposure to the reference oral formulation or that the buffering capacity of the diluted oral solution was equivalent to the buffered suspension used in the clinical studies.

The present application addresses these specific gaps: (i) Omeprazole Oral Suspension is an age-appropriate formulation which allows accurate administration of omeprazole doses of < 10 mg, (ii) Omeprazole Oral Suspension has been developed specifically and solely for oral administration and will be labelled accordingly, (iii) Omeprazole Oral Suspension is supported by appropriate pharmaceutical quality data and is stable for 28 days after reconstitution and (iv) comparative bioavailability has been established with the reference product used in adults and the clinical formulation used in the paediatric clinical studies.
In accordance with CHMP Guideline on the Investigation of Bioequivalence the applicant has successfully conducted *in vitro* dissolution testing which confirms the adequacy of waiving *in vivo* bioequivalence testing for the lower strength of Omeprazole Oral Suspension 1mg/ml detailed in this line extension.

Rationale for Development of Omeprazole Oral Suspension 1mg/ml

Omeprazole Oral Suspension 2mg/ml was previously authorised for use with following labelled paediatric posology:

Paediatric population

Children over 1 month of age
Treatment of reflux esophagitis
Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

The posology recommendations are as follows*:

Age	Weight	Posology
1 month to 1 year of age	-	1 mg/kg once daily. Doses above 1.5 mg/kg/day have not been studied.
≥ 1 year of age	10-20 kg	10 mg once daily. The dose can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dose can be increased to 40 mg once daily if needed.

* Individual dose measurements ≤ 2ml are not indicated

As per the labelled posology, individual dose measurements ≤ 2ml are not indicated due to limitations within the dosing syringe to accurately deliver volumes ≤ 2ml. [redacted]

Consequently dosing is limited to children 1 month to 1 year of age with a minimum weight of 4.2 Kg.

Clinically, there is a sub-set of the pediatric population, age 1-2 months with a body weight of < 4.2 Kg that cannot be dosed with Omeprazole 2mg/ml as highlighted in yellow in Table 2.5.1.1 [52]. As per Table 2.5.1.1, it can be seen that the subset of children aged 1-2 months with a body weight of < 4.2 Kg ranges from 25th percentile of the population at 1 month old down to 5th percentile of the population at 2 months old.

Table 2.5.1.1 | Age and Weight Distribution of Infants in terms of Percentiles

Age (Months)	3rd Percentile Weight (in Kg)	5th Percentile Weight (in Kg)	10th Percentile Weight (in Kg)	25th Percentile Weight (in Kg)	50th Percentile Weight (in Kg)	90th Percentile Weight (in Kg)	95th Percentile Weight (in Kg)
0	2.4	2.5	2.8	3.2	3.5	4.2	4.3
0.5	2.8	3.0	3.2	3.6	4.0	4.7	4.9
1	3.2	3.4	3.6	4.0	4.3	5.2	5.4
1.5	3.6	3.8	4.0	4.4	4.9	5.7	6.0
2	4.0	4.1	4.4	4.8	5.3	6.2	6.4
2.5	4.3	4.5	4.8	5.2	5.7	6.6	6.9

In order to be able to accurately administer Omeprazole Oral Suspension to this sub-set of the population, a lower strength of Omeprazole Oral Suspension 1mg/ml is required and has been developed as per this application. Utilising Omeprazole Oral Suspension 1mg/ml, it is possible to accurately administer volumes of ≥ 2.1ml. This facilitates dosing to children < 4.2 kg in weight and covers the subset of children not currently covered by existing authorised medicines and who clinically require an age appropriate formulation.

The following posology is proposed for Omeprazole Oral Suspension 1mg/ml:

Paediatric population

Children 1-12 months of age
Treatment of reflux esophagitis
Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

The posology recommendations are as follows*:

Age	Weight	Posology
1 month to 12 months of age	≤ 10 kg	1 mg/kg once daily. Doses above 1.5 mg/kg/day have not been studied.

* Individual dose measurements ≤ 2ml are not indicated

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2.5.2 OVERVIEW OF BIOPHARMACEUTICS

This section provides a summary of the pharmacokinetic and pharmacodynamic aspects of omeprazole relevant to the application, with particular reference to the paediatric setting.

The pharmacokinetics of omeprazole have been studied in healthy subjects, subjects with renal and hepatic impairment and in paediatric patients[11].

Many of the Phase I/pharmacokinetic studies[12] reported in the SmPC of the reference product were performed using buffered oral aqueous suspension/solution formulations rather than EC capsules (to avoid influences of dosage form variables on PK/PD of the drug).

2.5.2.1 Pharmacokinetics

Absorption and bioavailability after oral administration

Omeprazole Oral Suspension is an immediate release product with a characteristic, immediate release profile (t_{max} < 1 hour) [Figure 2.5.2.1]. Absorption is rapid, with peak plasma concentrations of omeprazole occurring within 0.25 to 2 hours.

Absorption of omeprazole takes place in the small intestine and is usually substantially completed within 3-6 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg [Fig 2.5.2.2][16], but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Compared to the reference product (Losec capsule containing enteric coated pellets), Omeprazole Oral Suspension shows equivalent exposure by AUC, but with no T_{lag}, faster T_{max} and a higher C_{max}.

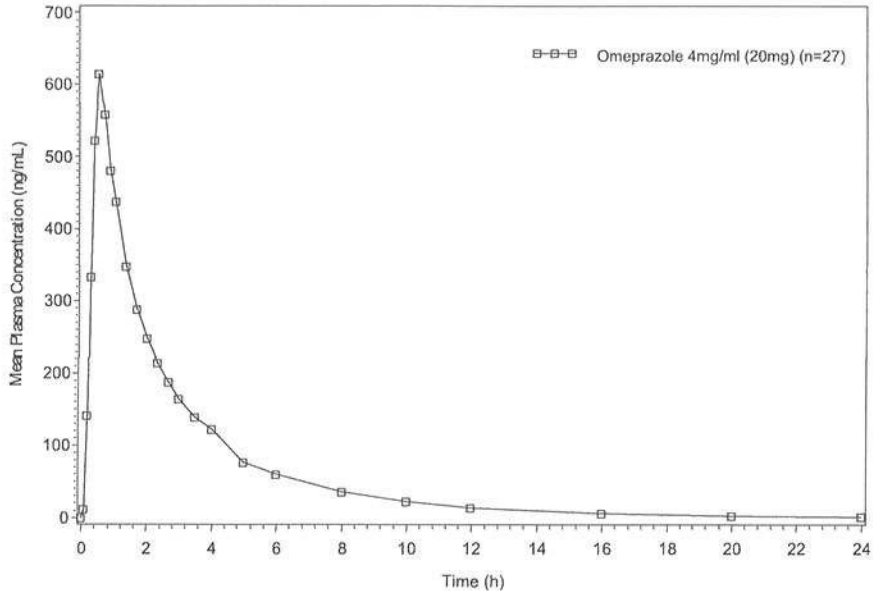


Figure 2.5.2.1 | Mean plasma concentration vs. time curve for Xeolas ***Omeprazole 4mg/ml Oral Suspension*** after administration of a 20 mg dose (5 ml) [Study 376-15]

In Xeolas's pivotal bioavailability study (376-15) comparing Omeprazole Oral Suspension with the reference capsule product the AUC_{0-t} ratio (log-transformed) was 99.1% (93.57 - 104.94%) and the corresponding ratio for C_{max} was 137.9% (122.79 - 154.98%). The C_{max} of both formulations showed considerable variability and the range of individual C_{max} values was similar; the C_{max} range for Omeprazole Oral Suspension was 225.403 to 1493.503 ng/ml and for the reference product it was 135.758 to 1430.262 ng/ml.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound[14].

Biotransformation

Omeprazole is completely metabolised by the cytochrome P450 system (CYP)[14]. The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes. The other major metabolite is omeprazole sulfide.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole[14].

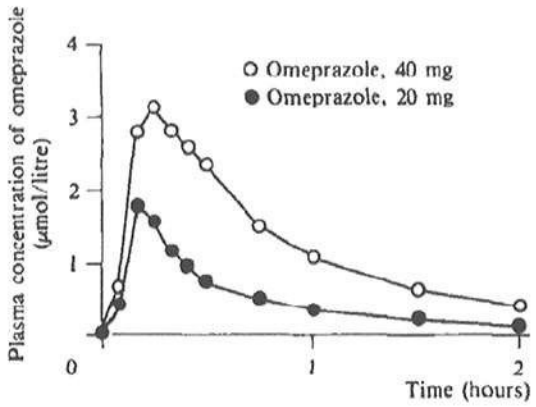


Figure 2.5.2.2 | Mean plasma omeprazole concentrations in healthy subjects following a single oral dose of (●) 20 or (O) 40 mg omeprazole buffered suspension[13].

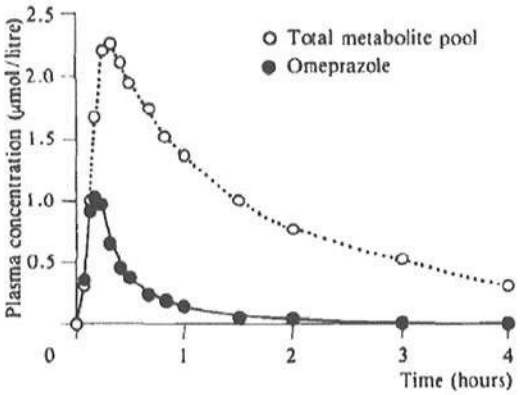


Figure 2.5.2.3 | Median plasma concentration-time curves for (●) omeprazole and (O) the total pool of radioactive metabolites in healthy subjects following a single oral dose of "C-labelled omeprazole as a buffered solution[13].

Elimination

The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing[14]. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.
Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Table 2.5.2.1 | Pharmacokinetic Parameters for Omeprazole Oral Suspension (n = 27) in Xeolas Study 376.15

Parameter	Omeprazole Oral Suspension 4mg/ml (20mg)*
T_{max} (h)**	0.500 (0.250 - 1.667)
λ_z (1/h)	0.770 ± 0.3640
$t_{½}$ (h)	1.303 ± 1.1413

*Mean ± SD

**T_{max} is represented in median (min-max) value.

Linearity/non-linearity

The AUC of omeprazole increases with repeated administration irrespective of formulation[14]. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone).

No metabolite has been found to have any effect on gastric acid secretion.

Pharmacokinetics in special populations

Hepatic impairment

The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing[14]. In patients with impaired hepatic function a daily dose of 10–20 mg may suffice.

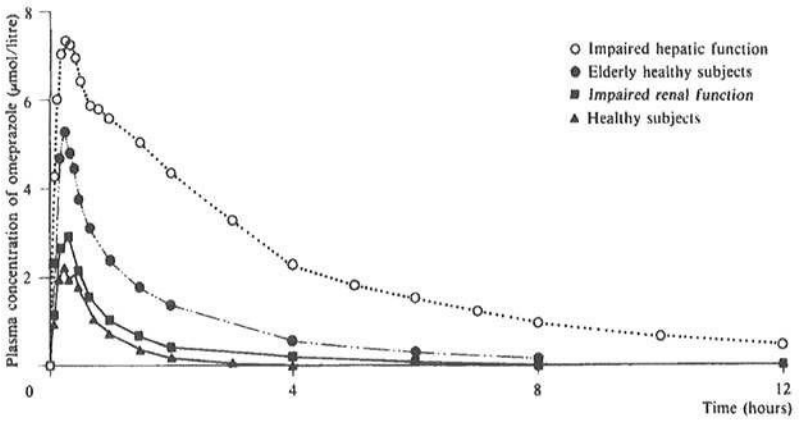


Figure 2.5.2.4 | Mean plasma concentration-time curves for omeprazole after a single oral dose of 40 mg, as a buffered bicarbonate solution in young healthy subjects, elderly healthy subjects, patients with various degrees of renal function impairment, and patients with various degrees of liver function impairment [13].

Renal impairment

The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function[14]. Dose adjustment is not needed.

Elderly

The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age)[14].

Method of administration in pharmacokinetic and clinical studies

In the various paediatric clinical studies, omeprazole was administered either once or twice daily (in all cases before meals i.e. fasted condition). The ESPHGAN / NASPGHAN guidelines[2] recommend a once daily administration and this is consistent with the design of Xeolas Study 376-15, the pivotal comparative bioavailability study which confirmed equivalent extent of availability between the oral suspension and the reference capsule product (Losec), [redacted]

In addition, considering the immediate release characteristics, Omeprazole Oral Suspension is recommended to be taken 30-60 minutes before meals. This is also in line with Xeolas Study 376-15, performed under fasting conditions, AstraZeneca study 251, AstraZeneca study 250 and NASPGHAN / ESPHGAN[2] guidelines.

Taking into account the proposed patient population, a pragmatic recommendation informed by the bioavailability data is "once daily, on an empty stomach 30-60 minutes before meals".

Effect of food and drinks on absorption

Omeprazole oral suspension is recommended to be taken in the fasted state i.e. before meals.

In Xeolas study 0104-16, when Omeprazole Oral Suspension was taken with milk in a fed study relevant to the paediatric setting, bioavailability was decreased by approximately 20% relative to the fasted condition.

Pharmacokinetics of Omeprazole in the Paediatric population

Pharmacokinetic studies in children are challenging in respect of the willingness of parents/guardians to provide informed consent for their child given the need for multiple blood sampling. Accordingly, the applicant relies on published pharmacokinetic data as much as possible.

[redacted].

AstraZeneca Study 250[Error! Bookmark not defined.,15] was an open-label, randomized PK/PD study with 24 paediatric patients aged 0 to 24 months in need of acid suppression therapy. The primary objectives were to characterize the single dose PK parameters and intraesophageal and/or intragastric pH. Patients were randomized to receive a single oral dose of either 1.0 mg/kg or 1.5 mg/kg from a 2 mg/mL omeprazole suspension in 8.4% sodium bicarbonate.

Methods: For determination of omeprazole plasma concentrations, blood samples were collected at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, and 6 hours post-dose [fasted 1 hour before dosing and allowed to eat 30 minutes post-dose]. For assessment of esophageal or gastric pH, a pH probe was placed in either the esophagus or stomach (when medically indicated) at least 12 hours prior to dose administration and pH was continuously measured until at least 12 hours post-dose. Twenty-four patients completed the PK portion of the study, including plasma concentration determinations over 6 hours. 13 of the 24 patients were also monitored for effects on intraesophageal and/or intragastric pH (12 completed).

Note: Study 250 was initially designed as a PK study for single and repeated daily oral dosing but was later amended to single dose only due to the difficulty enrolling a sufficient number of subjects.

Table 2.5.2.2 | PK parameters after a single dose of omeprazole (Study 250)[16]

Omeprazole Dose	PK Parameter	n	Geometric Mean	95% CI
1.0 mg/kg	AUC $_{0\text{-}t}$ (ng•h/mL)	12	658.0	(340.4,1272.1)
	AUC $_{0\text{-}\infty}$ (ng•h/mL)	7	1248.5	(569.3,2738.2)
	C_{max} (ng/mL)	12	447.6	(253.6,789.9)
1.5 mg/kg	AUC $_{0\text{-}t}$ (ng•h/mL)	12	580.7	(274.6,1227.8)
	AUC $_{0\text{-}\infty}$ (ng•h/mL)	9	827.0	(352.3,1941.6)
	C_{max} (ng/mL)	12	345.6	(137.7,867.4)

Table 2.5.2.3 |Summary of percentage of time pH<4.0 in Study 250[16]

Omeprazole Dose		Predose	Postdose	Change
1.0 mg/kg	**Oesophageal**			
	n	7	7	
	Mean	4.8	2.7	-2.1 (p≤0.26)
	SD	5.2	2.5	4.5
	Gastric			
	n	7	7	
	Mean	64.2	42.4	-21.8(p≤0.02)
	SD	29.3	26.1	18.8
1.5 mg/kg	**Oesophageal**			
	n	5	5	
	Mean	13.2	6.8	-6.4 (p≤0.25)
	SD	12.6	8.8	10.6
	Gastric			
	n	5	5	
	Mean	58.0	46.2	-11.9 (p≤0.07)
	SD	28.7	33.9	10.5

Results and Comments: The mean age of the patients was 8.7 months [7.8±6.4 months for 1.0mg/kg and 10.2±7.7 months for 1.5mg/kg, weights 6.7±2.6 kg and 8.4±3.4 kg respectively]. 12 patients were < 6 months and 17 patients were < 12 months. The 2 mg/ml omeprazole suspension was made by suspending the granules of *Prilosec* delayed release capsules in 8.4 % sodium bicarbonate.

In general, exposure was highly variable between individuals [similar to the adult population]. In patients 0.5-24 months, omeprazole was rapidly absorbed, with a mean t_{max} of less than 1 hr. The geometric mean AUC_t after a single dose of omeprazole was similar for the two dose levels. The analysis of pH indicates that a single dose of bicarbonate buffered omeprazole suspension 1.0mg/kg or 1.5mg/kg significantly decreases the fraction of time with gastric pH less than 4 and reduces esophageal acid exposure in paediatric patients aged 0.5 month to 24 months. All doses were safely administered and well tolerated in this paediatric population. Although no clear relationship between AUC and time with pH < 4.0 was observed, there was a tendency to a relationship between AUC and change in gastric pH similar to that shown in adults (Figure 2.5.2.5).

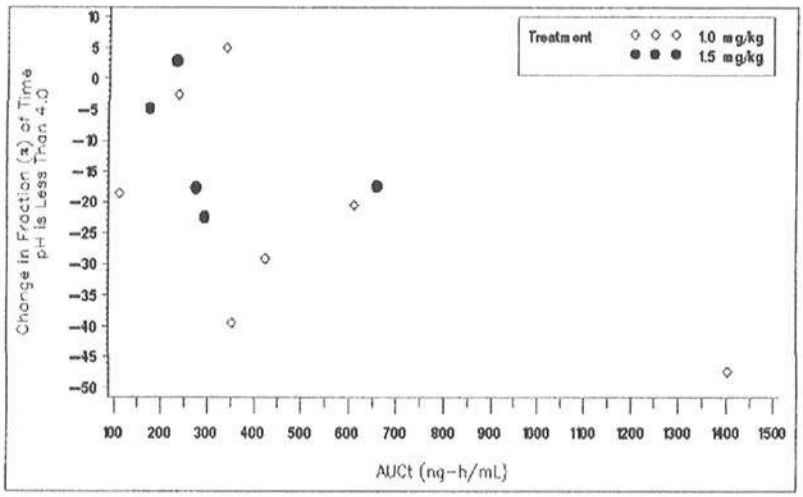


Figure 2.5.2.5 | AUC_{0-t} vs. change of time with gastric pH <4 (Study 250)[Error Bookmark not defined.]

The ***Faure*** study[17] was designed to determine both the pharmacokinetics and the optimal dosage of intravenous omeprazole in patients < 30 months.

Patients and methods: Nine children (three girls), aged 4.5 to 27 months (2 children < 6 months, 3 children < 12 months), with normal liver and renal functions requiring intravenous omeprazole were studied. After enrolment in the study and randomization, omeprazole was administered once daily, in the morning, as a 1-hour infusion to fasted patients. Group 1, consisting of the first four patients, received 20mg/1.73 m^2, and group 2, consisting of the following five patients, received 40mg/1.73 m^2. At day 3, a 24-hour intragastric pH and a pharmacokinetic study of omeprazole were performed.

Results: Patients in group 2 had a significantly higher median pH (6.99 vs. 3.35; P = 0.01) and percent of monitored time with gastric pH >4 than children given 20 mg/1.73 m^2 (90.6% vs. 44.8%; P < 0.01). Four had a pH of more than 4 during more than 90% of the time versus none of the patients of group 1. The plasma concentration versus time curves showed rapid elimination of the drug. Systemic clearance was not different between the two groups: median values were 0.68 and 0.42 $L \cdot kg^{-1} \cdot h^{-1}$ (p = 0.22).

Conclusions: Intravenous administration of omeprazole was effective in infants. The results indicated that the dose of 20mg/1.73 m^2 (~ 0.5mg/kg) was not effective in maintaining 24-hour gastric pH > 4 and that a dose of 40mg/1.73 m^2 (~1.1mg/kg) was required. The AUC of omeprazole was significantly correlated with the percentage of time with pH > 4 during 24 hours.

Solana[18] developed a population pharmacokinetic model for intravenous omeprazole in critically ill children.

Methods: One hundred and eighty-six omeprazole concentration-time data from 40 critically ill children were analysed using the nonlinear mixed-effects approach. Patients were randomised into 2 groups and received intravenous omeprazole at a dose of 0.5 or 1 mg/kg twice daily. The average age of the patients was 7 months (range 4-12 months for 0.5mg/kg and 4-60 months for 1 mg/kg. The median weight was 6.2 Kg (range 3.5 – 24.4 Kg). 70 % of the patients were less than 12 months old and weighed < 10 Kg. Blood samples were drawn at 0.5, 2, 6, 12, 24, and 48 hours after the first infusion.

Results: The pharmacokinetic profile was best described by a 2-compartment model with a first-order elimination process. Between - patient variability could only be associated with plasma clearance (CL). The typical values for plasma CL were 24.9 $L \cdot h^{-1} \cdot 70\ kg^{-1}$ (10.08%), with a distributional clearance of 53.9 $L \cdot h^{-1} \cdot 70\ kg^{-1}$ (11.00%) and central and peripheral compartment distribution volumes of 4.23 L/70 kg (19.62%) and 674 L/70 kg (0.89%), respectively. Allometric size models seemed to predict changes adequately in all the pharmacokinetic parameters. High values of between - patient variability of CL [75.50% (2.60%)] and residual variability [130.0% (5.26%)] were still found in the final model. The model-based simulations suggested that the most suitable dose was 1 mg/kg because this yielded similar exposure (defined by the area under the concentration-time curve) to that obtained in adults after a 20 mg dose of omeprazole intravenously.

Comments: In critically ill children, the pharmacokinetics of omeprazole were described using a 2-compartment model (following IV administration) according to zero-order kinetics and linear elimination. The allometrically scaled model adequately described the data over a 7-fold weight range (from 3.5 to 24.4 kg). Even with the wide range of age values (1 month to 7 years), no age-related changes in clearance were detected.

Li[19] *examined the effect of developmental changes on omeprazole* (OME) pharmacokinetics (PK) in paediatric subjects.

Methods: OME plasma concentration time courses following single oral doses of 0.5-1.5 mg/kg, 10 and 20 mg in 84 paediatric subjects aged from 15 days to 16 years old were fitted to a one-compartment disposition model with zero, first, simultaneous zero/first, and sequential zero/first order absorption models. An allometric model was used to describe the relationship of apparent clearance and volume of distribution to body weight. The effect of age on these two PK parameters was modelled by an exponential function.

Results: A one-compartment disposition with sequential zero and first order absorption model described the data best. Age was a significant covariate to impact the OME apparent clearance. The estimated metabolic maturation half-life of OME metabolism was approximately one month.

Conclusions: From single oral dose data in paediatric subjects, it was estimated that OME apparent clearance reached maturation at approximately six months of age when body weight was normalized by an allometric model.

Marier[20] assessed the pharmacokinetics of omeprazole in healthy adults and in children with GERD. Omeprazole capsules were administered orally to 18 healthy adults (mean age 36.8 years, 20mg dose) and 12 children (capsules or EC granules in orange juice) with GERD (mean age 6.1 years (0.5 – 13 years, dose 0.69±0.10 (0.56 – 0.83) mg/kg). Blood samples were collected over 5 hours, and plasma concentrations were assessed using liquid chromatography. Population pharmacokinetic parameters were calculated using NONMEM®. A 1-compartment model with zero-order absorption was used. Oral clearance (CL/F) and apparent volume of distribution (Vss/F) in healthy adults (Mean ± SD: 0.62 ± 0.27 L/h/kg and 0.76 ± 0.26 L/kg, respectively) were not significantly different than those in children with GERD (0.51 ± 0.34 L/h/kg and 0.66 ± 0.25 L/kg, respectively). The plasma profiles obtained and a plot of CL/F normalized for bodyweight vs. age are presented.

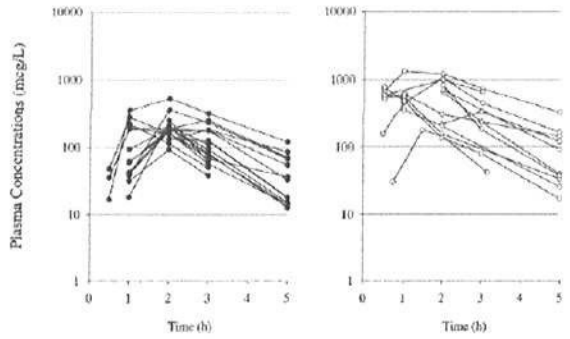


Figure 2.5.2.6 | Individual pharmacokinetic profiles of omeprazole after multiple doses in healthy adults (●) and children with GERD (o)[20]

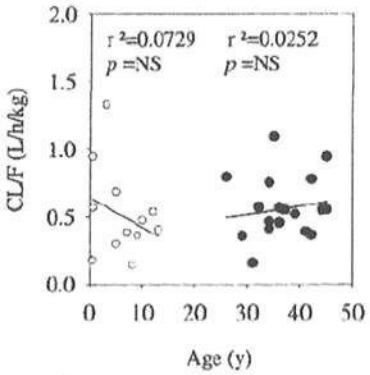


Figure 2.5.2.7 | Graphic representation of the effect of age (years) on oral clearance of omeprazole in healthy adults (●) and children with GERD (o)[20]

	Healthy Adults	Children with GERD	Pooled Populations
V_{ss}/F (L)	53.4 (35.9%)	14.5 (63.7%)	36.1 (55.5%)
V_{ss}/F (L/kg)	0.54 (33.9%)	0.64 (38.2%)	0.59 (25.9%)
k_{el} (h^{-1})	0.75 (18.7%)	0.81 (39.4%)	0.718 (77.4%)
Lag time (h)	0.59 (29.9%)	0.11 (52.9%)	0.23 (41.0%)
k_0 (h)	16.5 (28.0%)	14.3 (71.6%)	15.3 (48.5%)
R^2	0.995	0.983	0.983
MOF	655.698	507.811	1236.207
Residual variability	33.1%	22.8%	44.9%

V_{ss}/F, apparent volume of distribution; k_{el}, rate constant of elimination; Lag time, absorption lag time; k_0, zero-order absorption; R^2, coefficient of determination; MOF, minimum objective function

Table 2.5.2.4 | Geometric Mean and Coefficient of Variability (CV%) for the Population Pharmacokinetic Parameters of Omeprazole in Healthy Adults, Children with GERD, and Pooled Population[20]

	Healthy Adults	Children With GERD
CL/F (L/h/kg)	0.62 ± 0.27	0.51 ± 0.34
V_{ss}/F (L/kg)	0.76 ± 0.26	0.66 ± 0.25
k_{el} (h^{-1})	0.80 ± 0.13	0.74 ± 0.27
$T_{1/2}$ (h)	0.90 ± 0.17	1.07 ± 0.42
Lag time (h)	0.62 ± 0.15	0.12 ± 0.03*
k_0 (mg/h)	15.5 ± 6.5	13.7 ± 10.6

Data are mean ± SD; CL/F, oral clearance; V_{ss}/F, apparent volume of distribution; k_{el}, rate constant of elimination; $T_{1/2}$, elimination half-life; Lag time, lag time; k_0, zero-order absorption. *$P < 0.05$ vs healthy adults.

Table 2.5.2.5 | Descriptive Statistics of Pharmacokinetic Parameters of Omeprazole in Healthy Adults and Children with GERD[20]

In a US FDA published document[21] associated with the approval of omeprazole in children 1 – 12 months at a dosage of ~0.5-1.0mg/kg, data was included on the following: (i) PK/PD relationship in both children and in adults, (ii) Population PK modelling assessment in small children, and (iii) Proposed doses in children giving an exposure similar to the exposure in adults taking the esophagitis dose approved in EU/US (20 mg).

Simulated exposures for a 0.5-1.0mg/kg dosing regimen in children < 1 year appeared to match those from adults and those from the approved doses in children 1 -16 years of age (Figure 2.5.2.8). Exposures were predicted based on the population PK model in children 1 month to 16 years of age using data from 253 paediatric subjects available from three studies (245, 250 and I- 678). PK variability defined across the paediatric population was used in combination with the database of demographics of infants with the final population PK covariate model to simulate the anticipated range of exposures for the proposed dosing regimen. Additionally, the projected exposures did not exceed those expected for a dose of 1.5 mg/kg (green box, Figure 2.5.2.8), a dose that was studied in Studies 251 and BA 04/07.

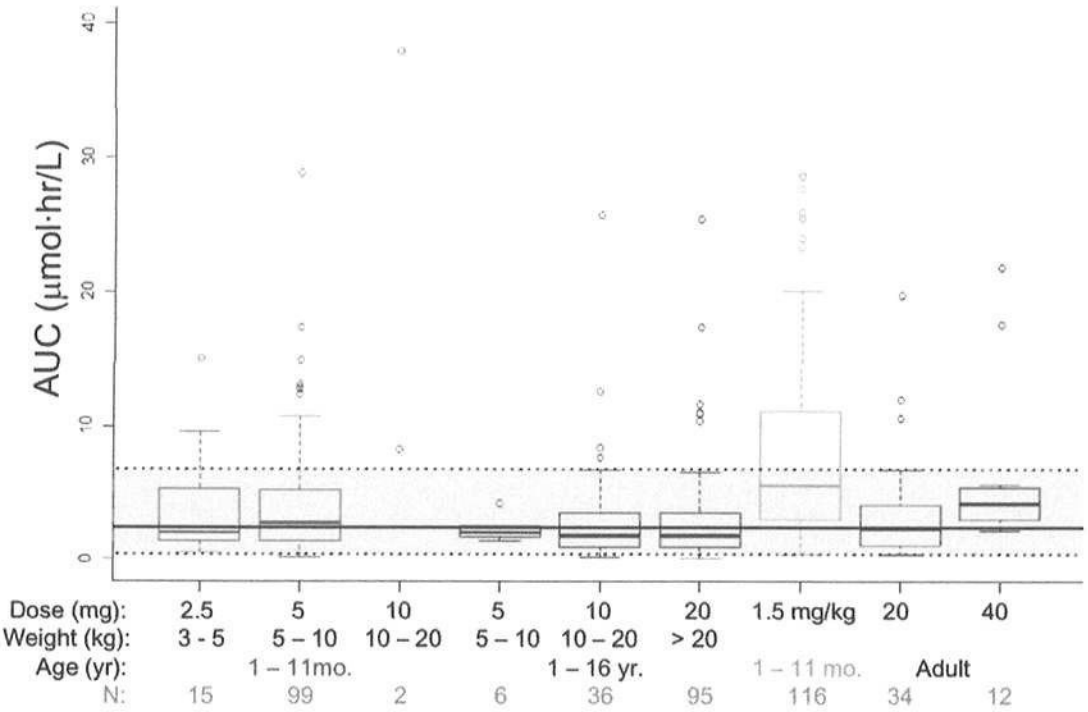


Figure 2.5.2.8 | Omeprazole AUC after simulation at the proposed dosing regimen in infants (red boxes) appears to match exposures from the adult 20mg regimen (left of the black boxes)[21].

Similarly, an exposure response assessment for both children and adults and for both omeprazole and esomeprazole is shown in Figure 2.5.2.9. The endpoint for omeprazole/esomeprazole effect was the "% time above intragastric pH 4", which was compared to the AUCs from the respective studies.

The omeprazole and esomeprazole exposure-response (time that intragastric pH >4) between adults and children are similar so that the matching of omeprazole exposure between adult and pediatric populations was considered feasible[21].

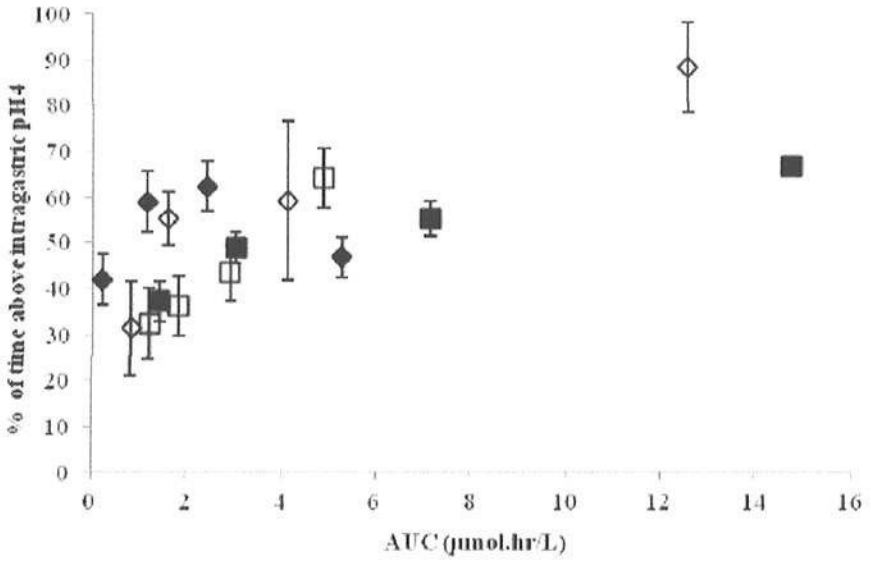


Figure 2.5.2.9 | Exposure-response relationship for omeprazole (open symbols) and esomeprazole (closed symbols) in adult (squares) and paediatric subjects (diamonds). Each group of subjects represented by median AUC and mean % time above intragastric pH 4. For omeprazole, there were PD data from 14 children 4.5 – 27 months of age and 36 adults. For esomeprazole PD data were available from 52 neonates and infants and 52 adults[21].

Using the same data and combined with published IV data, a population PK model for omeprazole administration in children was constructed. The final covariate model for oral absorption was a one-compartment model with 1st order absorption with a lag-time implemented as a series of transit compartments. CL/F and V/F were scaled allometrically by body weight. The simulated AUCs were compared to the previously observed adult exposures following treatment with either 20mg or 40mg omeprazole. The exposure in children 1-16 years showed a good agreement with the target exposure. In the younger age group, 1 – 11 months, the observed simulated exposure was higher: however median exposures in each group were well below the equivalent exposure for 40mg dose in adults.

Summary of PK/PD for Children

In summary, the pharmacokinetics and pharmacodynamics of omeprazole in children < 24 months are similar to older children and to adults. The PK/PD data supports omeprazole dosing on a milligram-per-kilogram basis in these patients.

Pharmacokinetic interactions of omeprazole with other active substances

Effects of omeprazole on the pharmacokinetics of other active substances[14]

Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated. Co-administration of omeprazole (40 mg once daily) reduced mean nelvinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended. Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Other active substances

The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism

Saquinavir

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Methotrexate

When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Effects of other active substances on the pharmacokinetics of omeprazole[14]

Inhibitors CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

The above pharmacokinetic interactions are reflected in the proposed SmPC.

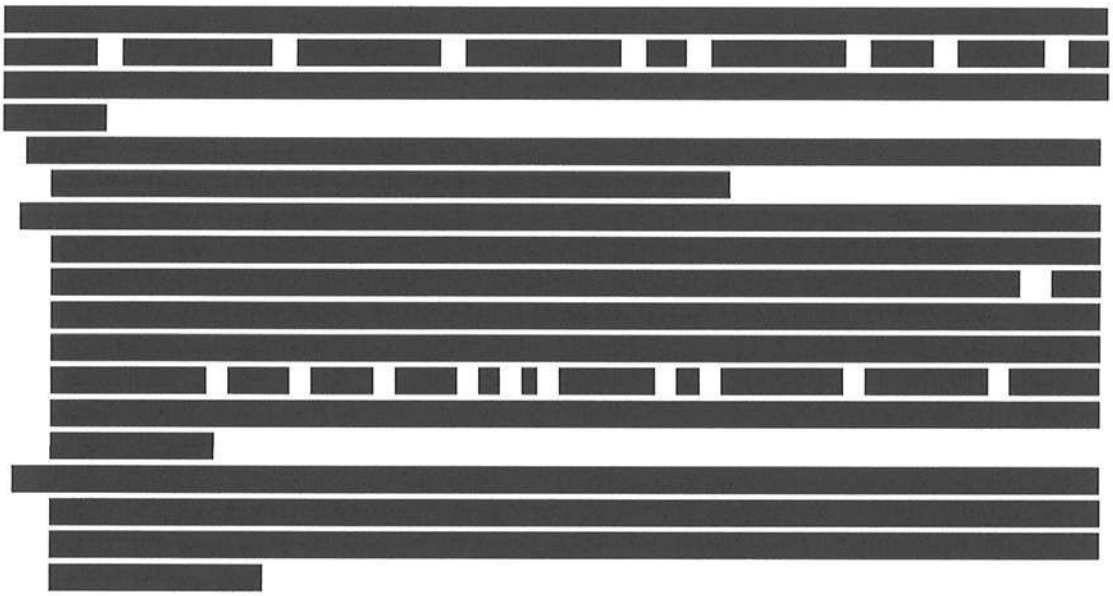
[redacted]

b. Similarly, there is no temporal relationship between efficacy and plasma concentration. Specifically, the effect on gastric acid secretion is long-lasting, although the disappearance of omeprazole from plasma is rapid. Accordingly, the effect is not a direct function of blood concentration at any time, but rather a function of the total amount of omeprazole reaching the general circulation i.e. directly proportional to the AUC. This means that the same pharmacological effect is achieved with dosage forms of omeprazole producing equal AUCs. The role of the formulation approach taken (i.e. buffering or enteric coat) is only to protect the active substance from pre-absorption degradation. Effectively, the shapes of the plasma concentration-time curves are of no importance for this active substance.

(2) Mechanism of action

Insights into the pharmacological basis for omeprazole activity at the cellular level elucidate the relationship between pharmacological activity, pharmacodynamic response and pharmacokinetics, including providing a mechanistic rationalisation for the direct relationship between pharmacodynamic/clinical response and total absorption/concentration (AUC) but not the plasma concentration at a particular time (expressed by plasma profile or C_{time}/ C_{max}). Omeprazole is a pro-drug, with a very specific mechanism of action, determined by accumulation of omeprazole in the parietal cells, chemical transformation to the active inhibitor within the parietal cell and specific enzyme inhibition. For this reason, there can be no direct relationship between plasma concentration at a particular time and pharmacodynamics.

(3) [redacted]



In OSB –IR-06[22] the PK and PD profiles of the test product (Omeprazole sodium bicarbonate-IR powder for suspension 20 mg) and the reference product (Prilosec Delayed Release Capsule 20 mg) were compared after multiple once daily administration in 35 fasting healthy subjects. The reference and test products showed comparable systemic exposures in terms of AUCs; the reference and test products were equivalent in terms of extent of absorption after single dose administration and at steady state (Day 7). However, the mean C_{max} for the test product was 57-60 % higher relative to the reference product after single dose administration and at steady state. This difference in C_{max} did not appear to translate into clinically important pharmacodynamic differences as similar acid secretion inhibition profiles were observed for Omeprazole sodium bicarbonate-IR powder for suspension 20 mg and Prilosec Delayed Release Capsule 20 mg; the reference and test products were similar on all the determined PD parameters (integrated gastric acidity, mean gastric acid concentration, median intragastric pH and % time gastric pH ≤ 4) particularly on day 7. Interestingly, the test product Omeprazole sodium bicarbonate-IR powder for suspension 20 mg contained 1680 mg (20 mEq) sodium bicarbonate per dose.

In OME-IR (CAP)-C02[23] the PK and PD profiles of the test product (Zegerid IR capsule 40 mg) and the reference product (Prilosec DR capsule 40 mg) were compared after multiple once daily administration in 35 healthy subjects. The reference and test products showed comparable systemic exposure in terms of AUCs; the reference and test products were equivalent in terms of the extent of absorption after single dose administration and at steady

state (Day 7). However, the mean C_{max} of Zegerid IR capsules was 17 % higher than that of Prilosec DR capsules after 7 days administration. This difference in C_{max} had no apparent effect on the pharmacodynamics or safety of Zegerid 40 mg in this trial. The pharmacodynamic data show that both Zegerid Capsules 40 mg and Prilosec Capsules 40 mg were equally effective in decreasing integrated gastric acidity at steady state; both products were generally similar on all the assessed PD markers (integrated gastric acidity, mean gastric acid concentration, median gastric pH, % time gastric pH ≤ 4.0). The test product Zegerid IR capsule 40 mg contained 1100 mg (13 mEq) sodium bicarbonate per dose.

In OME-IR (CAP)-CO1[26] the PK and PD profiles of the test product [Zegerid IR Capsule 20 mg] and the reference product [Prilosec DR Capsule 20 mg] were compared after multiple dose administration in 30 healthy subjects. The reference and test products showed comparable systemic exposure in terms of AUCs; the reference and test products were equivalent in terms of extent of absorption after single dose administration and at steady state (Day 7). However, the mean Cmax of Zegerid IR Capsules was 45 % higher than that of Prilosec DR capsules after 7 days administration. This difference in C_{max} had no apparent effect on the pharmacodynamics or safety of Zegerid 20 mg in this trial. The pharmacodynamic data show that both Zegerid Capsules 20 mg and Prilosec Capsules 20 mg were equally effective in decreasing integrated gastric acidity at steady state; both products were generally similar on all the assessed PD markers (integrated gastric acidity, mean gastric acid concentration, median gastric pH, % time gastric pH ≤ 4.0). The test product Zegerid IR capsule 20 mg contained 1100 mg (13 mEq) sodium bicarbonate per dose.

In addition to confirming the clinical efficacy of these formulations, the pharmacokinetics of immediate release omeprazole oral suspension have been well characterised in adults (Xeolas Studies 376-15, 375-15 and 454-14) and children (AstraZeneca Study 250).

Further information on these clinical studies is included in Section 2.5.4.

Insights into PK/PD/clinical relationships for omeprazole from an understanding of the mechanism of action:

As one of the most widely prescribed drugs, Omeprazole has been extensively studied. The molecular, biochemical and cellular basis for it's efficacy and safety are well understood, and in particular their relationship to pharmacodynamics and clinical response.

The success of omeprazole in the clinic (high efficacy, good safety profile) can be ascribed to a very effective inhibition of gastric acid secretion, achieved through a highly targeted mechanism of action.

At the molecular level, omeprazole is a specific inhibitor of the gastric H^+K^+-ATPase – the "acid pump" or "proton pump"- located within the parietal cell[24].

This proton pump is located in the secretory membranes of the parietal cell of the gastric mucosa and constitutes the final step of acid secretion (Figure 2.5.2.10).

In non-clinical whole-body autoradiographic studies, omeprazole was found to label only the tubulovesicles and secretory membranes of the parietal cell, which contain the H^+K^+-ATPase[25]. Electrophoretic analyses of such membranes, purified after administration of radio-labelled

omeprazole, demonstrated that the radiolabel specifically associated with the 92-kDa proteins known to hold the catalytic subunit of H^+K^+-ATPase [27]. *From this, it could be concluded that omeprazole binds only to the H^+K^+-ATPase in the gastric mucosa and nowhere else in the body.*

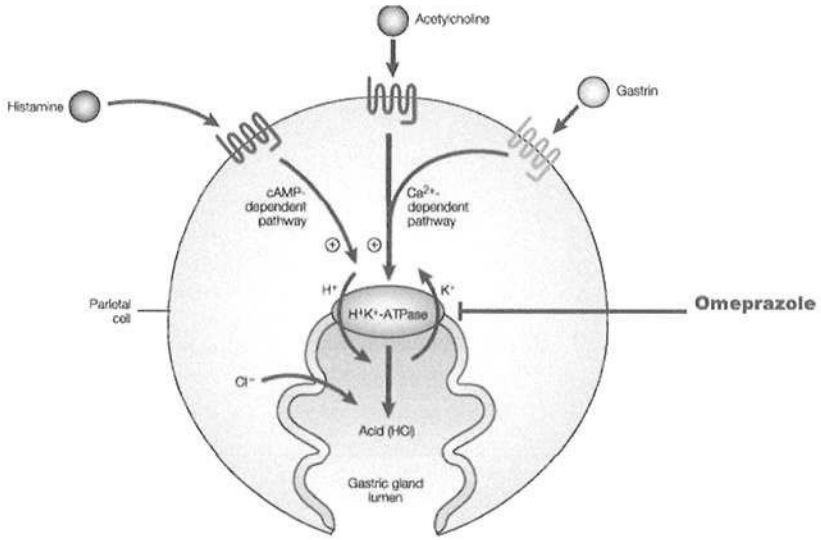


Figure 2.5.2.10 | *Gastric acid is secreted by parietal cells of the stomach in response to stimuli that result in the activation of histamine, acetylcholine or gastrin receptors. Activation of these receptors, located in the basolateral membrane of the parietal cell, initiates signal transduction pathways that converge on the activation of the H^+K^+-ATPase — the final step of acid secretion. Inhibition of this proton pump by omeprazole reduces acid secretion*[24].

However, omeprazole itself is not the active inhibitor of the H^+K^+-ATPase enzyme. A transformation of omeprazole under acid conditions is required to inhibit the H^+K^+-ATPase (Figure 2.5.2.11) in vitro and in vivo, and untransformed omeprazole is devoid of inhibitory action. Investigations of the acidic reactions of omeprazole have revealed an intermediate compound — a sulphenamide — that effectively inhibits the H^+K^+-ATPase enzyme. The H^+K^+-ATPase inhibition is associated with the modification of mercapto groups in the enzyme, through disulphide adduct formation to yield an enzyme–inhibitor complex. As such, the sulphenamide formed from omeprazole can be considered to be the active inhibitor, which binds covalently (irreversibly) to H^+K^+-ATPase (Figure 2.5.2.11).

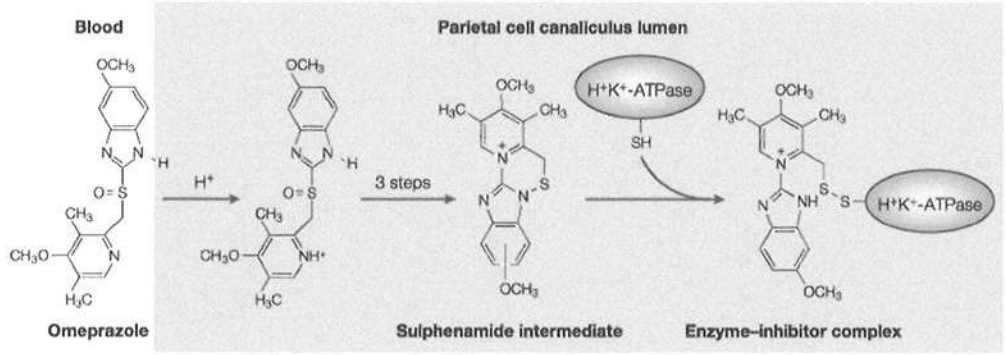


Figure 2.5.2.11 | *Omeprazole, is a prodrug that is converted to the active form in acidic environments. Chemically, omeprazole is a weak base, and concentrates in the acidic secretory canaliculi of the parietal cell, where it is activated by a proton-catalysed process to generate a sulphenamide. The sulphenamide interacts covalently with the sulphydryl groups of cysteine residues in the extracellular domain of the H^+K^+-ATPase - thereby inhibiting its activity. The specific concentration of omeprazole in the secretory canaliculi of the parietal cell is reflected in a favourable side-effect profile[24].*

Physicochemically, omeprazole has several characteristics that are important for its unique mechanism of action. First, omeprazole is lipophilic, so that it easily penetrates cell membranes. Second, it is a weak base, such that it concentrates in acid compartments. Third, it is very unstable in an acidic environment. The half- life of omeprazole at pH 1 is ~2 minutes, whereas at pH 7.4 it is ~20 hours. So, omeprazole is a pro-drug that accumulates within the acid space of the target cell, where it is transformed to the active inhibitor.

For omeprazole, these insights into the mechanism of action illuminate an important aspect of the particular PK/PD relationship for this molecule, in particular why there can be ***no direct relationship between the clinical response and the plasma level at a particular time (C_{time}/C_{max}), since only total absorption relates to accumulation in the target parietal cells, conversion to the active inhibitor and covalent binding to the target enzyme.***

Whereas the half-life of omeprazole in blood plasma is rather short ~ 1–2 hours in man — the half-life of the inhibitory complex is much longer. On the basis of the duration of action in humans, the half-life at the site of action is estimated to be ~24 hours.

Response/exposure relationship, correlation of AUC with pharmacodynamic responses, temporal relationship

For omeprazole, all pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion[14]. The pharmacodynamics/clinical relationship between the time with pH < 4 parameter as a measure of acid reflux and clinical response is well established for the molecule.

Specifically, esophagitis severity (endoscopic assessment) has been correlated with 24 hour esophageal pH monitoring (% time with pH < 4, 178 patients) and with clinical trials of omeprazole (277 patients, 10mg or 20mg daily)[26].

For the response/exposure relationship of omeprazole, there are several studies showing that the AUC correlated with pharmacodynamic responses. ***Lind*** [27] studied the effect of omeprazole on pentagastrin stimulated gastric acid secretion in healthy adults in a placebo-controlled study. Doses of 20-80mg orally, administered as a buffered suspension, produced a significant dose dependent inhibition of acid secretion compared with placebo, the mean

percentage inhibition being 36±8.5, 65±14.9, 90±5.3, and 99±0.42% with the 20, 40, 60, and 80mg doses, respectively. The degree of inhibition remained unchanged throughout the study (Fig.2.5.2.12)(Table 2.5.2.6). Omeprazole also reduced the volume secretion but to a lesser extent than acid secretion (21-87%) resulting in a decreased acidity (Table 2.5.2.6). Incidentally, the placebo (bicarbonate) solutions had no effect on acid output. The acid secretion inhibitory effect was related to the AUC. The AUC increased with increasing doses and showed a significant correlation with per cent inhibition of acid secretion (R=0.93, p< 0.001).

Omeprazole dose	*Before administration*		*After administration*		*Omeprazole AUC µmol/h/l*
	Acid	*Volume*	*Acid*	*Volume*	
Placebo	7·1±0·34	66·5±5·10	6·4±0·51	65·5±3·14	—
20 mg	7·6±0·78	72·0±4·05	4·3±0·67	58·5±4·11	0·94±0·19
40 mg	6·6±0·74	60·0±5·65	2·1±0·77	38·0±7·50	2·4±0·83
60 mg	7·4±0·78	67·5±4·43	0·57±0·30	20·6±5·90	3·8±0·84
80 mg	6·8±0·48	67·0±4·48	0·06±0·02	11·1±1·88	5·7±1·1

Table 2.5.2.6 | Pentagastrin (30 µg/h intravenously) stimulated acid (*mmol*/15 min) and volume (ml/15 min) output before and after (60-180 min) administration of omeprazole suspension and AUC in six healthy subjects. Values are mean ± SEM[27].

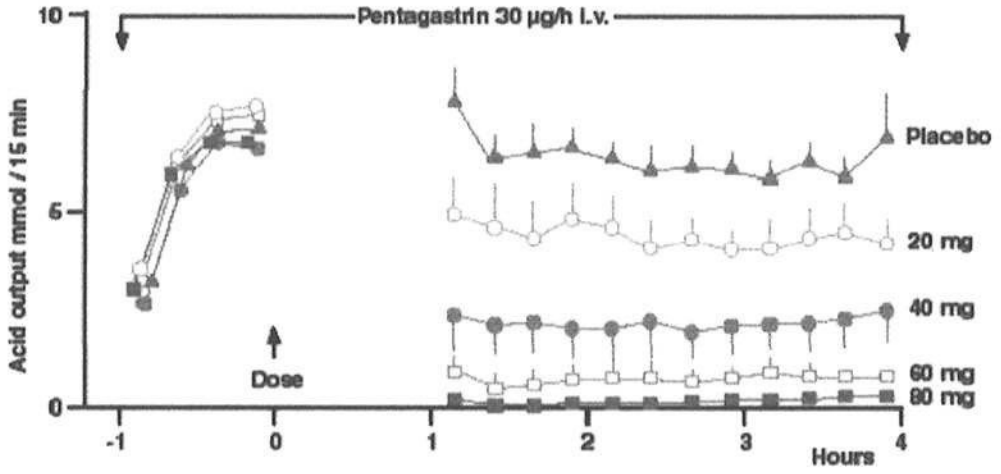
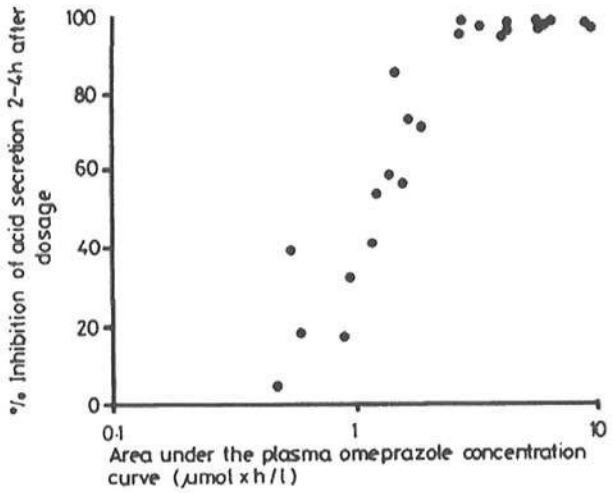


Figure 2.5.2.12 | Effect of oral omeprazole [suspension] on pentagastrin induced acid secretion in six healthy subjects. Values are mean ± 1 SEM[27].

Figure 2.5.2.13 demonstrates the sigmoid relationship that was observed between the response and dose[27]. For different doses of omeprazole and inhibition of acid secretion the response/exposure relationship followed an Emax model of Hill function with γ~1 when the exposure examined was AUC. In studies using either % inhibition of peptone-induced acid secretion or % inhibition of pentagastrin-induced acid secretion, the AUC increased with increasing doses and showed a significant correlation with percent inhibition of acid secretion ($r = 0.93$, $p < 0.001$).

Figure 2.5.2.13 | Relationship between % inhibition of pentagastrin induced acid secretion during the second to fourth hour after omeprazole administration and AUC. Correlation coefficient = 0.93, p<0.001, n=24)[27].



Cederberg[13] described the time-course of the plasma concentration profiles (Figure 2.5.2.14) after omeprazole administration and the pharmacokinetics after single doses, using data from other single dose studies[27,28]. Omeprazole is rapidly absorbed; plasma concentrations of omeprazole reached a peak after < 30-40 minutes. Studies with oral administration of ^{14}C-labelled omeprazole showed that the plasma concentration- time curve for both omeprazole and the total pool of metabolites declined quickly indicating rapid elimination from the body (half-life of less than 1 hour) (Figure 2.5.2.14); however, the inhibitory effect of omeprazole on acid secretion lasted for more than the duration of the experiment.

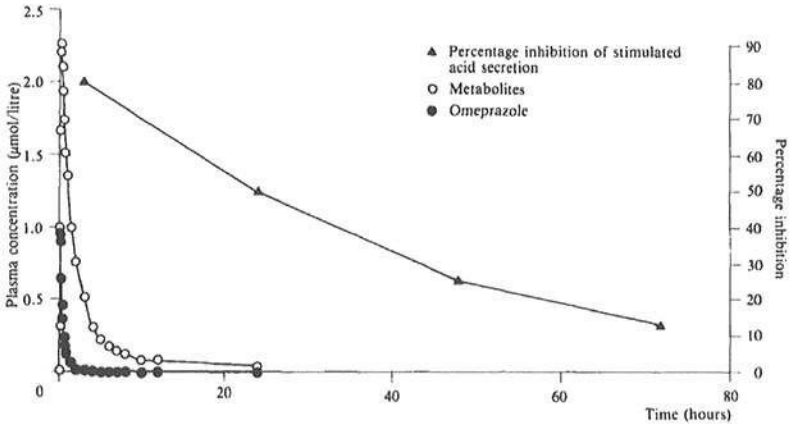


Figure 2.5.2.14 | Mean percentage inhibition of acid secretion at various time points following a single oral dose of omeprazole, 20 mg, as buffered suspension and median plasma concentration-time curves for omeprazole and the total pool of metabolites following a single oral dose of "C-labelled omeprazole as a buffered solution (n=6)[13].

The acid inhibitory effect of omeprazole lasts longer than circulating plasma levels of omeprazole or it's metabolites. The return of acid output to baseline level is linear in contrast to the exponential elimination of drug from plasma. Indeed, omeprazole has a long duration of action: more than 24 hours following a single dose, since parietal cells turn over in about 3–5 days. The long-lasting binding of the active form of omeprazole to the H^+K^+-ATPase in the parietal cells accounts for the lack of correlation between plasma concentration (a very short $t_{1/2}$) and degree of acid inhibition at any given time.

Thus, the degree of acid inhibition at any given time or duration of acid inhibition is independent of the plasma concentration (C_{time} or C_{max}) of omeprazole or any of its metabolites. However, if plasma concentrations are integrated over time (AUC), a clear relationship (gastric acid suppression/AUC) following the classical sigmoidal maximum effect (E_{max}) model can be observed. Accumulation of the drug within the parietal cells is consistent with the long duration of action despite the short plasma half-life. The omeprazole AUC reflects the product of the concentration of omeprazole in plasma and the time it is available in the systemic circulation and, therefore, available to the parietal cells.

Accordingly, the inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time. Using AUC as a parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Conclusion

The use of AUC as the primary parameter for comparing omeprazole immediate-release and delayed-release formulations is endorsed on PK/PD, mechanism of action and clinical grounds.

MODULE 2.5 – CLINICAL OVERVIEW

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY OF OMEPRAZOLE

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

Mechanism of action

Omeprazole, a racemic mixture of two enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action[14]. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H^+K^+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus[14].

Pharmacodynamic effects

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion (SmPC)[14].

Effect on gastric acid secretion

Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment[14]. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the esophagus in patients with gastro-esophageal reflux disease[14].

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.
No tachyphylaxis has been observed during treatment with omeprazole.

Effect on H. pylori

H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease[14]. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.

In adults, eradication of *H. pylori* with omeprazole and a combination of the antimicrobials amoxicillin and clarithromycin is associated with, high rates of healing and long-term remission of peptic ulcers.

Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination therapies.

A randomised, double blind clinical study (Héliot study[29]) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis: *H. pylori* eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

When selecting appropriate combination therapy consideration should be given to official local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

Other effects related to acid inhibition

During long-term treatment, gastric glandular cysts have been reported in a somewhat

increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped at least 5 days before CgA measurement. If CgA and gastrin levels have not normalised after 5 days, measurements should be repeated 14 days after cessation of omeprazole treatment.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

MODULE 2.5 – CLINICAL OVERVIEW

2.5.4 OVERVIEW OF EFFICACY

Omeprazole Oral Suspension is indicated for the treatment of acid-related disorders.

Compared to the reference product, the main change proposed concerns a change to the patient population in children – extending the population to children < 1 year of age - as follows:

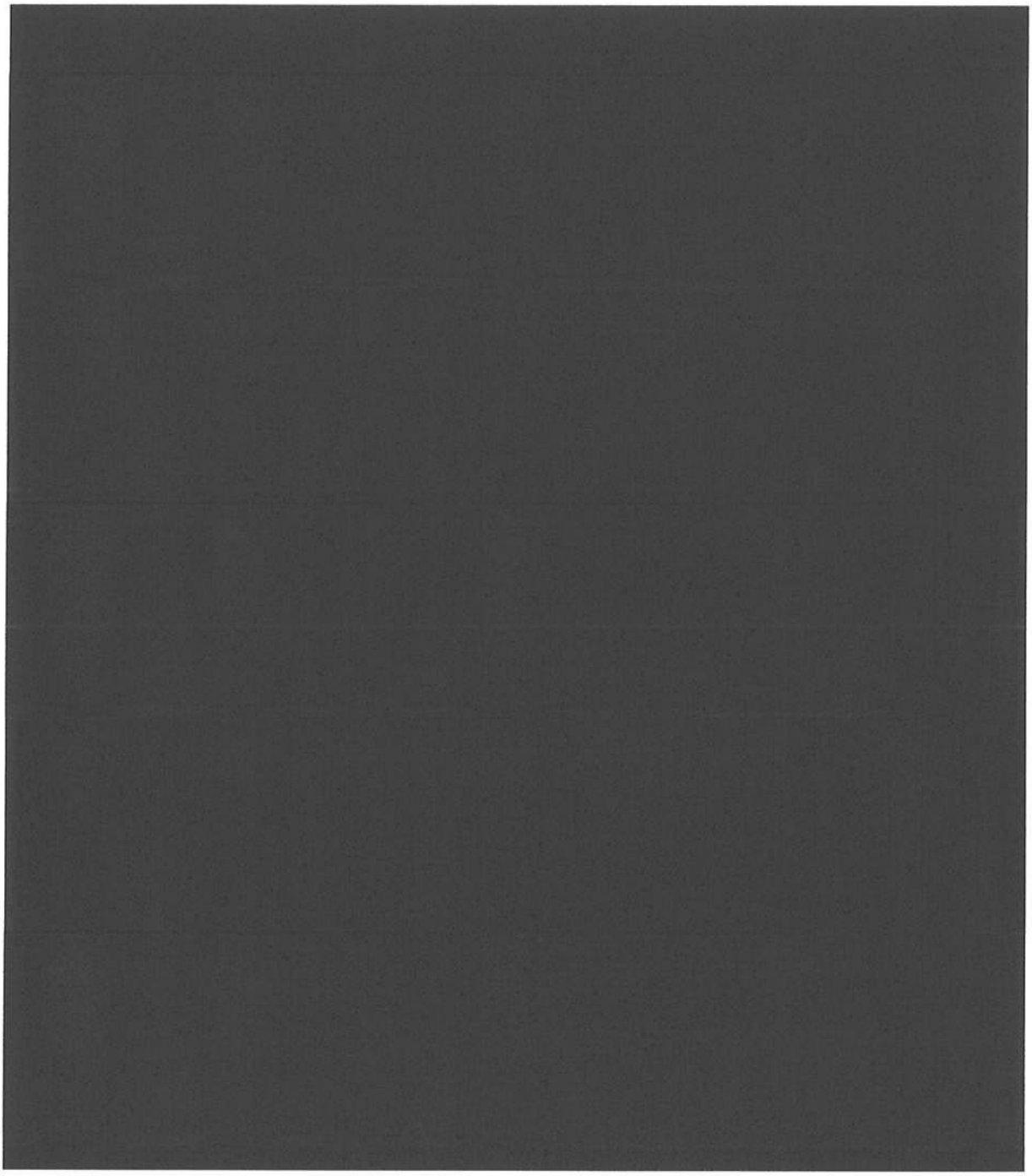
Children (over 1 month of age)
- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

This application includes 5 clinical studies, as follows:

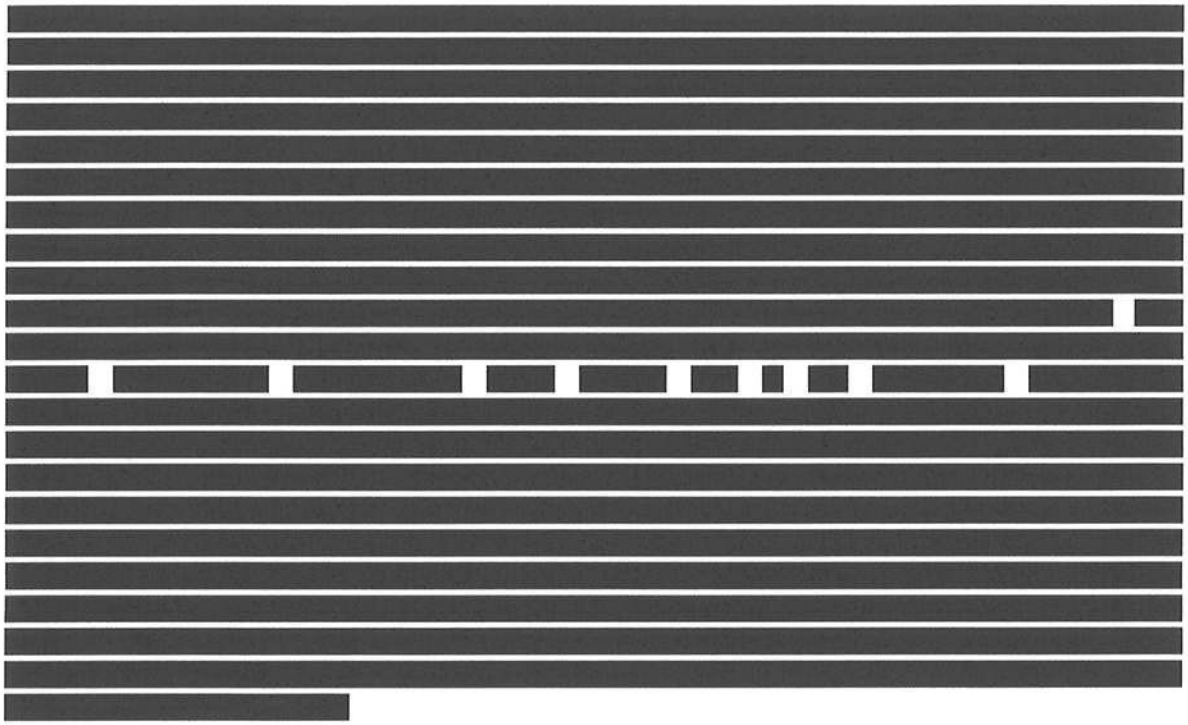
Reference	Study No.	Details
2.5.4.1	376-15	Pivotal comparative bioavailability study comparing Omeprazole Oral Suspension 4mg/ml with the reference product, Losec 20mg capsules
2.5.4.2	BA 04/07	Supportive efficacy/PD study of Omeprazole Oral Suspension (enabling formulation) in paediatric patients
2.5.4.3	454-14	Supportive comparative bioavailability study comparing Omeprazole Oral Suspension 2mg/ml (intermediate formulation) with the reference product, Losec 10mg capsules
2.5.4.4	375-15	Supportive comparative bioavailability study comparing Omeprazole Oral Suspension 4mg/ml (intermediate formulation) with the reference product, Losec 20mg capsules
2.5.4.5	0104-16	Supportive comparative bioavailability study comparing Omeprazole Oral Suspension 4mg/ml with the clinical formulation of Losec 20mg capsules used in paediatric efficacy/PK studies and a fasted/fed arm with Omeprazole Oral Suspension 4mg/ml relevant to the paediatric setting

Table 2.5.4.1 | Clinical Studies included in this Application

The investigational product used in the studies 2.5.4.1-5 evolved progressively throughout formulation development. Information on the evolution of the formulation and test formulations used in the clinical studies is presented in the following Table.



Omeprazole Oral Suspension originated as an immediate release formulation . The original immediate release was evaluated in the supportive efficacy / PD study BA 04/07 in *paediatric patients.*



2.5.4.1 STUDY 376-15

PIVOTAL COMPARATIVE BIOAVAILABILITY STUDY OF OMEPRAZOLE 4MG/ML ORAL SUSPENSION WITH THE REFERENCE PRODUCT, LOSEC 20MG CAPSULES

Study 376-15, the pivotal clinical study included in this application, is a pharmacokinetic study comparing the bioavailability of the proposed product – Omeprazole Oral Suspension – to the reference product, *Losec Capsules*. This application is a 10.3 application or "hybrid application" such that the main study establishes comparative bioavailability to the reference product, together with a small clinical study in a young paediatric population, additional pharmacokinetic studies, and references to other clinical studies.

Title of Study:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover oral comparative bioavailability study of Omeprazole 4 mg/mL (i.e. 20 mg/5 mL) oral suspension (Balanced Formulation) with that of LOSEC capsules 20 mg in healthy, adult, human subjects under fasting conditions.

Study Objectives:

To determine comparative bioavailability of the sponsor's test product Omeprazole 4 mg/mL (20 mg/5 mL) Oral Suspension with that of the European sourced reference product (LOSEC capsules 20 mg) in healthy, adult, human subjects under fasting conditions. And to monitor the adverse events and to ensure the safety of the subjects.

Methodology:

The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose/suspension, crossover, comparative bioequivalence study in

healthy, adult, human subjects under fasting conditions, with a screening period of 28 days prior to the dosing in Period-I. A total of 48 blood samples were collected from each subject except for the discontinued subjects during the conduct of study to analyse the pharmacokinetic profile of the test as well as the reference product.
The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 6.4 (Certara L.P.) for Omeprazole. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC GLM of SAS® Version 9.3 (SAS Institute Inc.) to assess the bioavailability between test and reference formulation.

Table 2.5.4.3 | Number of Subjects (planned and analysed)

Planned for inclusion		28
Pre-dose Discontinued		01
Dosed	Period-I	28
	Period-II	27
Post-dose Discontinued subject		01
Analysed		28 (In which, withdrawn Subject No. 1012 was also analysed as per protocol requirement)
Considered for statistical analysis		27

Test and Reference product

Test Product : **Omeprazole 4 mg/mL Oral Suspension**

Manufactured by: Xeolas Pharmaceuticals

Reference Product : **LOSEC Capsules 20 mg**

Marketing Authorization Holder: AstraZeneca

Market: UK

Dose and mode of administration:

For Test Product:

After an overnight fast of at least 10 hours, subjects were administered 5 mL of constituted suspension containing Omeprazole 20 mg (4 mg/mL) with 240 mL of drinking water at ambient temperature in sitting posture.

For Reference Product:

After an overnight fast of at least 10 hours, subjects were administered a single oral dose of one capsule (containing Omeprazole 20 mg) with 240 mL of drinking water at ambient temperature in sitting posture.

The IMP administration was as per randomization schedule and under open label conditions.

Criteria for evaluation:

Efficacy:

For efficacy evaluation, a total of 48 blood samples (i.e. 25 blood samples for test formulation and 23 blood samples for reference formulation) were collected in each period at the time points specified in the protocol. Standard non-compartmental model of Phoenix® WinNonlin® Version 6.4 was used to derive pharmacokinetic parameters for Omeprazole.

Safety:

Safety was assessed from the screening period to the end of the study. It was assessed through clinical examination, vital signs assessment, 12-lead electrocardiogram (ECG), chest x-ray (posterior-anterior view) recording, clinical laboratory parameters (e.g. biochemistry, hematology, immunology and urine analysis) and subjective symptomatology.

Analytical methods:

The plasma samples of subjects were analysed using a validated LC-MS/MS method.

Statistical methods:

Descriptive statistics are calculated and reported for all pharmacokinetic parameters of Omeprazole.

ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Omeprazole.

The 90% confidence interval for the ratio of the geometric least-squares means between drug formulations are calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Omeprazole.

Comparative Bioavailability Evaluation:

The comparative bioavailability of the suspension to the capsule was to be evaluated by comparing the extent of absorption based upon AUC_{0-t} data. This comparative bioavailability evaluation was to be based on the statistical results of 90% confidence interval for the ratio of the geometric least squares means of ln-transformed pharmacokinetic parameter AUC_{0-t} for Omeprazole. C_{max} was to be examined as a secondary parameter as only the extent of absorption will influence the clinical efficacy of this product and as the liquid is not enteric coated it was expected that the rates of absorption of these two products may differ from one another.

All statistical analyses for Omeprazole are performed using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

EFFICACY RESULTS (STUDY 376-15)

Primary PK parameter

The pharmacokinetic parameters of Omeprazole for Test Product-T and Reference Product-R are summarized in the following table:

Table 2.5.4.4 | Evaluation of Omeprazole in Project No. 376-15

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	99.1	93.57 - 104.94	12.4

[1]Estimated from the Residual Mean Squares.

Table 2.5.4.5 | Pharmacokinetic Data and Descriptive Statistics of Formulation Means for Omeprazole (n = 27) in Study 376-15

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	0.500 (0.250 - 1.667)	2.000 (1.000 - 4.500)
C_{max} (ng/mL)	696.478 ± 329.2992	557.612 ± 358.7416
AUC_{0-t} (ng.h/mL)	1510.547 ± 1940.2799	1620.518 ± 2041.1823
$AUC_{0-\infty}$ (ng.h/mL)	1532.929 ± 1969.7339	1648.390 ± 2093.6886
λ_z (1/h)	0.770 ± 0.3640	0.802 ± 0.3897
$t_{½}$ (h)	1.303 ± 1.1413	1.392 ± 1.4429
AUC_%Extrap_obs (%)	1.787 ± 0.7237	1.691 ± 0.9857
T_{lag} (h)*	0.000 (0.000 - 0.083)	0.667 (0.000 - 3.333)

*T_{max} and T_{lag} are represented in median (min-max) value.

Table 2.5.4.6 | Additional Pharmacokinetic Data for Omeprazole in Project No. 376-15

Plasma concentration curves where	Related Information
$AUC_{(0-t)}/AUC_{(0-\infty)} < 0.8$	None
C_{max} is the first point	None
Pre-dose sample > 5% C_{max}	None

The relative bioavailability analysis (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for Omeprazole are summarized in the following Table 2.5.4.7:

Table 2.5.4.7 | Relative Bioavailability Results for Omeprazole (n = 27) Study 376-15

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
$lnAUC_{0-t}$	868.050	876.040	99.1	93.57 - 104.94	12.4	100.0
$lnAUC_{0-\infty}$	883.870	891.251	99.2	93.76 - 104.90	12.1	100.0
lnC_{max}	621.821	450.759	137.9	122.79 - 154.98	25.4	93.5

SAFETY RESULTS (STUDY 376-15):

Adverse events

There were no adverse events during the conduct of the study.

CONCLUSION FOR STUDY 376-15:

Test Product-T (Omeprazole Oral Suspension) and Reference Product-R (LOSEC capsules) were comparable with respect to AUC_{0-t} for Omeprazole under fasting conditions.

Data from this study demonstrated that the test and the reference products were well tolerated. There were no adverse events during the conduct of the study. There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects in the study.

The results of this study demonstrated that the criteria used to assess comparative bioavailability between the test and reference formulations were fulfilled. The test to reference ratio with corresponding 90% CI for the ratio of geometric least squares means of ln-transformed pharmacokinetic parameter AUC_{0-t} was within the acceptance range. Therefore, Test Product-T and Reference Product-R are comparable with respect to AUC_{0-t} for Omeprazole under fasting conditions. The Test Product-T (Omeprazole Oral Suspension) and Reference Product-R (LOSEC capsules) were equivalent in terms of AUC_{0-t} and hence extent of absorption / exposure for Omeprazole under fasting conditions.

As expected, for this comparison of an immediate release suspension with a delayed release capsule, the ratio of geometric least squares means of ln-transformed pharmacokinetic parameter C_{max} (secondary parameter) showed a faster absorption profile and higher C_{max} for the test product than the reference product of 137.9% (122.79 – 154.98%). Omeprazole exhibits significant patient-to-patient variability with respect to absorption and it is notable from a safety perspective that the C_{max} range for the test product was 225.403 to 1493.503 ng/ml and for the reference product it was 135.758 to 1430.262 ng/ml i.e. similar range of individual values, including maximum plasma concentrations. Also peak plasma concentration of Omeprazole after administration for Test product-T was achieved faster than the Reference product-R as shown by T_{max} and T_{lag}.

The Reference Product-R (Delayed-Release Capsules) is an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach and the enteric coating on the granules dissolves. Test Product-T is an immediate release suspension and employs a buffering system in lieu of the enteric coat to protect the omeprazole in the stomach. Though omeprazole is acid-labile, extent of absorption of Omeprazole from the Test Product-T and Reference Product-R is comparable. The Test Product-T (Omeprazole Oral Suspension) and Reference Product-R (LOSEC capsules) were equivalent in terms AUC_{0-t} and hence extent of absorption / exposure for Omeprazole under fasting conditions. The composition of Test Product –T (Omeprazole Oral Suspension) represents the final formulation proposed for marketing.

Based on this study Omeprazole Oral Suspension 4mg/ml has been shown to be equivalent to the reference product, Losec 20 mg Capsules in terms of the extent of absorption / availability of omeprazole.

2.5.4.2 STUDY BA 04/07

SUPPORTIVE EFFICACY / PD STUDY TO EVALUATE THE GASTRIC ACID SUPPRESSION EFFECTIVENESS OF AN ENABLING FORMULATION OF OMEPRAZOLE ORAL SUSPENSION IN INFANTS

Title: A pilot, single-centre, open-label study to evaluate the gastric acid suppression effectiveness of Omeprazole Oral Suspension in infants with GERD.

Study Objective: To determine the reflux index (RI), i.e. the percentage of time with a gastric pH lower than 4 following treatment with omeprazole oral suspension.

Study Design: BA 04/07 was an open label study designed to evaluate the safety and clinical outcome of omeprazole treatment in paediatric patients < 1 year with GERD. There was no control group.

Dose: The dose selected for this study was 1.5 mg/kg/day. [redacted] Based on 1.5mg/kg/day dose, the calculated administration volume was >20% of liquid feeding requirements (breast/infant formula milk) so that the dose was administered in two divided doses (morning and afternoon) [*note: the final formulation proposed for marketing requires only 5ml volume to administer a dose of 10 mg (2 mg/ml) or 20 mg (4 mg/ml)].

Treatment Procedure: Patients' parents/guardians were informed about the study when the investigator considered that patients were suitable for study participation. The study procedures were fully described to the parent/guardian. After all questions were answered and the parent/guardian provided the informed consent, the investigator requested admission of the patient to the study.

Patients were evaluated on Days 0, 1, 3, and 4. Throughout the evaluations, patients remained hospitalized.

On Day 0, the investigator placed a dual sensor esophageal and intra-gastric catheter in patients to measure the pH for 24 hours.

The principal investigator checked the pH-monitoring values, and those values considered to be pathological (the reflux index was considered: percentage of time with esophageal pH values lower than 4) were used to confirm GERD and patients were included in the study (screening).

Later (Day 1 evaluation), with the catheter still inserted, the first dose of Omeprazole Oral Suspension was administered by oral syringe in the presence of their parents/guardian to observe the pH changes during the first 24 hours.

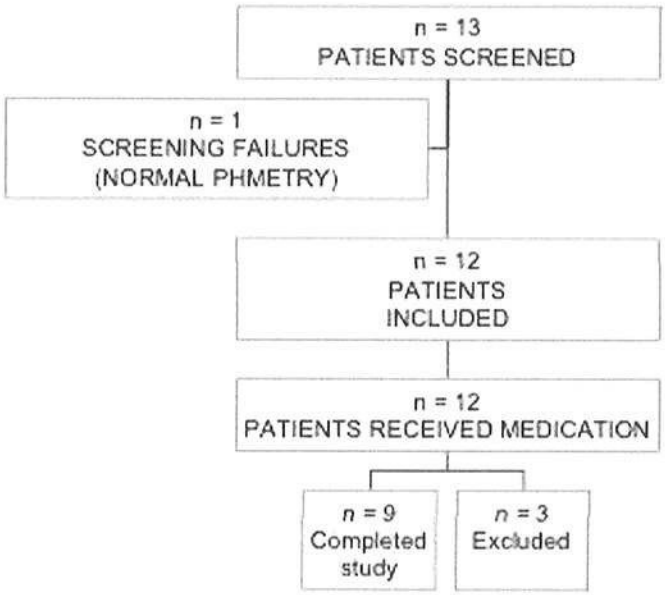
After that, the gastric pH catheter was removed from patients who remained hospitalized for observation; the same daily dose was administered for 3 consecutive days, and on Day 3, after 72 h of treatment, a second pH study was performed. To measure the pH (on Day 3), patients were administered the morning dose of omeprazole suspension before inserting the catheter. During the evaluation on Day 4, the pH catheter was removed from patients.

Signs and symptoms of infants suffering from GERD were recorded on the case report form (CRF) before and after treatment (irritability, unexplained crying, dysphagia, abdominal pain, vomiting, etc.) so as to determine any clinical improvement besides the gastric pH changes.

Table 2.5.4.8 | Study BA 04/07 Study Days & Flow Chart

Study Day	**0**	**1**	**2**	**3**	**4**
Visits	X	X		X	X
Informed Consent	X				
Current disease	X				
Treatment (omeprazole)		X	X	X	
pH-measurement	X	X		X	
Adverse events		X	X	X	X

Study Population and disposition:



Data Sets Analysed

Patients who complied with inclusion criteria were included in the protocol after signing the informed consent form.
Nine patients completed all the protocol stages for 4 days (corresponds to patients No. 3, 4, 5, 6, 7, 10, 11, 12, and 13).

[redacted]

Demographic and Other Baseline Characteristics

Patients younger than 1 year (infants) exclusively breastfed or bottle-fed on infant formula suffering from GERD, n = 9.

[redacted]

REASONS FOR CONSULTATION	n = 13
Respiratory symptoms	5
Apparent Life Threatening Event (ALTE)	4
Vomiting	1
Vomiting, poor weight gain, and choking	1
Vomiting and irritability	2
TOTAL	13 patients

GERD RELATED SIGNS AND SYMPTOMS (n = 13)	
Vomiting	12 patients
Irritability and cry	9 patients
Poor weight gain	2 patients
Extra-digestive or neurological symptoms	3 patients
Growth delay	1 patient

Efficacy Results and Individual Patient Data for Study BA 04/07

Analysis of efficacy

Nine (9) infants (5 male and 4 female, with a mean age of 52.89 ± 23.36 days and a mean body weight of 4.6 kg).
Period of time during gastric pH < 4 in each infant is shown in Table 2.5.4.9.

Table 2.5.4.9 | Time with gastric pH <4 in each infant

PATIENT	BASELINE VALUE		POST-OMEPRAZOLE	
	PERCENTAGE TIME	HOURS	PERCENTAGE TIME	HOURS
3	32.61	7.82	0	0
4	52.44	12.59	0	0
5	31.81	7.63	0	0
6	46.94	11.27	0.75	0.18
7	53.31	12.8	0	0
10	52.84	12.68	2.23	0.53
11	29.24	7.02	0.07	0.01
12	43.03	10.33	0	0
13	63.21	15.17	0	0

When comparing the baseline pH-monitoring values to post-treatment values, a significant reduction in gastric acidity is evident as shown in Table 2.5.4.10.

Table 2.5.4.10 | Mean ± standard deviation of time with a gastric pH value lower than 4

	PERCENTAGE TIME	HOURS
BASELINE VALUE	45.05 ± 11.73	10.81 ± 2.82
Post – Omeprazole	0.34 ± 0.75	0.08 ± 0.18

Non parametric Wilcoxon Test, $p < 0.01$

Statistical/analytical

Firstly, a descriptive analysis of the cohort used was performed. Nominal or ordinal qualitative variables were expressed as absolute or relative frequencies. Continuous quantitative variables were expressed as mean values ± standard deviation. Secondly, an inferential statistical analysis was performed in which baseline and post-omeprazole suspension results from the 24 hour gastric pH-monitoring values were compared considering for the analysis the total time expressed in hours and minutes as well as the percentage of time during which the gastric pH was lower than 4.

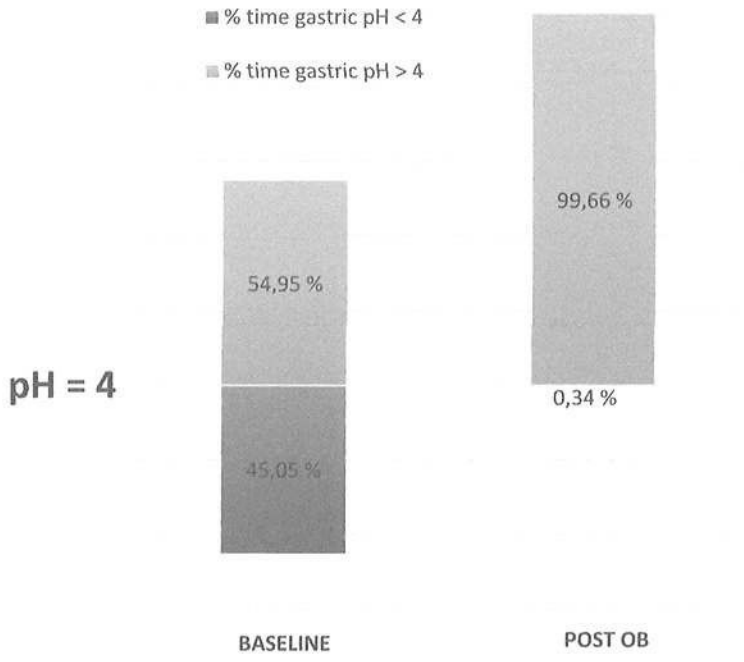
Data was expressed as mean values ± standard deviation and the non-parametric Wilcoxon test was used for comparing baseline and post-omeprazole powder for oral suspension.

Tabulation of individual response data

Table 2.5.4.11 | Time with gastric pH lower than 4 in each patient during pH-monitoring

Patients	BASELINE			POST TREATMENT		
	Time of pH-monitoring values in hours	% time	Hours *	Time of pH-monitoring values in hours	% time	Hours *
3	**20 h 57´**	**32.61**	**7.82**	**23 h 23´**	**0**	**0**
4	**20 h 07´**	**52.44**	**12.59**	**24 h**	**0**	**0**
5	**22 h 38´**	**31.81**	**7.63**	**23 h 24´**	**0**	**0**
6	**22 h 32´**	**46.94**	**11.27**	**22 h**	**0.75**	**0.18**
7	**21 h 38´**	**53.31**	**12.8**	**20 h 32´**	**0**	**0**
10	**21 h 59´**	**52.84**	**12.68**	**22 h 25´**	**2.23**	**0.53**
11	**19 h 33´**	**29.24**	**7.02**	**21 h 48´**	**0.07**	**0.01**
12	**22 h 16´**	**43.03**	**10.33**	**22 h 41´**	**0**	**0**
13	**20 h 45´**	**63.21**	**15.17**	**20 h 40´**	**0**	**0**

* pH values expressed in hours were calculated on a 24-hour basis since this measurement was not conducted on all the patients.



	Mean value	
	BASELINE	**POST Omeprazole**
time with pH < 4	45.05	0.34
time with pH > 4	54.95	99.66

Omeprazole dose and relationships to response

The recommended dose was 1.5 mg/kg/day administered twice daily for 3 consecutive days, after which time a further pH-monitoring assessment was performed.

Once the morning dose was administered, the syringes containing the remaining Omeprazole Oral Suspension were stored in the refrigerator for the second daily dose. Based on information from medical records, there were no missed doses.

[redacted]

Efficacy/Safety Conclusion and Comments

Efficacy Conclusion: The results of this study showed that omeprazole oral suspension induced significant and intensive gastric acid suppression in infants with GERD.

Safety Conclusions: There were no adverse events reported for the twelve (12) patients who received the medication. No adverse events were reported during the 4 days treatment/monitoring with omeprazole suspension.

Other observations and comments: There were no treatment discontinuations due to taste, an important consideration in this age group. The investigator reported that patient recruitment was difficult, although the investigator had treated many other infants during the period. The investigator reported that parents/guardians/family physicians were reluctant to enrol the children in a clinical trial, a recurring issue with paediatric clinical trials in this age group.

The investigators concluded that the study results indicated that Omeprazole Oral Suspension was a therapeutic option for GERD in this paediatric population, with the important advantage of being a suitable formulation for this age group.

In the context of the present application, the study supports the pharmacokinetic data provided and informed the final development to the formulation proposed for marketing. [redacted]

2.5.4.3 STUDY 454-14

SUPPORTIVE COMPARATIVE BIOAVAILABILITY STUDY OF AN INTERMEDIATE FORMULATION OF OMEPRAZOLE 2mg/ml (10mg/5ml) ORAL SUSPENSION WITH THE REFERENCE PRODUCT, LOSEC 10MG CAPSULES

Study 454-14 was carried out using an intermediate formulation of Xeolas's Omeprazole 2mg/ml Oral Suspension (compared to Study 376-15, carried out using Omeprazole 4mg/ml Oral Suspension). The reference product was the same, Losec, but the capsule strength used was lower, Losec 10mg capsules. As well as confirming comparative bioavailability at the lower strength, the study informed the design of the pivotal study 376-15.

Title of Study:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover oral comparative bioavailability study of omeprazole 10 mg/5 ml suspension with that of Losec capsules 10 mg in healthy adult, human subjects under fasting conditions.

Study Objectives:

To determine comparative bioavailability of the sponsor's test product (Omeprazole 10 mg/5 ml suspension) with that of the European sourced reference product (Losec capsules 10 mg) in healthy, adult, human subjects under fasting conditions.

To monitor the adverse events and to ensure the safety of the subjects.

Methodology:

The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, comparative bioavailability study in healthy, adult, human subjects under fasting conditions. In the study, 18 blood samples, including one pre-dose blood sample, were collected from each subject in each period to analyze the pharmacokinetic profile of the test as well as the reference product.

The pharmacokinetic parameters were calculated from the drug concentration vs. time profile by non-compartmental model for Omeprazole. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC GLM of SAS® to assess the bioavailability of both the formulations.

Table 2.5.4.12 | Number of Subjects (planned and analysed)

Planned for inclusion		24
Enrolled		26
Checked In		26
Dosed	Period-I	24
	Period-II	22
Discontinued/Withdrawn		02
Analysed		22
Considered for pharmacokinetic and statistical analysis		22

Test and Reference product:

Test Product : Omeprazole 2 mg/ml Oral Suspension

[redacted]

Reference Product : LOSEC capsules 10 mg

Marketing Authorization Holder: AstraZeneca UK

Market: UK

Dose and mode of administration:

For Test Product: After an overnight fast of at least 10 hours, subjects were administered 5ml constituted suspension-containing Omeprazole 10mg (2mg/ml) in sitting posture with 240 ml of drinking water at ambient temperature.

For Reference Product: After an overnight fast of at least 10 hours, subjects were administered a single oral dose of one capsule (containing Omeprazole 10 mg) with 240 mL of drinking water at ambient temperature in sitting posture.

The IMP administration was as per randomization schedule and under open label conditions.

Criteria for evaluation:

Efficacy:

For efficacy evaluations, a total of 18 blood samples were collected in each period at the time points specified in the protocol. Standard non-compartmental pharmacokinetic parameters were derived for Omeprazole.

Safety:

Safety was assessed from the screening period to the end of the study. It was assessed through clinical examination, vital signs assessment, 12-lead electrocardiogram (ECG), chest x-ray (posterior-anterior view) recording, clinical laboratory parameters (e.g. biochemistry, hematology, immunology and urine analysis) and subjective symptomatology.

Analytical methods:

The plasma samples of subjects were analysed using a validated LC-MS/MS method.

Statistical methods:

Descriptive statistics are calculated and reported for all pharmacokinetic parameters of Omeprazole.

ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Omeprazole.

The 90% confidence interval for the ratio of the geometric least-squares means between drug formulations are calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Omeprazole.

Comparative Bioavailability Evaluation:

The comparative bioavailability of the suspension to the capsule was to be evaluated by comparing the extent of absorption based upon AUC_{0-t} data. This comparative bioavailability evaluation was to be based on the statistical results of 90% confidence interval for the ratio of the geometric least squares means of ln-transformed pharmacokinetic parameter AUC_{0-t} for Omeprazole.

C_{max} was to be examined as a secondary parameter as only the extent of absorption will influence the clinical efficacy of this product and as the liquid is not enteric coated it was expected that the rates of absorption of these two products would be different.

EFFICACY RESULTS (STUDY 454-14)

Primary PK parameter

The pharmacokinetic parameters of Omeprazole for Test Product-T and Reference Product-R are summarized in the following table:

Table 2.5.4.13 | Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	103.2	95.09 - 111.98	15.8

[1]*Estimated from the Residual Mean Squares.*

Table 2.5.4.14 | Pharmacokinetic Data and Descriptive Statistics of Formulation Means for Omeprazole (n = 22) in Study 454-14

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	0.333 (0.167 - 0.750)	1.500 (1.000 - 4.000)
C_{max} (ng/mL)	503.750 ± 228.7079	328.549 ± 198.0992
AUC_{0-t} (ng.h/mL)	916.700 ± 1041.9447	921.873 ± 1084.1895
$AUC_{0-\infty}$ (ng.h/mL)	950.696 ± 1120.0246	989.087 ± 1241.0935
λ_z (1/h)	0.742 ± 0.2653	0.709 ± 0.2895
$t_{½}$ (h)	1.175 ± 0.7708	1.297 ± 0.9329
AUC_%Extrap_obs (%)	1.343 ± 2.2060	2.376 ± 4.5821
T_{lag} (h)*	0.000(0.000-0.000)	0.167(0.000-2.000)

*T_{max} and T_{lag} are represented in median (min-max) value.

The relative bioavailability analysis (i.e. geometric least squares means ratio, 90% confidence interval and power) of Test Product-T vs. Reference Product-R for Omeprazole are summarized in the following table:

Table 2.5.4.15 | Relative Bioavailability Results for Omeprazole (n = 22)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%		
$lnAUC_{0-t}$	583.837	565.790	103.2	95.09-111.98	99.6
$lnAUC_{0-\infty}$	591.929	580.226	102.0	94.37-110.29	99.8
lnC_{max}	453.252	271.679	166.8	147.17-189.12	90.3

SAFETY RESULTS (STUDY 454-14):

Adverse events

Two (02) adverse events (AEs) were reported by one (01) subject during the conduct of the study after administration of the Test Product-T. Both the AEs were mild in nature and considered by the investigator to be unrelated to the treatment.

CONCLUSION FOR STUDY 454-14:

Test Product-T (Omeprazole Oral Suspension 2mg/ml) and Reference Product-R (Losec 10mg capsules) are comparable with respect to AUC_{0-t} for Omeprazole under fasting conditions. The ratio of geometric least squares means of Test Product-T and Reference Product-R for ln-transformed pharmacokinetic parameter, AUC_{0-t} was 103.2%. The 90% confidence interval for the ratio of geometric least squares means was found to be 95.09-111.98%. The Test Product-T (Omeprazole Oral Suspension) and Reference Product-R (LOSEC capsules) were equivalent in terms of AUC_{0-t} and hence extent of absorption / exposure for Omeprazole under fasting conditions.

Data from this study demonstrated that the test and the reference products were well tolerated. Two (02) adverse events (AEs) were reported by one (01) subject during the conduct of the study and were considered significant. Both adverse events were mild and causality was considered unlikely by the investigator. There were no deaths or serious adverse events during the conduct of the study. There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects in the study.

The results of this study demonstrate that the criteria used to assess comparative bioavailability between the test and reference formulations were fulfilled. The test to reference with corresponding 90% CI for the ratio of geometric least squares means of ln-transformed pharmacokinetic parameter AUC_{0-t} was within the acceptance range. Therefore, Test Product-T and Reference Product-R are comparable with respect to AUC_{0-t} for Omeprazole under fasting conditions. The Test Product-T (Omeprazole Oral Suspension) and Reference Product-R (LOSEC capsules) were equivalent in terms of AUC_{0-t} and hence extent of absorption / exposure for Omeprazole under fasting conditions.

As expected, for this comparison of an immediate release suspension with a delayed release capsule, the ratio of geometric least squares means of ln-transformed pharmacokinetic parameter C_{max} (secondary parameter) showed a faster absorption profile for the test product than the reference product. Omeprazole exhibited significant patient-to-patient variability with respect to absorption and it is notable that the C_{max} range for the test product was 161.957 to 1006.624 ng/ml and for the reference product it was 53.942 to 939.382 ng/ml i.e. similar range of individual values, including maximum plasma concentrations. Also the peak plasma concentration of Omeprazole after administration for Test product-T was achieved faster than the Reference product-R as shown by T_{max} and T_{lag}.

The Reference Product-R (Delayed-Release Capsules) is an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach and the enteric coating on the granules dissolves. Test Product-T is an immediate release suspension which was not enteric

coated. Though omeprazole is acid-labile, the extent of absorption of Omeprazole from the Test Product-T and Reference Product-R is comparable, confirming the effectiveness of the formulation.

Based on the study, Omeprazole Oral Suspension 2mg/ml has been shown to be equivalent in terms of extent of absorption / extent of availability of omeprazole to the reference product, Losec 10mg capsules. [redacted].

2.5.4.4 STUDY 375-15

SUPPORTIVE COMPARATIVE BIOAVAILABILITY STUDY OF AN INTERMEDIATE FORMULATION OF OMEPRAZOLE 4MG/ML ORAL SUSPENSION WITH THE REFERENCE PRODUCT, LOSEC 20MG CAPSULES

Study 375-15 was carried out using an intermediate formulation of Xeolas's Omeprazole 4 mg/ml Oral Suspension.

Title of Study:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, crossover oral comparative bioavailability study of omeprazole 4 mg/ml (i.e. 20 mg/ 5ml) oral suspension (original formulation) with that of Losec capsules 20 mg in healthy adult, human subjects under fasting conditions

Study Objectives:

To determine comparative bioavailability of the test product [Omeprazole 4 mg/mL (20 mg/5 mL) Oral Suspension (Original Formulation)] with that of the European sourced reference product (LOSEC capsules 20 mg) in healthy, adult, human subjects under fasting conditions. And to monitor the adverse events and to ensure the safety of the subjects.

Methodology / Dose and mode of administration/Criteria for evaluation / Statistical methods/ Comparative Bioavailability Evaluation

Refer to Study 376-15 (same methodology)