**Table** 2.5.4.16 | Number of Subjects (planned and analysed):

| | | |
|---|---|---|
| Planned for inclusion | | 28 |
| Dosed | Period-I | 28 |
| | Period-II | 28 |
| Analysed | | 28 |
| Considered for statistical analysis | | 28 |

**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 UK

Market: UK

## EFFICACY RESULTS (STUDY 375-15)

### Primary PK parameter

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

**Table** 2.5.4.17 | Pharmacokinetic Parameters

| Pharmacokinetic Parameter | Geometric Mean Ratio Test/Reference | 90% Confidence Intervals | CV%[1] |
|---|---|---|---|
| $AUC_{(0-t)}$ | 88.4 | 80.57 - 96.99 | 20.6 |

[1]Estimated from the Residual Mean Squares

**Table** 2.5.4.18 | Pharmacokinetic Data and Descriptive Statistics of Formulation Means for Omeprazole (n = 28) in Study 375-15

| Parameters (Units) | Mean ± SD (untransformed data) | |
|---|---|---|
| | Test Product-T | Reference Product-R |
| $T_{max}$ (h)* | 0.417 (0.333 - 1.000) | 2.000 (1.000 - 5.017) |
| $C_{max}$ (ng/mL) | 780.620 ± 483.6521 | 594.888 ± 459.2378 |
| $AUC_{0-t}$ (ng.h/mL) | 1754.720 ± 2382.0173 | 1910.189 ± 2413.7862 |
| $AUC_{0-\infty}$ (ng.h/mL) | 1771.316 ± 2396.8790 | 1931.103 ± 2437.7411 |
| $\lambda_z$ (1/h) | 0.700 ± 0.2736 | 0.764 ± 0.3471 |
| $t_{½}$ (h) | 1.295 ± 0.8882 | 1.328 ± 1.0927 |
| AUC_%Extrap_obs (%) | 1.676 ± 0.9909 | 1.621 ± 0.8763 |
| $T_{lag}$ (h)* | 0.000 (0.000 – 0.083) | 0.667 (0.333 – 1.667) |

*$T_{max}$ 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** 2.5.4.19 | Relative Bioavailability Results for Omeprazole (n = 28)

| Parameters | Geometric Least Squares Means | | | 90% Confidence Interval | Power (%) |
|---|---|---|---|---|---|
| | Test Product-T | Reference Product-R | Ratio (T/R)% | | |
| $lnAUC_{0-t}$ | 855.291 | 967.544 | 88.4 | 80.57 - 96.99 | 98.8 |
| $lnAUC_{0-\infty}$ | 869.915 | 983.528 | 88.4 | 80.71 - 96.93 | 98.9 |
| $lnC_{max}$ | 654.241 | 451.455 | 144.9 | 128.30 - 163.69 | 91.6 |

**SAFETY RESULTS (STUDY 375-15):**

**Adverse events**

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

**CONCLUSION FOR STUDY 375-15:**

Test Product-T (Omeprazole Oral Suspension 4mg/ml) and Reference Product-R (Losec 20mg 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 88.4%. The 90% confidence interval for the ratio of geometric least squares means was found to be 80.57 - 96.99%. 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.

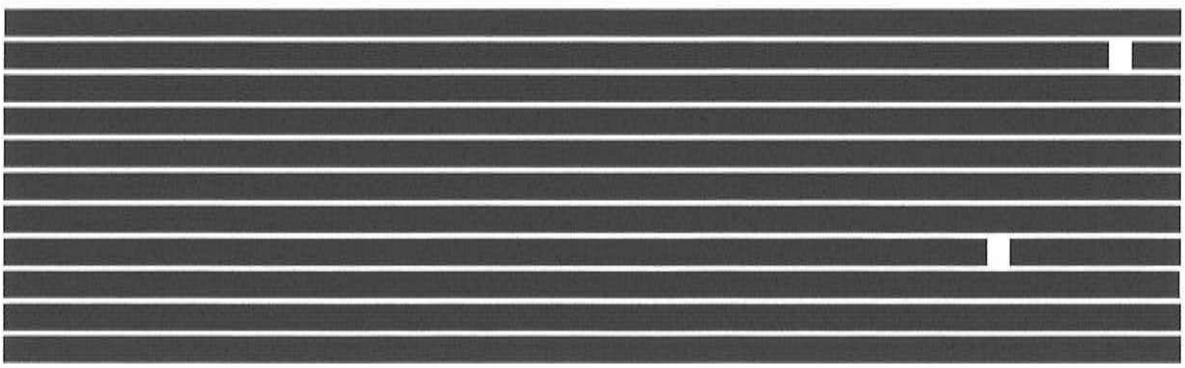
Data from this study demonstrated that the test and the reference products were well tolerated. There were no adverse events during the conduct of the study. There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects in the study.

The results of this study 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.

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. 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 the formulation employs a buffering system in lieu of an enteric coat to protect omeprazole from the acidic contents of the stomach. 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. 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.

Based on the study, Omeprazole Oral Suspension 4mg/ml ("original" formulation) has been shown to be equivalent in terms of extent of absorption / availability of omeprazole to the reference product, Losec 20mg capsules.



[redacted]

## 2.5.4.5 STUDY 0104-16

**SUPPORTIVE COMPARATIVE BIOAVAILABILITY STUDY OF XEOLAS'S OMEPRAZOLE 4mg/ml (i.e. 20 mg/ 5ml) ORAL SUSPENSION WITH THAT OF THE REFERENCE PRODUCT, LOSEC CAPSULES 20 mg ("Paediatric Clinical Formulation") AND OMEPRAZOLE 4mg/ml (i.e. 20 mg/ 5ml) ORAL SUSPENSION ADMINISTERED WITH MILK ("Fed Study") IN ADULTS.**

Study 0104-16 is a three-way pharmacokinetic study.
In the first arm, Omeprazole Oral Suspension (Test, T1) was compared to the reference product, *LOSEC Capsules,* [redacted]
In the second arm of the study, Omeprazole Oral Suspension (fasted) was compared to Omeprazole Oral Suspension taken with milk ("fed") i.e. a fasted/fed study relevant to the young paediatric population.

***Title of Study:***

An open label, balanced, randomized, three-treatment, three-period, three-sequence, crossover oral comparative bioavailability study of omeprazole 4 mg/ml (i.e. 20 mg/5 ml) oral suspension with that of LOSEC capsules 20 mg and omeprazole 4 mg/ml (i.e. 20 mg/5 ml) oral suspension administered with milk 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; (T1)] with that of the European sourced reference product (LOSEC capsules 20 mg) in healthy, adult, human subjects under fasting conditions.

To determine comparative bioavailability of the test product [Omeprazole 4 mg/mL (20 mg/5 mL) Oral Suspension (administered with 70 mL milk (infant formula milk), T2)] compared to fasting condition (T1) in healthy, adult, human subjects.

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

***Methodology:***

The study was an open label, balanced, randomized, three-treatment, three-period, three-sequence, single oral dose/suspension, crossover, comparative bioavailability study in healthy, adult, human subjects under fasting conditions, with a screening period of 28 days prior to the dosing in Period-I. In each study period, 25 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn subjects to analyze 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 three formulations (two tests and one reference formulation) was carried out using PROC MIXED of SAS® Version 9.3 (SAS Institute Inc., USA) to assess the bioavailability between two tests and one reference formulations.

**Table** 2.5.4.20 | Number of Subjects (planned and analysed)

| | | |
|---|---|---|
| Planned for inclusion | | 27 |
| Pre-dose discontinued / withdrawn subjects | | 00 |
| Dosed | Period-I | 27 |
| | Period-II | 25 |
| | Period-III | 25 |
| Post-dose withdrawn subjects | Period-I | 02 |
| | Period-II | 01 |
| | Period-III | 00 |
| Analysed | | 27 (In which, withdrawn Subject Nos. 1006, 1007 & 1027 were also analyzed as per protocol requirement) |
| Considered for statistical analysis | | 26 |

***Test and Reference product:***

**Test Product-T1** : **Omeprazole 4 mg/mL Oral Suspension**

Manufactured by: Xeolas Pharmaceuticals, Ireland.

**Test Product-T2** : **Omeprazole 4 mg/mL Oral Suspension**

Manufactured by: Xeolas Pharmaceuticals, Ireland.

**Reference Product-R** : **LOSEC capsules 20 mg**

Manufactured by: AstraZeneca

Marketing Authorization Holder: AstraZeneca UK Ltd.

Market: UK

***Dose and mode of administration:***

For Test Product-T1:

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 Test Product-T2:

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 70 mL of milk (infant formula milk) and 170 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. [redacted]

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

***Criteria for evaluation:***

***Efficacy:***

For efficacy evaluation, a total of 25 blood samples were collected in each period at the time points specified in the protocol. Standard non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.) 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), subjective symptomatology and monitoring of adverse events.

***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 computed 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.

**Criteria for conclusion of Comparative Bioavailability were as follows:**

Bioavailability of the Test Products-T1 with that of the Reference Product-R and two test products i.e., Test Products-T1 and Test Products-T2 is concluded as comparable, if the 90% confidence interval falls within the acceptance range as defined below for ln-transformed pharmacokinetic parameter for Omeprazole.

| Parameter | Acceptance Range of 90% CI |
|---|---|
| $AUC_{0-t}$ | 80.00 – 125.00% |

$C_{max}$ is examined as a secondary parameter, as only the extent of absorption is influencing the clinical efficacy of this product.

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

**Table** 2.5.4.21 | Relative Bioavailability Results for Study 0104-16

| T1 vs. R | | | | | | |
|---|---|---|---|---|---|---|
| Parameters | Geometric Least Squares Means | | | 90% Confidence Interval | Intra Subject CV (%) | Power (%) |
| | Test Product-T1 (n = 26) | Reference Product-R (n = 25) | Ratio (T1/R)% | | | |
| $lnC_{max}$ | 856.929 | 945.557 | 90.6 | 80.42 - 102.12 | 25.7 | 92.4 |
| $lnAUC_{0-t}$ | 1561.089 | 1615.989 | 96.6 | 85.37 - 109.31 | 26.6 | 90.9 |
| $lnAUC_{0-\infty}$ | 1585.689 | 1639.126 | 96.7 | 85.64 - 109.28 | 26.2 | 91.5 |
| **T2 vs. T1** | | | | | | |
| Parameters | Geometric Least Squares Means | | | 90% Confidence Interval | Intra Subject CV (%) | Power (%) |
| | Test Product-T1 (n = 26) | Test Product-T2 (n = 25) | Ratio (T2/T1)% | | | |
| $lnC_{max}$ | 856.929 | 675.355 | 78.8 | 69.93 - 88.82 | 25.7 | 92.4 |
| $lnAUC_{0-t}$ | 1561.089 | 1231.754 | 78.9 | 69.72 - 89.30 | 26.6 | 90.8 |
| $lnAUC_{0-\infty}$ | 1585.689 | 1255.138 | 79.2 | 70.06 - 89.43 | 26.2 | 91.5 |

**SAFETY RESULTS (STUDY 0104-16):**

**Adverse events**

Seven (07) adverse events (AEs) were reported by seven (07) subjects during the conduct of the study. Three (03) AEs were reported in Period-I, one (01) AE was reported in Period-II, one (01) AE was reported in Period-III and two (02) AEs were reported during post-study safety assessment.

Four (04) AEs were reported in subjects after administration of Test Product-T1, two (02) AEs were reported in subjects after administration of Test Product-T2 and one (01) AE was reported in one subject after administration of Reference Product-R.

All the AEs were mild in nature and the subjects were followed up until resolution of their AEs except Subject Nos. 1023 and 1024. Both these subjects did not report for their adverse event follow-up and hence were considered to be lost to follow-up.

The causality assessment was judged as possible for two (02) AEs and as unlikely for five (05) AEs.

There were no deaths or serious AEs reported during the conduct of the study.

**CONCLUSION FOR STUDY 0104-16:**

The results of this study demonstrate that the criteria used to assess bioavailability were fulfilled for Test Product-T1 (Omeprazole Oral Suspension 4mg/ml) vs. Reference Product-R [redacted] but not for Test Product-T1 vs. Test Product-T2 (Omeprazole Oral Suspension 4mg/ml administered with milk, simulating paediatric fed conditions).

The test to reference ratio of geometric least squares means with corresponding 90% CI for ln-transformed pharmacokinetic parameters $AUC_{0-t}$ was well within the acceptance range of 80.00-125.00% for the comparisons of Test Product-T1 vs. Reference Product-R. For the secondary ln-transformed pharmacokinetic parameter $C_{max}$, the test to reference ratio of geometric least squares means with corresponding 90% CI was also within the acceptance range of 80.00- 125.00% specified by CHMP for bioequivalence. [redacted]

It should be noted that the composition of Omeprazole Oral Suspension 4 mg / ml (T1) used in the current study (Study 0104-16) was the same as that of the Test Product-T evaluated in the pivotal pK study (Study 376-15) and represents the final formulation proposed for marketing.

**Comparison of the PK parameters between Omeprazole Oral Suspension (T1) and the reference paediatric clinical formulation (R)**

| Parameter | n | Point Estimate (T1/R)% | 90% CI |
|---|---|---|---|
| $AUC_{0-t}$ | 25 | 96.8 | 85.35 – 109.73 |
| $AUC_{0-\infty}$ | 25 | 96.9 | 85.61 – 109.69 |
| $C_{max}$ | 25 | 90.7 | 80.29 – 102.37 |

The effect of milk appears to reduce the extent of absorption by approximately 20%. Although this does not satisfy the protocol requirements, and the study results suggest administration under fasting condition, the small difference is not considered to be clinically significant. The milk arm results of Study 0104-16 can provide additional information relevant to prescribers in the paediatric setting.

## 2.5.4.6 CLINICAL STUDIES WITH OMEPRAZOLE IN THE PAEDIATRIC SETTING

In this section, clinical studies performed with omeprazole in the paediatric setting are reviewed. Table 2.5.4.27 summarises the relevant studies reviewed in this section. Particular emphasis in this review is given to studies that were not included in the PdAR (generally post 2007, marked*).

**Study 251**: Main Efficacy Trial in the Paediatric Setting 0 – 2 years
AstraZeneca's Study 251[Error! Bookmark not defined., 16, 30] was the main efficacy trial for omeprazole in the paediatric population and reviewed in the PdAR. In this study, efficacy was studied in a Phase 3 trial with 115 patients with clinically diagnosed GERD aged 0 to 2 years old, with 85% of the patients < 1 year and 59 % of the patients < 6 months.

**Title:** A Multicentre, Randomized, Single-Blind Study to Evaluate Omeprazole for the Treatment of Clinically Diagnosed GERD in Paediatric Patients Aged 0-24 months, inclusive.

**Study Objectives:**

**Primary:** To investigate whether once-daily treatment with omeprazole safely and effectively reduced the number of regurgitation episodes related to GERD in paediatric patients 0 months through 24 months, inclusive.

**Secondary:** To investigate whether once-daily treatment with omeprazole safely and effectively relieved the intensity of regurgitation/vomiting episodes and pain-related symptoms of GERD. Data was collected on daily diary cards in paediatric patients 0 months through 24 months (inclusive) and to evaluate the Physician's Global Assessment.

**Study Design:** Study 251 was a Phase 3, multicentre, randomized single-blind study.

**Treatment Procedure:** Patients were screened (Visit 1) within 2 days prior to dosing (Table 2.5.4.22). After informed consent, a complete physical examination including vital signs was performed, and a routine analysis of blood and urine was performed. Also at Visit 1, the investigator completed a Physician's Global Assessment on the overall impression of the patient's GERD symptoms. Patients who met the inclusion and exclusion criteria were dosed with 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg of omeprazole depending on the randomization schedule. Patients were dosed once daily for approximately 56 days. Patients returned to the site approximately every 14 days for the next 56 days for a total of 5 visits.

**Table** 2.5.4.22 | Study 251 Study Flow Chart

| Visit/Study Day | Visit 1 Day-2 -0 | Visit 2 Day 14±2 | Visit 3 Day 28±2 | Visit 4 Day 42 ±2 | Visit 5 Day 56 ±2 |
|---|---|---|---|---|---|
| Informed Consent | X | | | | |
| Medical History | X | | | | |
| Physical Exam | X | X | X | X | X |
| Vital signs | X | X | X | X | X |
| Laboratory Evaluation | X | | | | X |
| Inclusion/Exclusion Criteria | X | | | | |
| Physician Global Assessment | X | | | | X |
| Dispense Study Medication | X | X | X | X | |
| Review Dosing Instructions | X | X | X | X | |
| Return Study Medication | | X | X | X | X |
| Distribute Symptom Diary | X | X | X | X | |
| Recall previous 72 hr symptoms | X | | | | |
| Collect/ Review Symptom Diary | | X | X | X | X |
| AE Reports | | X | X | X | X |
| Prior/Concomitant Medications | X | X | X | X | X |

**Investigational Product and Dosing:** The administered investigational product was an omeprazole 2mg/ml bicarbonate suspension. *Prilosec®/Losec®/Antra® 20 mg capsules* [redacted] The amount of oral suspension dispensed was determined by the patient's weight. The administered dose was 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg on a randomised basis. Patients were dosed orally once daily for approximately 56 days. Omeprazole Oral Suspension was administered via oral syringe or, in some instances, via nasogastric or percutaneous gastrostomy tube.

**Efficacy Assessment:** The assessment used the data recorded in the patient' s diary card and on the Physician' s Global Assessment.

*Physician's Global Assessment:* A global assessment of overall symptoms was completed by the investigator at the baseline (Visit 1) and Visit 5 or the final visit and recorded on the CRF. A secondary evaluation of the proportion of patients with successful treatment was defined by an assessment of none or mild symptoms at the end of the study.

**Primary Efficacy Endpoint:**

- The average number of vomiting/regurgitation episodes per day per patient in the last 72 hours of treatment.

**Secondary Efficacy Endpoints:**

- Proportion of patients who had no moderate or severe regurgitation/vomiting symptoms during the last 72 hours.
- Proportion of patients who had no moderate or severe pain-related symptoms during the last 72 hours.
- Proportion of patients who were successfully treated, where successful treatment is defined as no moderate or severe overall evaluation, as defined by the Physician's Global Assessment.

**Study Population:**

**Inclusion criteria:** Patients (i) had to be male or female 0 months through 24 months of age, inclusive; (ii) must have had at least a 2-month history of GERD-related symptoms; (iii) in the judgment of the investigator, were considered for treatment with an acid inhibition agent based on symptoms of GERD; (iv) must have had clinically normal laboratory results and physical exam findings at screening; and, (v) parent/guardian must have provided written informed consent.

**Statistical population:** There were 2 populations for purposes of the efficacy analysis: intent-to-treat (ITT) population (100 subjects) and per-protocol (PP) population (96 subjects). The ITT population consisted of all patients taking at least 1 dose of omeprazole and having at least one day of diary data. The PP population consisted of a subset of the ITT population.

**Results:**

**Efficacy Findings:**

**Primary efficacy findings: changes from baseline in average number of vomiting/regurgitation episodes per day in the last 72 hours of treatment.**

Patients had approximately -4.35 (95% CI: -8.2, -0.46), -2.97 (95% CI: -7.0, 1.06) and -4.34 (95% CI: -8.5, -0.15) decrease in vomiting/regurgitation episodes per day during the last 72 hours in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, respectively. All treatment groups had approximately 50% reduction in the number of vomiting/regurgitation episodes. While no significant differences were detected between any of the pairwise comparisons in the treatment groups, the high and low dose demonstrated a significant decrease from baseline. No difference was seen between the analyses with the PP population compared to the ITT population. Table 2.5.4.23 summarizes the adjusted mean (LSMEAN) change from baseline at Visit 1 on the average number of vomiting/regurgitation episodes per day during the last 72 hours for each treatment group in the ITT population (100 subjects).

**Table** 2.5.4.23 | Analysis of Covariance Change from Baseline (Visit 1) on the Average Number of Vomiting/Regurgitation Episodes Per Day During the Last 72 Hours ITT Population

| Omeprazole Dose | N | LSM | LSM Standard Error | 95% CI for LSM |
|---|---|---|---|---|
| 1.5 mg/kg | 33 | -4.35 | 1.99 | (-8.2, -0.46) |
| 1.0 mg/kg | 33 | -2.97 | 2.05 | (-7.0, 1.06) |
| 0.5 mg/kg | 34 | -4.34 | 2.14 | (-8.5, -0.15) |

LSM = Least Square Means

*Graphical Analysis:* The average number of vomiting/regurgitation episodes per day is presented in Figure 2.5.4.1. Week 0 represents baseline symptoms at Visit 1. By Week 1, the higher doses (1.0mg/kg and 1.5 mg/kg) showed effect in decreasing the number of vomiting/regurgitation episodes, while the low dose (0.5 mg/kg) did not show effect until Week 3. For all treatment groups, the number of vomiting/regurgitation episodes continues to decrease considerably until Week 3 and then begins to plateau for both 1.0 mg/kg and 1.5 mg/kg treatment groups at Week 4.

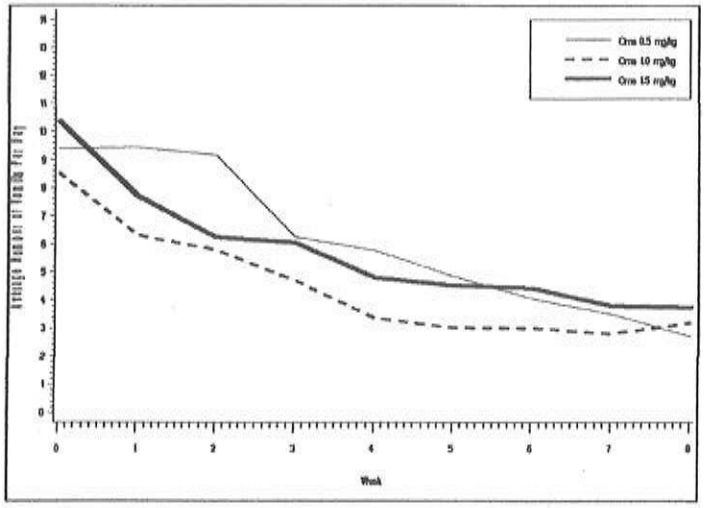


**Figure** 2.5.4.1 | Average Number of Vomiting/Regurgitation Episodes by Week During the Last 72 Hours of Each Week ITT Population

An additional analysis using the adjusted mean (LSMEAN) change from baseline at Visit 1 on the average number of vomiting/regurgitation episodes per day per patient during the last 72 hours for each treatment group was conducted. Three patients from the ITT population were excluded from the analysis (extreme outliers). After adjustment, patients had approximately -5.23 (95% CI: -7.6, -2.9), -3.97 (95% CI: -6.4, -1.5) and -2.89 (95% CI: -5.4,- 0.34) decrease in vomiting/regurgitation episodes per day per patient during the last 72 hours in 1.5 mg/kg, 1.0 mg/kg and·0.5 mg/kg treatment groups, respectively. These adjusted results indicate that the number of vomiting/regurgitation episodes per patient decreases with each increased dose group of omeprazole.

**Secondary efficacy findings: changes from baseline in patients with no moderate or severe symptoms on the following secondary efficacy endpoints:**

- Severity of overall vomiting/regurgitation of GERD
- Severity of overall pain-related symptoms of GERD
- Physician's Global Assessment

For the severity of overall vomiting/regurgitation episodes in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, the observed rates of patients with no moderate or severe symptoms during the last 72 hours of treatment were 69.7%, 69.7% and 70.6%, respectively. No statistical differences were detected between treatment groups.

For severity of overall pain-related symptoms of GERD, the observed rates of patients with no moderate or severe symptoms during the last 72 hours of treatment were 75.8%, 66.7% and 73.5%, respectively. No statistical differences were detected between treatment groups. For the Physician's Global Assessment, the observed rates of patients with no moderate or severe symptoms during the last 72 hours of treatment were 93.3%, 93.3% and 96.4%, respectively. No statistical differences were detected between treatment groups.

A similar analysis performed with patients having only moderate or severe pain-related symptoms of GERD at baseline showed similar results (Table 2.5.4.24). No statistical differences were detected between treatment groups.

**Table** 2.5.4.24 | Categorical Analysis on Secondary Endpoints ITT Population for Study 251

| Endpoint | Dose mg/kg | n | Success* | | Failure* | | Overall Mantel-Haenszel Chi-square (p-value) | Overall Estimated Odds Ratio | Overall 95% CI of Odds Ratio |
|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | % | | | |
| Severity of Overall Vomiting/Regurgitation of GERD | 1.5 | 33 | 23 | 69.7 | 10 | 30.3 | 0.94 | 1.01 | (0.78, 1.31) |
| | 1.0 | 33 | 23 | 69.7 | 10 | 30.3 | | | |
| | 0.5 | 34 | 24 | 70.6 | 10 | 29.4 | | | |
| Severity of Overall Pain-related symptoms of GERD | 1.5 | 33 | 25 | 75.8 | 8 | 24.2 | 0.85 | 0.97 | 0.75, 1.27) |
| | 1.0 | 33 | 22 | 66.7 | 11 | 33.3 | | | |
| | 0.5 | 34 | 25 | 73.5 | 9 | 26.5 | | | |
| Physician's Global Assessment | 1.5 | 30 | 28 | 93.3 | 2 | 6.7 | 0.62 | 1.16 | (0.65, 2.04) |
| | 1.0 | 30 | 28 | 93.3 | 2 | 6.7 | | | |
| | 0.5 | 28 | 27 | 96.4 | 1 | 3.6 | | | |

* Success = None or mild symptoms only during last 72 hours of treatment, Failure = Moderate or severe symptoms

The average number of vomiting/regurgitation episodes at baseline (Visit 1) and Final Visit in the Intention-To-Treat population (100 subjects) was established. The number of vomiting/regurgitation episodes decreased from baseline for all treatment groups. For 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg, respectively, patients had on average 9.9 (34/34), 8.6 (33/33) and 10.5 (33/33) vomiting/regurgitation episodes at baseline with a decrease in vomiting/regurgitation episodes of -5.5, -3.7 and -5.5 per day during the last 72 hours of treatment.

A sensitivity analysis excluded three patients with extreme values. Results showed a trend in which the number of vomiting/regurgitation episodes decreased with each increased dose of omeprazole. For 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg, respectively, the patients had on average 8.6 (33/34), 8.7 (32/33) and 10.3 (32/33) vomiting/regurgitation episodes at baseline with a decrease in vomiting/regurgitation episodes of -4.7, -5.3 and -6.6 per day during the last 72 hours of treatment.

For all treatment groups, the average intensity of pain-related symptoms decreased. Symptoms prior to treatment were approximately moderate and reduced to less than mild. Similar results occurred in the average intensity of vomiting/regurgitation episodes.

Only 30.0% (30 of 100) of ITT patients had pain after eating, with 69.6% (80 of 115) of randomized patients having pain after eating at baseline. Similar results were found in pain during the night.

The Physician's Global Assessment indicates that omeprazole improved overall GERD-related symptoms. Most patients improved (90%), a few patients remained the same (9%) and 1 got worse (1%).

**Actual Patient Population and Doses**

The ages of the patients treated ranged from 0.7 to 21.8 months. 85 % of the patients were < 12 months; 59 % of the patients were less than 6 months. The average actual dose of omeprazole suspension administered was 4.0 mg, 7.3mg and 9.7mg, respectively, for the 0.5mg/kg, 1.0mg/kg and 1.5mg/kg treatment groups. The treatment group 0.5 mg / Kg consisted of 37 patients with mean age 7.0 months, treatment group 1.0 mg / kg consisted of

38 patients with mean age 6.2 months and treatment group 1.5 mg / kg consisted of 40 patients with mean age 5.8 months.

**Overall Conclusion for Study 251:**

Omeprazole, administered as a bicarbonate suspension exhibited efficacy across all treatment groups. Omeprazole Oral Suspension effectively reduced the number of vomiting / regurgitation episodes by approximately 50% and the intensity of vomiting/regurgitation episodes as well as the intensity of pain-related GERD symptoms. There was no statistical difference detected among the treatment groups. Patients demonstrated -4.35 (95% CI: -8.2, -0.46), -2.97 (95% CI: -7.0, 1.06) and -4.34 (95% CI: -8.5, -0.15) decrease in vomiting/regurgitation episodes per day during the last 72 hours in 1.5 mg/kg, 1.0 mg/kg and 0.5 mg/kg treatment groups, respectively. Results with a sensitivity and graphical analysis suggested greater efficacy with larger doses. All 3 dosages of omeprazole were safely administered and well tolerated in this paediatric population. There was no apparent dose relationship to the occurrence of adverse events.

**Other Clinical Studies of Omeprazole in the Paediatric Setting**

In addition to studies BA 04/07 and 251, other studies conducted in children are reviewed. In general, there is considerable heterogeneity in terms of study design, omeprazole formulation, dose, setting etc. Indeed, such heterogeneity is a common problem in studies involving children, taking into account the practical, logistical and other issues involved, including lack of suitable formulations to administer the required doses.

***Study 292***[Error! Bookmark not defined., 16] was a multicentre, retrospective, multiple dose study whose purpose was to determine the esophageal and/or gastric pH profile after multiple doses of omeprazole in neonates and infants.

*Patients and Methods*: Patients were aged 0 to 24 months at the time of first pH assessment. The age of the children (n = 43) ranged from 1.1 to 23.6 months with a mean age of 6.2 months. The mean dose was 1.8 mg/kg/day and the formulation used was mainly EC granules dispersed/suspended in 8.4% sodium bicarbonate. The mean time between first and second pH assessment was 8.2 weeks. The average treatment duration was 45 days.

*Conclusion:* the conclusion from the study was that omeprazole was effective in raising intra-esophageal pH and treating acid reflux in this population.

***Bishop et al***[31] aimed to prospectively determine the dosage of omeprazole required to treat symptomatic gastroesophageal reflux in children younger than 2 years.

*Patients and Methods*: Children under 2 years with clinically suspected GERD underwent 24-hour dual-channel intraesophageal/gastric pH monitoring. A reflux index above 10% in children under 1 year and above 6% in children older than 1 year was deemed significant. Treatment with omeprazole at an initial dosage of 0.7 mg/kg/day (in 2 divided doses) was followed by dual-channel pH study after 14 days. The dosage was increased in increments of 0.7 mg/kg/day, and pH studies were repeated until the gastroesophageal reflux was controlled. A twice-daily regimen was followed. A formulation of omeprazole dissolved in 8.4% bicarbonate at a concentration of 2 mg/mL was used.

*Results:* Ten children (5 boys, 5 girls) younger than 2 years (median 7.75 months, range 1.25–20 months) were treated for GERD and underwent dual-channel pH probe monitoring. The median weight was 7.4 kg (range 3.0–10.9 kg).

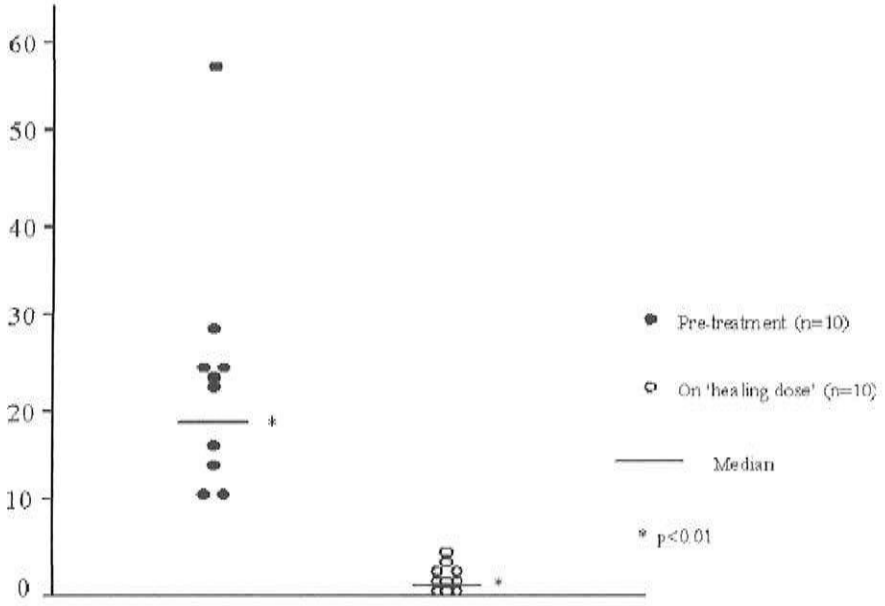



**Figure** 2.5.4.2 | Esophageal pH (% time pH < 4) before and during treatment with esophageal pH-controlling dosages of omeprazole [31].

All of the patients had improvement of the GERD while receiving omeprazole treatment, as assessed by the follow-up pH studies. Five children responded to the initial dosage of 0.7 mg/kg/day, four had 1 dose increment, and one patient had 3 dose increments to achieve adequate resolution of symptoms and a satisfactory pH response.

The median dosage required was 1.05 mg/kg/day. Four children required 1.4 mg mg/kg/day, and 1 required 2.8 mg mg/kg/day. There were no serious complications or side effects.

*Conclusions*: The authors concluded that Omeprazole should be considered an effective treatment in children under 2 years old, in whom long-term use is not generally forecast, using the dosage of 1–2 mg/kg/day.

***Kaufman*** et al[32] investigated the use of omeprazole to prevent stress-related gastric bleeding in a critically ill, at-risk group of paediatric patients undergoing liver or intestinal transplantation, or both.

*Patients and Methods*: Twenty-two patients ranging in age from 0.9 to 108 months (23.8 ± 6.5) underwent isolated liver (n=10) or intestinal (11 with composite liver allografts) transplantation. Omeprazole was delivered in 8.4 % sodium bicarbonate suspension (2mg/ml) through a nasogastric tube. Therapy was started after surgery at 0.5 mg/kg every 12 hours. Gastric pH monitoring was performed approximately 2 days later.

*Results:* For the entire group, near-neutral gastric pH was maintained, mean gastric pH equalled 6.1 ± 0.3. No patient experienced bleeding attributable to gastric erosion.

*Conclusions*: The authors concluded that Omeprazole suspended in sodium bicarbonate was an effective acid-suppressing agent in paediatric recipients of liver or intestinal transplant, or both. A dosage of 0.5 mg/kg every 12 hours (1mg/kg/day) was sufficient for most patients, but dosing every 6 to 8 hours (~1.5mg/kg/day) might be required to assure maximal acid

suppression in all. The authors also remarked that they now use omeprazole almost exclusively in paediatric patients after transplantation.

***Moore** et al*[33] assessed the efficacy of omeprazole in treating irritable infants with gastroesophageal reflux and/or esophagitis.

*Patients and Methods*: Irritable infants (n = 30) 3 to 12 months of age met the entry criteria of esophageal acid exposure >5% (n = 22) and/or abnormal esophageal histology (n = 15). They completed a 4-week, randomized, double-blind, placebo- controlled crossover trial of omeprazole. Cry/fuss diary (minutes/24 hours) and a visual analogue scale of infant irritability as judged by parental impression were obtained at baseline and the end of each 2-week treatment period. Omeprazole EC capsules were used (infants from 5 to 10 kg were given 10 mg daily and >10 kg were given 10 mg twice daily) for 2 weeks and an identical appearing placebo for 2 weeks (periods 1 and 2). The omeprazole and placebo were presented in a capsule as microspheres. The contents of each capsule was emptied into a teaspoon of applesauce and administered to the infant.

*Results:* The reflux index fell significantly during omeprazole treatment compared with placebo (- 8.9% ± 5.6%, -1.9% ± 2.0%, P < .001). Cry/fuss time decreased from baseline (267 ± 119), regardless of treatment sequence (period 1, 203 ± 99, P < .04; period 2, 188 ± 121, P < .008). Visual analogue score decreased from baseline to period 2 (6.8 ± 1.6, 4.8 ± 2.9, P = .008). There was no significant difference for both outcome measures while taking either omeprazole or placebo.

*Conclusions*: Compared with placebo, omeprazole significantly reduced esophageal acid exposure but not irritability. No adverse events were recorded.

The ***Hassall*** et al[34] study (also referred to as I-678) was a multicentre, open, uncontrolled, study which enrolled 65 patients. The study was divided into two phases; a dose finding and healing phase and a maintenance phase. The dose finding and healing phase was designed to assess the dose of omeprazole required to achieve verified healing of erosive reflux esophagitis in children of different ages. When healed, the children were allowed to enter the maintenance phase and remain on long-term maintenance treatment with omeprazole in order to assess safety and tolerability of omeprazole during long-term treatment.

*Patients and methods*: The age of inclusion was 1 to 16 years. The children were required to have endoscopically verified esophagitis. Many of the children in this study were seriously ill patients with other conditions.

The dose-finding started with a daily dose of 0.7 mg/kg body weight. If the dose was not effective, it was increased at each visit by increments of 0.7 mg/kg.

The therapeutic goal was intraesophageal pH < 4.0 for not more than 6% of 24 hours.

65 patients were included in the study and all are included in the report (healing phase). The effective dose was then used for healing. When a suitable dose had been found the child was treated for 3 months. The total time required for the dose-finding and the healing phase was 83-421 days.

*Results*: Sixty-five patients entered the dose-finding part but 8 of them discontinued during that period, thus 57 patients started the healing treatment. Of the 57 patients that entered the healing part, 29 children had GERD symptoms without any other disease as the cause of their

symptoms, 21 children with cerebral palsy or another neurologic condition and there were 7 with esophageal atresia.

Healing phase: data from 65 children were available for an All Patients Treated analysis.

Maintenance phase: 46 of the 54 patients that were healed entered the maintenance phase.

Patients were observed in the maintenance phase for 137-749 days.

After the first healing period 51 patients were healed (which lasted between 10 and 325 days, depending on the accessibility of children for endoscopy) and 6 required further treatment. Three of these children left the study at this point and the remaining 3 were healed after a second treatment period which lasted between 100 and 187 days. Healing was defined as esophagitis grade 0 or 1. During the study a reduction in various reflux symptoms was reported.

Nineteen (41%) of the 46 patients, that entered the maintenance phase, had no relapse during the maintenance phase. Among the patients who relapsed, 15 had their first relapse before the 3 months visit. Ten (22%) of the 46 patients had more than one relapse.

Thirty-two patients completed the study i.e. had data from the 21 month visit. Of these patients, 26 (81%) were healed at the last visit, three had no final endoscopy and three were unhealed.

At the last clinic visit in the maintenance phase, 63 % were assessed as having no overall symptoms and 24 % had only mild symptoms. One patient had severe heartburn/epigastric pain and one had severe dysphagia/odynophagia. The percentage of patients that experienced regurgitation/vomiting was reduced from 70% at baseline to 20%. No adverse events were attributed to omeprazole, and no patient discontinued the drug because of an adverse event.

*Conclusions and comments:* This was an open study but the data is supported by the fact that the patients included had an endoscopically verified esophagitis and intra-esophageal pH was measured. The results showed highly clinically relevant efficacy of omeprazole.

***Omari*** et al [35] was a randomized, double blind, placebo-controlled, crossover trial of omeprazole therapy in infants. Patients were given omeprazole for 7 days and then placebo for 7 days in randomized order. Twenty-four-hour esophageal and gastric pH monitoring was performed on days 7 and 14 of the trial.

*Patients and Methods*: Ten infants with symptoms suggestive of GERD who had not responded to conservative therapy (feed thickeners, postural changes, antacids) and who had undergone 24-h pH monitoring, which confirmed significant esophageal acid exposure were enrolled in the study. The mean postnatal age was 50 ± 9d and the mean weight was 2.2kg ± 0.11 kg. The dose of omeprazole buffered suspension was 0.7mg/kg omeprazole administered via a nasogastric tube.

*Results:* Omeprazole therapy (0.7mg/kg/day) significantly reduced gastric acidity, esophageal acid exposure and the number and duration of acid reflux episodes compared to placebo (Table 2.5.4.25). Before randomization, the infants had clinical symptoms suggestive of GERD and an esophageal acid reflux index of >5% on 24-h esophageal pH monitoring. Omeprazole given once daily is effective in reducing the frequency of acid reflux episodes and the overall degree of esophageal acid exposure. In most infants, omeprazole therapy reduced esophageal acid exposure to below normal levels.

**Table** 2.5.4.25 | Effect of omeprazole 0.7 mg/kg on acid GER and gastric acidity

| | Placebo week | Omeprazole week |
|---|---|---|
| Esophageal pH | | |
| No. acid GER | 119.4 ± 20.9 | 59.6± 26.7* |
| Longest acid GER, min | 48.6 ± 10.1 | 16.3 ± 8.0** |
| % time pH <4 | 19.0± 4.5 | 4.9± 3.4** |
| *Gastric pH* | | |
| % time pH <4 | 53.8 ± 6.8 | 13.9 ± 5.1*** |

*Data presented as mean ± SEM or median (interquartile range). Paired t test: *P < 0.05, **P < 0.01, ***P < 0.0005.*

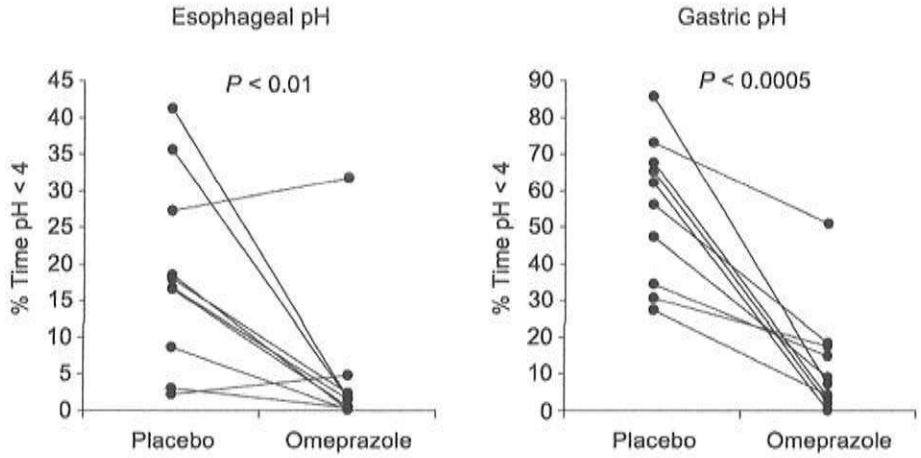



**Figure** 2.5.4.3 | Percentage time esophageal and gastric pH <4 during placebo and omeprazole weeks. Individual patient data shown[38].

Omeprazole therapy was not associated with the occurrence of any serious adverse events.

**Alliet** et al[36] evaluated the use of omeprazole in infants with $H_2$ antagonist resistant GERD. Twelve neurologically normal infants (age 2.9 ± 0.9 months) with GERD who did not respond to cimetidine were treated with omeprazole, 0.5 mg/kg once a day, for 6 weeks. The effectiveness of omeprazole was evaluated in all infants by clinical assessment and endoscopy before and after treatment and by 24-hour gastric pH monitoring during treatment in seven infants.

*Methods:* Twelve neurologically normal infants (age 2.9 ± 0.9 months) with endoscopically confirmed GERD not responding to cimetidine were treated with omeprazole, (0.5 mg/kg), once a day for 6 weeks. The parents were asked to open the capsules to administer the granular content mixed with milk or water with a spoon. The effectiveness of omeprazole was evaluated by clinical assessment (n = 12), endoscopy before and after treatment (n = 12), and 24-hour intragastric pH monitoring during treatment (n = 7).
*Results:* Omeprazole therapy led to a marked decrease in symptoms, endoscopic and histologic signs of esophagitis, and intragastric acidity.

***Karami*** et al[37] studied the efficacy of omeprazole enteric coated granules and Omeprazole Oral Suspension in a randomised, parallel study in 34 paediatric patients. The oral suspension was an extemporaneous product manufactured using omeprazole active substance (powder) in 8.4% sodium bicarbonate solution at a concentration of 2mg/ml. The dose was 1 mg/kg/day. In the oral suspension group, the patient age ranged from 35 days to 3 years (mean age 7.3 months). The omeprazole oral suspension was effective in the treatment of all patients (100%), though 4 patients experienced vomiting. The study also compared the pharmacokinetics of the two formulations using plasma levels of omeprazole after 3 days of treatment ($C_1$) and 2 hours after the last dose ($C_2$). No significant difference was observed between the two dosage forms. However, the very limited blood sampling applied – presumably on ethical grounds considering the patient population – limits the usefulness of the study, bearing in mind the lack of a relationship between plasma level and efficacy of the molecule. Overall, the authors concluded that the suspension form of omeprazole - because of ease of administration, and versatility and precision in dosage adjustment - was the superior dosage form for paediatric patients.

***Solana*** *et al*[38] compared the effect of 2 doses of intravenous omeprazole on gastric pH, gastrointestinal bleeding, and adverse effects in critically ill children.

*Patients and methods:* A prospective randomized clinical trial in paediatric patients at risk of gastrointestinal bleeding. The effect of 2 intravenous omeprazole regimens (0.5 or 1 mg/kg every 12 hours) on the gastric pH and incidence of gastrointestinal haemorrhage in critically ill children was compared. The efficacy criteria were a gastric pH >4 and the absence of clinically significant gastrointestinal bleeding.

*Results*: Forty patients between 1 month and 7 years of age (median 7 months, IQR 4-30 months, 20 in each treatment group, were studied. The average age of the patients was 7 months. Overall, the gastric pH was > 4 for 57.8% of the time, with no significant difference between the doses (P = 0.66). The percentage of time with a gastric pH > 4 increased during the study (47.8% between 0 and 24 hours vs 76% between 24 and 48 hours, p =0 .001); the higher dose showed a greater increase in the percentage of time with a pH > 4: between hours 24 and 48 of the study, the gastric pH was greater than 4 for 84.5% of the time with the 1 mg/kg dose and for 65.5% of the time with the 0.5 mg/kg dose (P = .036). Plasma omeprazole levels were greater with the 1 mg/kg dose, but no correlation was found between omeprazole plasma levels and gastric pH. No adverse effects were reported, and there was no clinically significant bleeding.

*Conclusions* Adequate increase in gastric pH for both omeprazole regimens required more than 24 hours treatment. Between 24 and 48 hours, the 1 mg/kg dose maintained the gastric pH greater than 4 for a greater percentage of the time. Similar to adults, omeprazole in children requires repeated administration to reach a therapeutic plateau. There was a dose-response relationship similar to that observed in adults. Finally, as with adults, there was no correlation between omeprazole plasma levels and gastric pH – most likely because inhibition of acid secretion is correlated with AUC. Finally, the authors were able to use the PK data to develop a population pharmacokinetic model for intravenous omeprazole in critically ill children and this population pharmacokinetic model is discussed in Section 2.5.2.1.

The ***Faure***[17] study was designed to determine both the pharmacokinetics and the optimal dosage of intravenous omeprazole in patients younger than 30 months of age.
*Patients and methods*: Nine children (three girls), aged 4.5 to 27 months, with normal liver and renal function 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 20 mg/1.73 $m^2$, and group 2, consisting of the following five patients, received 40 mg/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 > 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 · kg-1 · h-1 (P = 0.22).

*Conclusions:* Intravenous administration of omeprazole was effective in infants. The results indicated that the dose of 20 mg/1.73 $m^2$ (~ 0.5mg/kg) was not effective in maintaining 24-hour gastric pH > 4 and that a dose of 40 mg/1.73 m2 (~1.1mg/kg) was required. The AUC of omeprazole was significantly correlated with the percentage of time with pH > 4 during 24 hours. Systemic clearance was 0.68 and 0.42 L/kg/h at the 20 and 40 mg regimens, respectively and was not significantly different between the groups. There was no presentation of exposure vs. age but no clear trend was visible looking at the table of results.

There is limited data on the use of omeprazole in neonates. However, **Kaguelidou** *et al*[39] reported a dose-finding study of omeprazole in neonates with GERD using a Bayesian sequential approach. The study included 54 neonates with a pathologic 24-hour intraesophageal pH monitoring defined as a reflux index > 5.0

**Table** 2.5.4.26 | **Efficacy parameters at baseline and 72 (± 12 hours) after omeprazole initiation**

| | Variable | 72 (± 12 hours) after omeprazole initiation | p-value |
|---|---|---|---|
| **Intraesophageal pH monitoring** | Reflux Index (%) | 0.2 (0-1.5) | <0.0001 |
| | Time with pH < 4 (min) | 2 (0-20) | <0.0001 |
| | Mean number of reflux episodes per hour | 0.3 (0.1-1) | 0.0002 |
| | Duration of the longest reflux episode (min) | 2 (0.2-11) | 0.0009 |

*Results and conclusions:* Omeprazole treatment was effective in this population with a significant improvement observed in all parameters of the esophageal pH monitoring, from baseline to 72 ± 12 hours after omeprazole initiation. The efficacy parameters are reported in Table 2.5.4.26.

With respect to effective dose, there was a difference according to gestational age. Premature infants of less than 32 weeks required a dose of 2.5 mg/kg/day whereas less premature and term infants required 1 mg/kg/day. Omeprazole was well tolerated clinically and no adverse events were attributed to Omeprazole treatment. There were two other notable aspects of the trial: 1) Study planning was initiated in 2004, the trial was registered in Eudract in 2006 and results reported in 2016 i.e. the trial took more than 10 years to complete due to recruitment. Also, of the planned 90 neonates, only 54 were recruited to the trial. This timeline and the low/slow recruitment highlights the difficulties in conducting efficacy trials in the paediatric population; and 2) To administer the low doses required on a mg/kg basis using the available registered formulation (*Mopral 10mg capsules*, *AstraZeneca*), the following protocol was used:

10mg capsules were opened, pellets were weighed using a microbalance (0.1mg) to titrate according to the mg dose, the weighed pellets were placed into individualised blank capsules for transfer to study personnel, individualised capsules were opened by study personnel and the pellets were mixed with formula milk for administration to the infants. Clearly this type of protocol is only possible within a clinical study by trained personnel and is not feasible in routine practice.

*Comments and summary regarding clinical studies in the 0-2 years paediatric setting*

Conducting efficacy studies for a molecule like omeprazole in the paediatric setting presents significant ethical, clinical and logistical challenges to the performance of clinical studies (i.e. ethical problems with using placebo in a vulnerable patient group, understandable parental resistance to research protocols and invasive procedures, unpredictability of access, accurate collection of symptom-based clinical data in pre-verbal children, wide availability of study medication through manipulation or extemporaneous compounding on an off-label/unlicensed basis etc.).

## DISCUSSION ON EARLIER CMAX WITH HIGHER AMPLITUDES FOR OMEPRAZOLE ORAL SUSPENSION WITH RESPECT TO PHARMACODYNAMIC AND CLINICAL EFFECTS ON SELECTED POPULATIONS

The treatment of GERD with omeprazole is the indication common to all age groups. 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 children 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 children and adults, is defined as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the gastroesophageal junction[10].

Acid-mediated GERD or erosive esophagitis has the same disease definition and has a similar endoscopic presentation in infants, older children and adults. In all age groups, the treatment is targeted to normalise esophageal pH by increasing intragastric pH and heal acid-induced injury. For all clinical indications of omeprazole, the intended clinical effect is to increase intragastric pH.

With reference to pharmacodynamics/clinical efficacy and the pharmacokinetic parameters AUC and $C_{max}$, the SmPC for the reference *Losec* product[5] is unequivocal:

*"For omeprazole, **all pharmacodynamic effects** observed can be explained by the **effect of omeprazole on acid secretion**"* and
*"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".*

Taking the different patient groups for whom the proposed Omeprazole Oral Suspension product is indicated:

a) Paediatric patients aged 1 month to 1 year

In the pivotal efficacy and pharmacokinetic/pharmacodynamics studies (Studies 251 and 250 respectively) conducted in children 0-2 years, the patients were dosed with a suspension of omeprazole, achieved by suspending the granules of *Prilosec/Losec capsules*, in 8.4% sodium bicarbonate "the paediatric clinical formulation" for ease of administration and dose titration.

[redacted]

**Study 250** was a pharmacokinetic and pharmacodynamic study in infants aged 0-2. The oral suspension was rapidly absorbed, and omeprazole had a $t_{max}$ < 1hr. The fraction of time gastric pH was <4.0 decreased on average from 64% to 42%, and from 58% to 46%, for the 1.0 mg/kg and 1.5 mg/kg treatment groups, respectively, during a 12-hour period after a single dose. Statistical significance was observed for the 1.0 mg/kg treatment group ($p \leq 0.02$). Conclusion: A single dose of omeprazole, 1.0 mg/kg or 1.5 mg/kg, significantly decreases the fraction of time with gastric pH less than 4, indicative of the drug's pharmacodynamic effect in children < 2 years.

**Study 251** was the main efficacy trial for omeprazole in the paediatric population and reviewed in the PdAR. In this study, efficacy was studied in a Phase 3 trial with 115 patients with clinically diagnosed GERD aged 0 to 2 years old.
The overall conclusion for Study 251 was that Omeprazole suspension exhibited efficacy across all treatment groups. Omeprazole suspension effectively reduced the number of vomiting / regurgitation episodes by approximately 50% and the intensity of vomiting/regurgitation episodes as well as the intensity of pain-related GERD symptoms.
The results from this study are summarised in the SmPC for the reference product in Section 5.1: "In a single-blind study, children aged 0–24 months with clinically diagnosed gastro-esophageal reflux disease were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment irrespective of the dose.

The applicant submitted 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 addition to the above studies, a number of other workers have used the same "paediatric clinical formulation" of the reference product

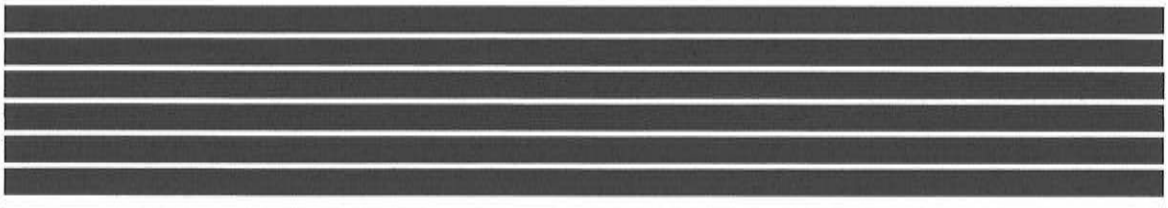
***Study 292*** was a multicentre, retrospective, multiple dose study whose purpose was to determine the esophageal and/or gastric pH profile after multiple doses of omeprazole in 43 patients aged from 1.1 to 23.6 months (mean 6 months). The average treatment duration was 45 days. The conclusion from the study was that omeprazole was effective in raising intra-esophageal pH and treating acid reflux in this population.

Similarly, ***Kaufman***[25] investigated the use of Omeprazole suspension in paediatric transplant patients. The authors concluded that Omeprazole (suspension) was an effective acid-suppressing agent. A dosage of 1mg/kg/day was sufficient for most patients.

***Omari***[26] was a randomized, double blind, placebo-controlled, crossover trial of omeprazole therapy in infants. Patients were given omeprazole suspension for 7 days and then placebo for 7 days in randomized order. Twenty-four-hour esophageal and gastric pH monitoring was performed on days 7 and 14 of the trial. *Results:* Omeprazole (suspension) therapy significantly reduced gastric acidity, esophageal acid exposure and the number and duration of acid reflux episodes compared to placebo. Before randomization, the infants had clinical symptoms suggestive of GERD and an esophageal acid reflux index of >5% on 24-h esophageal pH monitoring. Omeprazole given once daily is effective in reducing the frequency of acid reflux episodes and the overall degree of esophageal acid exposure. In most infants, omeprazole therapy reduced esophageal acid exposure to below normal levels.

**Alliet**[24] evaluated the use of omeprazole in infants with $H_2$ antagonist resistant GERD. Twelve neurologically normal infants (age 2.9 ± 0.9 months) with GERD who did not respond to cimetidine were treated with omeprazole, 0.5 mg/kg once a day, for 6 weeks. The effectiveness of omeprazole was evaluated in all infants by clinical assessment and endoscopy before and after treatment and by 24-hour gastric pH monitoring during treatment in seven infants.
*Methods:* Twelve neurologically normal infants (age 2.9 ± 0.9 months) with endoscopically confirmed GERD not responding to cimetidine were treated with omeprazole. The effectiveness of omeprazole was evaluated by clinical assessment (n = 12), endoscopy before and after treatment (n = 12), and 24-hour intragastric pH monitoring during treatment (n = 7).
*Results:* Omeprazole (suspension) therapy led to a marked decrease in symptoms, endoscopic and histologic signs of esophagitis, and intragastric acidity.

***Bishop***[27] aimed to prospectively determine the dosage of omeprazole required to treat symptomatic gastroesophageal reflux in children younger than 2 years.
*Patients and Methods*: Children under 2 years with clinically suspected GERD underwent 24-hour dual-channel intraesophageal/gastric pH monitoring. A reflux index above 10% in children under 1 year and above 6% in children older than 1 year was deemed significant. Treatment with omeprazole was followed by dual-channel pH study after 14 days. The dosage was increased in increments of 0.7 mg/kg/day, and pH studies were repeated until the gastroesophageal reflux was controlled. A twice-daily regimen was followed.
*Results:* Ten children (5 boys, 5 girls) younger than 2 years (median 7.75 months, range 1.25–20 months) were treated for GERD and underwent dual-channel pH probe monitoring. The median weight was 7.4 kg (range 3.0–10.9 kg). All of the patients had improvement of the GERD while receiving omeprazole treatment, as assessed by the follow-up pH studies. Five children responded to the initial dosage of 0.7 mg/kg/day, four had 1 dose increment, and one patient had 3 dose increments to achieve adequate resolution of symptoms and a satisfactory pH response. The median dosage required was 1.05 mg/kg/day.
*Conclusions*: The authors concluded that Omeprazole (suspension) was considered an effective treatment in children under 2 years old.



[redacted]

The ***Hassall***[28] study (also referred to as I-678) was a multicentre, open, uncontrolled, study which enrolled 65 patients. The study was divided into two phases; a dose finding and healing phase and a maintenance phase. The dose finding and healing phase was designed to assess the dose of omeprazole required to achieve verified healing of erosive reflux esophagitis in children of different ages. When healed, the children were allowed to enter the maintenance phase and remain on long-term maintenance treatment with omeprazole in order to assess safety and tolerability of omeprazole during long-term treatment.
*Patients and methods*: The age of inclusion was 1 to 16 years and the children were required to have endoscopically verified esophagitis.
The dose-finding started with a daily dose of 0.7 mg/kg body weight. If the dose was not effective, it was increased at each visit by increments of 0.7 mg/kg.
The therapeutic goal was intraesophageal pH < 4.0 for not more than 6% of 24 hours.
65 patients were included in the study and all are included in the report (healing phase). The effective dose was then used for healing. When a suitable dose had been found the child was treated for 3 months. The total time required for the dose-finding and the healing phase was 83-421 days.
*Results*: Sixty-five patients entered the dose-finding part but 8 of them discontinued during that period, thus 57 patients started the healing treatment. Of the 57 patients that entered the healing part, 29 children had GERD symptoms without any other disease as the cause of their symptoms, 21 children with cerebral palsy or another neurologic condition and there were 7 with esophageal atresia.
Healing phase: data from 65 children were available for an All Patients Treated analysis.
Maintenance phase: 46 of the 54 patients that were healed entered the maintenance phase. Patients were observed in the maintenance phase for 137-749 days.
After the first healing period 51 patients were healed (which lasted between 10 and 325 days, depending on the accessibility of children for endoscopy) and 6 required further treatment. Three of these children left the study at this point and the remaining 3 were healed after a second treatment period which lasted between 100 and 187 days. Healing was defined as esophagitis grade 0 or 1. During the study a reduction in various reflux symptoms was reported.
Nineteen (41%) of the 46 patients, that entered the maintenance phase, had no relapse during the maintenance phase. Among the patients who relapsed, 15 had their first relapse before the 3 months visit. Ten (22%) of the 46 patients had more than one relapse.
Thirty-two patients completed the study i.e. had data from the 21 months visit. Of these patients, 26 (81%) were healed at the last visit, three had no final endoscopy and three were unhealed.
At the last clinic visit in the maintenance phase, 63 % were assessed as having no overall symptoms and 24 % had only mild symptoms. One patient had severe heartburn/epigastric pain and one had severe dysphagia/odynophagia. The percentage of patients that experienced regurgitation/vomiting was reduced from 70% at baseline to 20%. No adverse events were attributed to omeprazole, and no patient discontinued the drug because of an adverse event.

*Conclusions and comments:* This was an open study but the data is supported by the fact that the patients included had an endoscopically verified esophagitis and intra-esophageal pH was measured. The results showed highly clinically relevant efficacy of omeprazole.

**Olsen**[29] characterized the pharmacodynamics and pharmacokinetics of the "paediatric clinical formulation" in critically ill paediatric liver/intestinal transplant patients. Eleven paediatric liver and/or intestinal transplant patients aged < 1year to 14 years (mean 4 years) administered at 1mg/kg/day via nasogastric tube before sequential measurements of omeprazole serum concentration and gastric pH monitoring. Gastric pH was monitored continuously for 48 hrs and plasma omeprazole concentrations were determined upon first and multiple dosing.
Results: The pharmacokinetic profile was characterised and showed a rapid absorption profile
Gastric pH remained >4.0 for 78.8% ±18.9% of the first dosage interval and 97.8% ±5.4% of multiple dosage intervals regardless of age.
Conclusion: The results support the use of omeprazole suspension at 1mg/kg/day to maintain gastric pH of >4.0 and to achieve maximal pharmacodynamic effect in paediatric liver and/or intestinal transplant patients.

The pharmacodynamic and clinical efficacy data for the "paediatric clinical formulation" extends across the paediatric population.

Some published studies have also evaluated the IV forms of *Losec* in children.

***Solana** et al*[11] compared the effect of 2 doses of intravenous omeprazole on gastric pH, gastrointestinal bleeding, and adverse effects in critically ill children.
*Patients and methods:* A prospective randomized clinical trial in paediatric patients at risk of gastrointestinal bleeding. The effect of 2 intravenous omeprazole regimens (0.5 or 1 mg/kg every 12 hours) on the gastric pH and incidence of gastrointestinal haemorrhage in critically ill children was compared. The efficacy criteria were a gastric pH >4 and the absence of clinically significant gastrointestinal bleeding.
*Results*: Forty patients, 20 per group, were studied. The age of the patients ranged from 4 to 60 month. Overall, the gastric pH was > 4 for 57.8% of the time, with no significant difference between the doses (P = 0.66). The percentage of time with a gastric pH > 4 increased during the study (47.8% between 0 and 24 hours vs 76% between 24 and 48 hours, p =0.001); the higher dose showed a greater increase in the percentage of time with a pH > 4: between hours 24 and 48 of the study, the gastric pH was greater than 4 for 84.5% of the time with the 1 mg/kg dose and for 65.5% of the time with the 0.5 mg/kg dose (P = .036). No correlation was found between omeprazole plasma levels and gastric pH but a dose-response relationship similar to that in adults was observed. Omeprazole IV was effective in this paediatric population and no adverse effects were reported.

The ***Faure***[30] study was designed to determine both the pharmacokinetics and the optimal dosage of intravenous omeprazole in patients younger than 30 months of age.
*Patients and methods*: Nine children (three girls), aged 4.5 to 27 months, with normal liver and renal function 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 20 mg/1.73 $m^2$, and group 2, consisting of the following five patients, received 40 mg/1.73 $m^2$. At day 3, a 24-hour intragastric pH and a pharmacokinetic study of omeprazole were performed.
*Conclusions:* Intravenous administration of omeprazole was effective in infants and no adverse events were reported. The results indicated that the dose of ~ 0.5mg/kg was less

effective in maintaining 24-hour gastric pH > 4 than a dose of ~1.1mg/kg. The AUC of omeprazole was significantly correlated with the percentage of time with pH > 4 during 24 hours.

c) Adult patients

The applicant has previously provided a comprehensive discussion on the relevance of the faster and higher $C_{max}$ of Omeprazole Oral Suspension compared to the reference product. The main points are:

i. In adults, the relationship between AUC and intragastric pH>4 has been well established from primary pharmacodynamic studies through to clinical efficacy across a range of formulations including capsules, parenteral forms of *Losec* and immediate release preparations of omeprazole. The pharmacology of omeprazole is well established at the molecular and cellular level linked to inhibition of the enzyme blocking acid secretion in the target parietal cells and increasing gastric pH. This comprehensive understanding explains there can be no direct temporal relationship between the plasma concentration of omeprazole at a particular time (e.g. $C_{max}$) and the pharmacodynamics and clinical efficacy of omeprazole. For omeprazole, pharmacodynamic effects and clinical efficacy are related to the AUC parameter and no relationship with $C_{max}$ has been shown or would be expected.
ii. Omeprazole absorption shows considerable patient-to-patient variability and the reference product shows more variability than Omeprazole Oral Suspension - indeed, many of the basic pharmacodynamic studies in adults were conducted using a buffered oral solution/suspension rather than capsules. Consequently, Omeprazole Oral Suspension exhibits faster $t_{max}$ and higher $C_{max}$ than the reference capsules. The suspension dosage form offers certain advantages including an ability to administer doses < 10mg, titrate doses on a mg/kg basis and is suitable for patients unable to swallow capsules/tablets. Finally, although Omeprazole Oral Suspension shows higher mean $C_{max}$ at 1.37 point estimate in the pivotal bioavailability study, the maximum individual $C_{max}$ ratio was only 1.04 so that the range of individual exposures for the two formulations is similar.
iii. The reference *Losec* oral formulation is a delayed release capsule. However, there is considerable clinical and post marketing experience with immediate release formulations of Omeprazole including prescription/OTC products outside the EU and Losec parenteral forms globally. The maximum plasma concentrations for the parenteral formulations on an equidose basis are two-threefold higher than the corresponding Cmax of oral formulations (solution, suspension or delayed release). The parenteral forms of Losec have similar posology and adverse event profiles to the oral formulations.
iv. Omeprazole is a molecule with a well-established safety profile from clinical trials and more than 30 years post-marketing experience. No dose-related safety issues have been raised.

Pharmacodynamic effects across the age spectrum from neonate to adult using pharmacokinetic and pharmacodynamic data have been assessed and is shown in Figure 2.5.4.4. Specifically, exposure-response relationship plots have been constructed for both omeprazole and the single optical isomer s-omeprazole (esomeprazole) including adult and paediatric subjects. The endpoint for pharmacodynamic effect was the "% time above intragastric pH4", 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. However, no such relationship has been shown for the $C_{max}$ parameter or would be expected on pharmacological grounds.

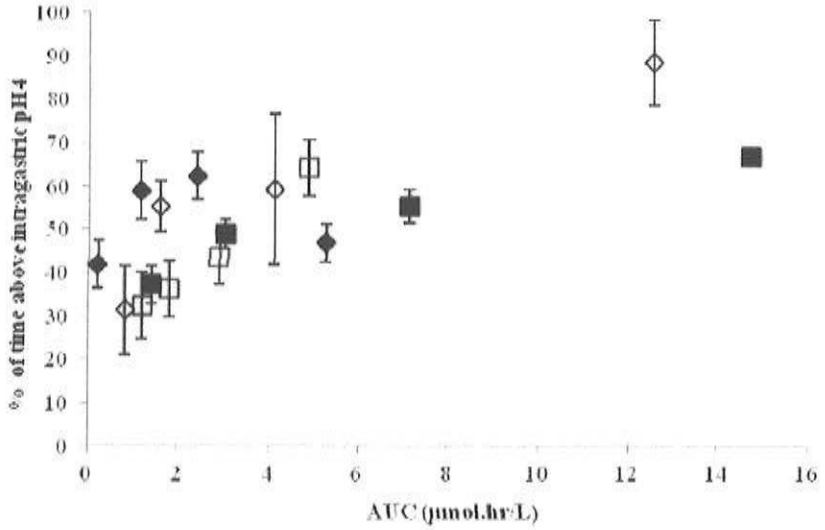



**Figure 2.5.4.4** | Exposure-response relationship for omeprazole (open symbols) and esomeprazole (closed symbols) in adult (squares) and paediatric subjects (diamonds). Each group of subjects represented by median AUC and mean % time above intragastric pH 4. For omeprazole, there were PD data from 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[12]

Overall, the combined PK/PD/efficacy findings indicate a similar exposure response relationship for omeprazole between infants, older children and adults and support the assertion in the SmPC for *Losec* preparations regarding AUC and clinical efficacy.

It is considered that the difference in $C_{max}$ profile between Omeprazole Oral Suspension and the reference product has any clinical significance for any of the indicated patient groups. This conclusion is based on a thorough understanding of mechanism of action at a molecular and cellular level and supported by available pharmacodynamic and clinical data across all ages from infancy to adulthood.

[redacted]

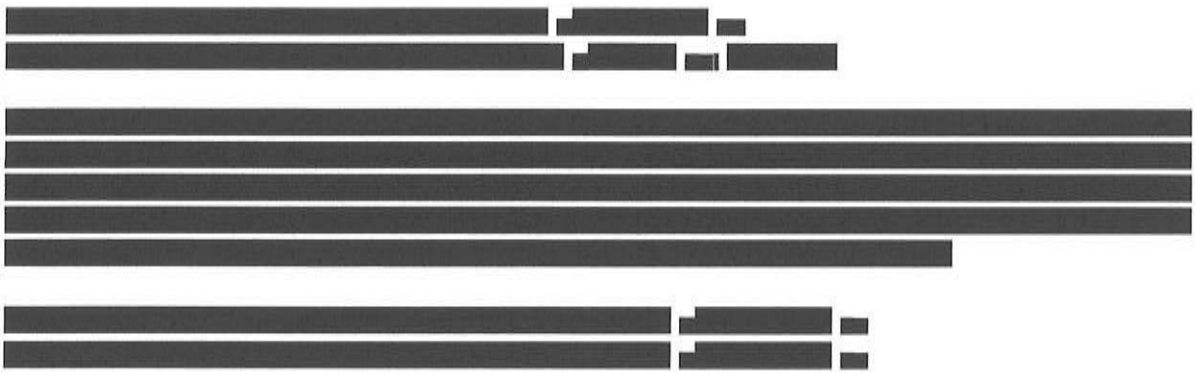
**Table 2.5.4 27 | Clinical studies with Omeprazole in children < 2 years /paediatric patients (literature) included in this report**

| Study Number or Identifier | Study Design | Primary Objective | Dosing Regimen | n | Study Population | Treatment Duration | Formulation(s) |
|---|---|---|---|---|---|---|---|
| Study 251 | Phase 3, single-blind, randomized; no control | Efficacy and safety | 0.5, 1.0 and 1.5mg/kg | 115 | 0.7 to 22 months | 8 weeks | Omeprazole EC Granules dispersed in 8.4% sodium bicarbonate buffer |
| Study 250 | Phase 1, open-label | PK and gastric or esophageal pH | 0.5, 1.0, 1.5 mg/kg; Single dose | 25 | 0.5 to 24 months | Single dose | Omeprazole EC Granules dispersed in 8.4% sodium bicarbonate buffer |
| Study 292 | Retrospective; no control. | Gastric or esophageal pH | 4 to 30 mg | 43 | 1 to 24 months with GERD | Average 45 days | Omeprazole EC Granules dispersed in 8.4% sodium bicarbonate buffer |
| Alliet [36] | Open label clinical trial | Efficacy | 0.5mg/kg/day | 12 | 2.9±0.9 months | 6 weeks | EC granules dispersed in milk or water |
| Hassall/I-678[40], | Open label clinical trial | Efficacy and PK | 0.7-3.5mg/kg/day | 57 (25 for PK) | 1-16 years | 12 weeks after dose-finding | Capsules, EC granules in weakly acidic vehicle or EC dispersed in 8.4% sodium bicarbonate buffer |
| Kaufman[32] | Open label clinical trial | PD | 1.0mg/kg/day; via nasogastric tube. | 22 | 0.9 – 108 months | 1-2 days | Omeprazole suspension in 8.4% sodium bicarbonate buffer |
| *Bishop[31] | Open label clinical trial | Efficacy | Initial dose 0.7mg/kg/day in two divided doses (up to dose of 2.8 mg/kg/day) | 10 | 1.25 to 20 months old with GERD | 14 days | Omeprazole pellets dispersed in 8.4% sodium bicarbonate buffer |
| *Omari[35] | Randomised, double-blind, placebo controlled | Efficacy and PK | 0.7mg/kg/day: via nasogastric tube | 10 | 50±9 days | 7 days | Omeprazole powder suspended in a kaline buffer |
| Moore[33] | Randomised, double-blind, placebo controlled | Efficacy (symptom assessment) | 10mg/day (5-10kg) 20mg/day > 10kg | 30 | 3-12 months | 2 weeks | EC granules dispersed in apple sauce |
| *Karami[37] | Open label, randomised | Pharmacokinetic | 1 mg/kg/day | 34 | 1.2 months to 17 years | 3 days | Omeprazole powder suspended in 8.4% sodium bicarbonate buffer |
| *Solana[38] | Single-blind, randomised | PK and Efficacy | 0.5mg/kg and 1.0mg/kg every 12 hours | 40 | 4 – 30 months (critically ill) | 48 hours | IV omeprazole |
| *Faure[20] | Open-label, randomised | PK and Efficacy (pH monitoring) | 20mg/1.73m$^2$ and 40mg/1.73m$^2$ | 9 | 4.5 – 27 months (critically ill) | 3-5 days (for PK) | IV omeprazole |
| *Kaguelidou[42] | Open-label randomised | Efficacy | 1-3 mg/kg/day | 54 | Neonates, median postnatal age 37.5 days, median post menstrual age 36 weeks | 3 days | EC granules dispersed in milk |

* Studies not included in PdAR

## 2.5.4.7 CLINICAL EXPERIENCE WITH SIMILAR [IMMEDIATE RELEASE] FORMULATIONS (INCLUDING EXTEMPORANEOUS PREPARATIONS) OF OMEPRAZOLE IN ADULTS

The final formulation proposed for marketing of Omeprazole Oral Suspension has been shown to be equivalent to the reference product *Losec capsules* in two studies in adults as follows:



The efficacy of omeprazole in immediate release buffered formulations is also supported by the availability of a number of similar formulations in the USA:

*Zegerid Powder for Oral Suspension*, a single dose sachet product, containing either 20 mg or 40 mg Omeprazole with 1680mg of sodium bicarbonate as buffering agent, and
Zegerid Capsules, containing either 20 mg or 40 mg Omeprazole and 1100 mg of sodium bicarbonate as buffering agent.

The availability of these Omeprazole immediate release products in the USA has led to a number of additional studies. These clinical studies generally involved special groups of patients including patients with refractory esophagititis, Barrett's esophagus, stress ulcers, nocturnal symptoms etc. PK/PD studies were also performed that provide additional insights into the link between AUC and efficacy for omeprazole. In addition, as with the paediatric experience, a number of studies have been carried out in adults using extemporaneous formulations similar to the present application (buffered suspensions).

A list of these adults studies is shown in Table 2.5.4.28 and briefly discussed, together with comments on their relevance to the present application. In general, the studies provide additional information confirming the efficacy of buffered omeprazole in a variety of clinical situations and contribute to the safety database.

### Zegerid Capsules PK/PD Studies

In study OME-IR-(CAP)-CO2[26] the PK and PD of omeprazole was evaluated when Zegerid IR 40 mg capsule (containing 1100 mg or 13 mEq of sodium bicarbonate) was given 1 hour pre-meal once daily versus Prilosec Delayed Release 40 mg capsule once daily for 7 days. The primary pharmacokinetic endpoint was AUC (0-∞) at steady state (Day 7). Zegerid Capsules 40 mg and Prilosec 40 mg administered once daily before breakfast were bioequivalent with respect to AUC (0-∞). The percent mean ratio was 101.01 % and the bounds of the 90 % CI were 92.56 % and 110.23 %. The Cmax for Zegerid 40 mg at steady state was greater than for Prilosec 40 mg (percent mean ratio of 116.54 %, 90 % CI of 99.05 % to 137.11 %). This difference in $C_{max}$ had no apparent effect on the pharmacodynamics or safety of Zegerid 40 mg in this trial. The pharmacodynamic data showed that Zegerid Capsules 40 mg were equivalent to Prilosec Capsules 40 mg with respect to % decrease from baseline in integrated

gastric acidity at Day 7. Total bioavailability of Zegerid Capsules 40 mg, AUC(0-∞) ,was decreased by 22 % when Zegerid was administered 1 hour after the beginning of a meal. The Day 1 pharmacokinetic results after fasting administration were similar to those after 7 days i.e. the Cmax of Zegerid IR 40 mg Capsules was considerably higher than that of Prilosec DR 40 mg Capsule but the reference and test products were equivalent with respect to AUC (0-∞).

In study OME-IR (CAP)-CO1[26] the PK and PD of omeprazole were evaluated when Zegerid IR 20 mg capsule (containing 1100 mg or 13 mEq of sodium bicarbonate) was given 1 hour premeal once daily versus Prilosec Delayed Release 20 mg Capsule given once daily for 7 days. The primary pharmacokinetic endpoint was AUC(0-∞) at steady state (Day 7). Zegerid Capsules 20 mg and Prilosec 20 mg administered once daily before breakfast were bioequivalent with respect to AUC (0-∞). The percent mean ratio was 113.30 % and the bounds of the 90 % CI were 105.02 % and 122.22 %. The Cmax for Zegerid 20 mg at steady state was greater than for Prilosec 20 mg (percent mean ratio of 145.46 %, 90 % CI of 123.56 % to 171.25 %). This difference in Cmax had no apparent effect on the pharmacodynamics or safety of Zegerid 20 mg in this trial. The pharmacodynamic data showed that Zegerid Capsules 20 mg were equivalent to Prilosec Capsules 20 mg at steady state (Day 7) with respect to the percent decrease from baseline in integrated gastric acidity. The day 1 pharmacokinetic results after fasting administration were similar to those after 7 days i.e. the Cmax of Zegerid IR 20 mg Capsule was considerably higher than that of Prilosec DR Capsule 20 mg but the reference and test products were equivalent with respect to AUC (0-∞).

**Zegerid Powder for Oral Suspension PK/PD Study**: Zegerid is a unit dose oral suspension formulation (sachet) and is also a buffered formulation of omeprazole. [redacted].

For omeprazole, the relationship between PK/ PD for an immediate release (oral suspension) and delayed release formulation (Losec/Prilosec) was shown in study no. OSB-IR-C06[25] entitled "Comparison of the Pharmacokinetics and Pharmacodynamics of Omeprazole/Sodium Bicarbonate Immediate-Release 20mg Suspension (IR, for immediate-release) and Prilosec 20mg Delayed Release Capsules (DR, for delayed-release) in Healthy Subjects". This combined PK/PD study evaluated primary and secondary PK and PD parameters of both an immediate release, buffered formulation (unit dose suspension) and a delayed release capsule formulation of omeprazole after 7/8 days treatment with each formulation administered in a randomised, crossover design.

PK: the following parameters were calculated after 1 and 7 days: $C_{max}$, $t_{max}$, AUC, and $t_{1/2}$.

PD: the following parameters were calculated: 1) percent decrease from baseline of the 24h integrated gastric acidity after 7 days treatment, expressed as mmol.hr/L) [*primary parameter*], 2) percentage time with gastric pH ≤ 4, 3) mean gastric acid concentration and 4) median gastric pH. These pharmacodynamic biomarkers are considered to be relevant surrogate markers in the treatment of acid-related gastrointestinal conditions, as the clinical symptoms and outcome of acid related disorders are directly related to acid output.

On days 1 and 7 (i.e. single dose and in steady state), the formulations were equivalent with respect to AUC(0-t) and AUC(0-inf): on Day 1 (97.80% mean ratio of IR/DR, 90% CI 91.71 – 104.29% and **95.90%** mean ratio of IR/DR, 90% CI **89.97 – 102.23%**, respectively) and Day 7

(107.21% mean ratio of IR/DR, 90% CI 100.76 – 114.07% and **106.71%** mean ratio of IR/DR, 90% CI **100.01 – 113.36%**, respectively).

However, as expected, the $C_{max}$ parameter did not show equivalence between the formulations [Day 1 (**160.44%** mean ratio of IR/DR, 90% CI **140.41 – 183.33%**) and Day 7 (**157.02%** mean ratio of IR/DR, 90% CI **141.50 – 174.24%)]**, due to the different release characteristics of the formulations and the formulation approach to protecting omeprazole. Similarly, $t_{max}$ of the IR formulation was 0.50/0.47 hr (Day 1/7), compared to 1.74/1.39 hr (Day 1/7) for the DR formulation.

The performance of the two formulations with respect to all the PD parameters evaluated was very similar, in particular with respect to median decrease in integrated gastric acidity, median gastric pH and % time with gastric pH ≤ 4, clinically meaningful parameters relevant to the treatment of acid related gastrointestinal conditions. The median decrease in integrated gastric acidity for both IR/DR formulations was 46% on Day 1. On Day 7, the corresponding median decreases were 82% and 78% respectively. The mean of the by-subject ratios (IR/DR) of the decrease from baseline integrated gastric acidity was 100% (CI, 94-108%).

The two formulations had equivalent AUC (primary parameter) but not $C_{max}$ (secondary parameter) and were equivalent with respect to pharmacodynamic effect (a surrogate of clinical efficacy). Although less important than PK data, this study provides additional pharmacodynamic confirmation regarding the importance of total absorption for the expression of clinical response i.e. immediate and delayed release formulations that exhibit different absorption profiles (by $C_{max}$ and $t_{max}$), but with equivalent total absorption (AUC) show an equivalent pharmacodynamic response.

While the basis for the approval of Zegerid was the PK equivalence of the formulations (PD data was supportive only), the availability of this formulation has led to a number of clinical studies of the formulation in diverse clinical applications, including comparisons with delayed release formulations. The clinical experience with this formulation (Zegerid omeprazole powder for suspension) includes the following studies, which also add to the safety database, particularly as a number of the studies used relatively high doses and specific patient groups.

**Conrad**[41] was a multi-centre, randomised, double-blind, controlled trial conducted in 359 critically ill patients to evaluate the ability of immediate release omeprazole to prevent upper GI bleeding and to compare the pharmacodynamic effects of IR omeprazole oral suspension delivered via a nasogastric or orogastric tube with intravenous cimetidine. Both study products were administered as a loading dose, followed by the maintenance dose of 40mg/day (IR oral suspension) and 50mg/h (cimetidine IV).

Results: After the first dose of omeprazole, a gastric pH > 4 was achieved in 99% of patients versus 84.6% of patients with IV cimetidine. A median gastric pH of ≥6 was maintained on all 14 trial days in IR omeprazole-treated patients and on 50% of days in IV cimetidine-treated patients ($p < 0.001$). With respect to clinically significant upper GI bleeding (the primary efficacy end point), in the intent-to-treat population, clinically significant bleeding occurred in 3.9% IR omeprazole suspension-treated patients and 5.5% of cimetidine-treated patients. In the per-protocol population, clinically significant bleeding occurred in 4.5% IR omeprazole suspension-treated patients and 6.8% of cimetidine-treated patients. It was concluded that IR omeprazole suspension was no less effective than IV cimetidine in preventing clinically significant upper GI bleeding in critically ill patients.

**Castell**[42] was a randomised, open-label, crossover trial performed to compare omeprazole IR oral suspension and pantoprazole delayed-release tablets, with respect to control of nocturnal

gastric acidity in patients with symptomatic GERD. In total, 36 patients with night-time symptoms of GERD were randomised to receive either night time omeprazole or pantoprazole.

Results: After repeated once or twice daily dosing, the median percentage of time with gastric pH > 4 was significantly greater for IR omeprazole 40mg than pantoprazole 40mg. Similarly, a single dose of IR omeprazole 40mg at bedtime controlled night-time pH better than twice daily dosing with delayed release-release pantoprazole 40mg tablets.

**Gerson**[43] was an open-label study designed to determine the control of esophageal reflux in patients with Barrett's esophagus after administration of omeprazole IR suspension 40mg twice daily (i.e. 80mg/day) for 21-28 days.

Results: 15 patients completed the protocol. All patients (100%) demonstrated normalisation of supine pH after omeprazole IR oral suspension treatment. One patient demonstrated abnormal upright reflux on the second day of monitoring; all the other patients demonstrated normal pH scores. Administration of twice daily omeprazole IR oral suspension 40mg demonstrated control of nocturnal esophageal reflux in 100% of patients with Barrett's esophagus, and complete control of esophageal pH during 97% of the 24-h recording periods.

**Orbelo** et al [44] was an open-label study comparing the effect of both single dose morning and night-time administration of 40mg omeprazole IR oral suspension for eight weeks on the healing of severe refractory reflux esophagitis.

Results: 92 patients with severe (Los Angeles grade C or D) erosive reflux esophagitis participated. Overall, 88% of subjects showed healed (76%) or improved (12%) erosions. There was no significant difference (morning vs. night) in mucosal healing, symptom resolution or acid regurgitation.

***Walker***[45] compared IR omeprazole 20mg powder for suspension to *Losec capsules*, in a multicenter, double-blind, double-dummy, randomized study for relief of heartburn associated with GERD.

*Patients and Methods:* Patients with a history of frequent (2-3 days/week) uncomplicated GERD, were randomized to receive omeprazole suspension (20mg) or Losec (20mg) with corresponding placebo. Study medication was self-administered on the first episode of heartburn, and could be taken for up to 3 days within a 14 day study period. Heartburn severity was self-assessed up to 180 minutes post dose (9 point Likert scale). Primary endpoint was median time to sustained response ( ≥ 3 point reduction in heartburn severity for ≥ 45 minutes).

*Results:* Of patients randomized to omeprazole suspension (n=122) or Losec (n=117), 228/239 had recorded evaluable heartburn episodes and were included in the modified intent-to-treat population. No significant between-group differences were observed for median time to sustained response (60.0 vs. 52.2 minutes, omeprazole suspension (n=117) and Losec (n=111), respectively), sustained partial response (both, 37.5 minutes) and sustained total relief (both, 105 minutes). Both treatments were well tolerated and did not raise any safety concerns.

*Conclusions:* Omeprazole suspension and Losec were equally effective for rapid heartburn relief in patients with GERD.

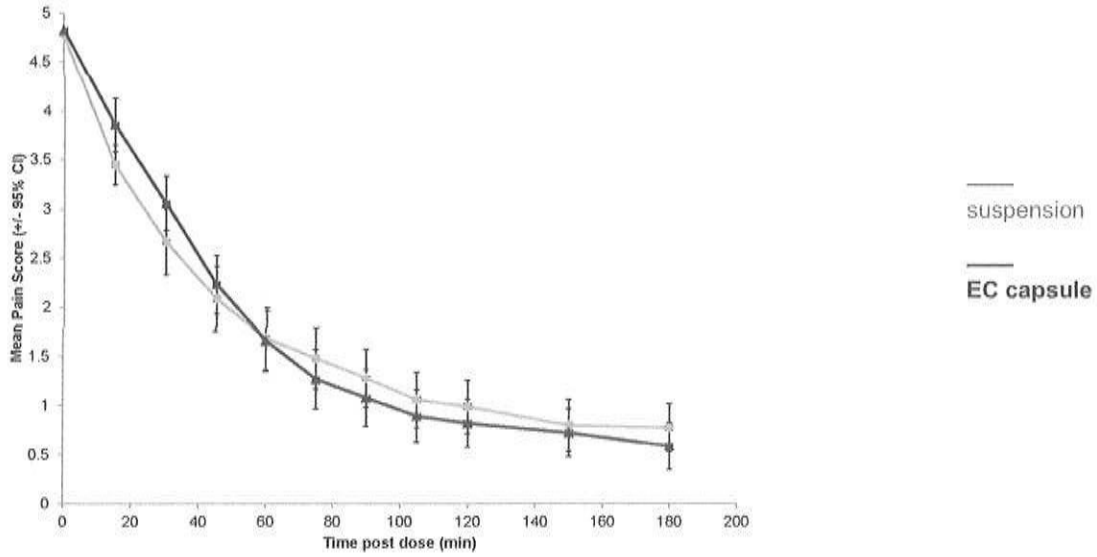



**Figure** 2.5.4.5 | Severity of heartburn by time (modified Intent-To-Treat set, n = 228)[45].

The ***Boussery***[46] study compared the bioavailability of an omeprazole multi-unit-particulate system (Losec MUPS) formulation with an extemporaneous suspension of omeprazole in 8.4% sodium hydrogen carbonate (4mg/ml) in tube-fed patients with severe neurodevelopmental problems.

GERD is a frequently occurring condition among institutionalised patients with severe neurodevelopmental problems. These patients often depend on a feeding tube for the administration of drugs because of oral motor dysfunction with uncoordinated and unsafe swallowing and may benefit from a liquid dosage form of omeprazole.

The study was a two-phase crossover study in 10 institutionalised patients suffering from severe neurodevelopmental problems with swallowing disorders and with a feeding tube in place. Study phases were two consecutive 14 day periods during which an omeprazole MUPS tablet or suspension formulation was administered through the feeding tube. The omeprazole suspension formulation was prepared by manipulation of omeprazole capsules. Omeprazole 40mg capsules were dispersed in 8.4% sodium hydrogen carbonate solution to give a 4mg/ml suspension. A dose of either 5ml (20mg) or 10 ml (40mg) was administered. On the last day of each 14-day period, a plasma concentration-time profile was determined. Although there are some limitations of study size and design (n=9 patients in final analysis for a drug with high variability, small number of blood sampling points, short sampling time of only eight hours), the authors were able to draw some conclusions. As expected $C_{max}$ was higher and $t_{max}$ faster for the oral suspension. The dose normalized to body weight AUC was higher for suspension than for tablets, but not statistically different. Boussery concluded that omeprazole MUPS formulation had no advantages over the more easily administered suspension formulation.

***Phillips***[47] characterized the absorption and pH control of omeprazole suspension 2mg/ml in 8.4% sodium bicarbonate solution administered via the nasogastric versus jejunal or duodenal route.

*Patients and methods*: Nine critically ill surgical patients, mechanically ventilated and unable to take oral medications, were enrolled in this randomized, crossover study. Patients received a single dose 40 mg omeprazole suspension by either nasogastric or jejunal/duodenal route.

Twenty-four-hour continuous intragastric pH monitoring was performed during the study period. Sequential blood samples were collected over 24 hours to characterize omeprazole suspension absorption and the pharmacokinetic parameters.

*Results:* Nasogastric administration of omeprazole suspension resulted in lower maximum serum concentrations compared to jejunal/duodenal dosing and absorption was slower when administered via nasogastric tube. All routes of administration resulted in similar $AUC_{0-\infty}$. Mean intragastric pH values remained above 4 one-hour post omeprazole administration and remained greater than 4 for the entire 24-hour study (6.32 ± 1.04, 5.57 ± 1.15, nasogastric vs jejunal/duodenal, p=0.015), regardless of administration route.

*Conclusions:* In critically ill surgical patients, pharmacokinetic parameters and subsequent pH control following the administration of omeprazole suspension were similar by the jejunal, nasogastric, or duodenal route. Omeprazole suspension offered an alternative acid control measure when patients are unable to take oral medications, yet have an enteral tube in place.

***Dabiri***[18] compared an extemporaneous suspension of omeprazole (40 mg per day as 2 mg/ml suspension made by dispersing capsule granules in 8.4% sodium hydrogen carbonate), a pantoprazole extemporaneous suspension (40 mg per day as a 2 mg/ml suspension) and Pantoprazole IV (40 mg per day) on the gastric pH of intensive care patients.

*Patients and Methods*: Critically ill adults admitted to ICU under mechanical ventilation and with nasogastric or orogastric tube fitted (NPO or non-per-oral, due to inability to swallow solids). A formulation of omeprazole capsule contents (granules/pellets) dispersed in 8.4% sodium hydrogen carbonate (concentration 2 mg/ml). The dose was 40mg/day and administered via a nasogastric feeding tube. The primary end point was the mean gastric pH on each trial day.

*Results:* Fifty-six patients were randomised. 18 were administered omeprazole oral suspension (treatment A). The median age was 61.5 years (60.1 for omeprazole group). On each day the mean gastric pH alteration values were significantly higher for omeprazole suspension group than for IV-pantoprazole-treated patients (p<0.001, all days). For omeprazole oral suspension, the average time to get to this pH was 1.35 days. 88.9% of patients achieved the target pH after first dose administration (no significant difference between the groups).

*Conclusions*: In a critically ill group of patients, administration of extemporaneous omeprazole oral suspension (2mg/ml, in 8.4% sodium hydrogen carbonate solution) via feeding tube was effective in raising gastric pH and more effective than IV pantoprazole.

Aside from the paediatric population, these studies draw attention to some particular patient populations for whom currently available treatments (formulations) are not suitable e.g. patients with severe neurodevelopmental problems [Boussery], patients with swallowing difficulties requiring a feeding tube [Dabiri] etc. Similar to the paediatric setting, in practice, these patients are frequently treated with extemporaneous formulation products or manipulated formulations.

## 2.5.4.8 COMPLIANCE WITH GOOD CLINICAL PRACTICES

The applicant has provided certificates confirming that Studies 376-15, BA 04/07, 375-15, 454-14 and 0104-16 were conducted under Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) guidelines.

Similarly, the sponsor of Studies 251, 250, 292, and 1-678 (Astrazeneca) has also confirmed that these were studies conducted under GCP guidelines. The other studies discussed were published in peer-reviewed journals and were generally performed within the last 20 years, so it is assumed that the studies were conducted in accordance with GCP guidelines.

### 2.5.4.9 PROPOSED THERAPEUTIC INDICATIONS AND POSOLOGY

The applicant has proposed the following therapeutic indications:

*Omeprazole Oral Suspension 1mg/ml is only indicated for:*

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

Compared to Omeprazole Oral Suspension 2mg/ml, the main change relates to an extension to allow dosing to children < 4.2 Kg in weight instead of ≥ 4.2 Kg along with a restriction to the administration of maximum 10mg.

The following therapeutic indications: have been proposed by the applicant and approved:

*Omeprazole Oral Suspension 2mg/ml is primarily indicated for:*

*Paediatric use*
*Children (> 1month)*
- *Treatment of reflux oesophagitis*
- *Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease*

*Children and adolescents over 4 years of age*
- *In combination with antibiotics in treatment of duodenal ulcer caused by H. pylori*

*Omeprazole Oral Suspension may also be used by patients having difficulty swallowing Omeprazole capsules/tablets in whom treatment with Omeprazole is indicated.*

Compared to the reference product, the main change relates to an extension of indication to children > 1 year to > 1 month in line with the utility of the new galenical form and supported by the clinical data.

For the adult population, the therapeutic indications are the same as the reference product, Losec, with the exception of Zollinger-Ellison syndrome. This is appropriate, as the dosages for this indication exceed the PK linearity of omeprazole. For the indications proposed by the applicant, the maximum daily dose is 40mg.

For the paediatric indications, the applicant proposes the following recommended posology in line with the available clinical data:

| *Age* | *Weight* | *Posology* |
|---|---|---|
| ***1 month – 1 year*** | ***Weight based dosing*** | ***1 mg/kg/day. Doses above 1.5mg/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* |

For the adult indications, the proposed posology is the same as the reference product.

**Table** 2.5.4.28 | Summary of published studies in adults with buffered/immediate release omeprazole suspension formulations

| Study | Study Design | Primary Objective | Dosing Regimen | n | Study Population | Duration | Formulation |
|---|---|---|---|---|---|---|---|
| **Boussery (2011)**[46] | Open label, two phase crossover study | PK parameters; Comparative bioavailability | 4mg/ ml OS vs 20/40mg tablet contents; dosing via feeding tube | 10 | Institutionalised patients (adults) with severe neurodevelopmental problems and swallowing disorders | 14 day periods | Extemporaneous omeprazole 4mg/ml oral suspension : EC granules dispersed and suspended in 8.4% sodium bicarbonate |
| **Dabiri (2015)**[48] | Randomised, single-blind study | Efficacy (raising gastric pH) | 2mg/ml OS; 40mg; via nasogastric tube | 18 | Critically ill patients (adults) in ICU with nasogastric or orogastric tube | Up to 14 days | Extemporaneous omeprazole 2 mg/ml oral suspension : EC granules dispersed and suspended in 8.4% sodium bicarbonate |
| **Phillips (2000)**[47] | Open label, randomised, cross-over study | Efficacy (raising gastric pH) and PK | 2mg/ml OS; 40mg; comparing nasogastric and jejunal/duodenal administration | 9 | Critically ill patients | 2 doses | Extemporaneous omeprazole 2mg/ml oral suspension in 8.4% sodium bicarbonate |
| **Sharma (1999)**[49] | Open label study | Efficacy (clinical raising gastric pH) | 2mg/ml OS; 20mg; administration by gastrostomy | 6 | Adults with established gastrostomy | 7 days | Extemporaneous omeprazole 2mg/ml oral suspension : EC granules dispersed and suspended in 8.4% sodium bicarbonate |
| **Walker (2015)**[45] | Randomised, multicentre, double-blind, double-dummy study | Efficacy (clinical symptoms of GERD - heartburn) | 20mg unit dose suspension (Zegerid) | 122 | Adult patients with uncomplicated GERD | 3 doses | 20mg unit dose sachet containing 20mg omeprazole and 1680mg sodium bicarbonate |
| **Orbelo (2014)**[44] | Open-label, randomised | Efficacy (healing of GERD and symptom resolution) | 40mg unit dose suspension (Zegerid) | 92 | Adult patients with severe refractory reflux esophagitis; comparing morning and night-time administration | 8 weeks | 40mg unit dose sachet containing 40mg omeprazole and 1680mg sodium bicarbonate |
| **Gerson (2012)**[43] | Open-label study | Efficacy in Barrett's esophagus | 40mg unit dose suspension (Zegerid); twice daily (80mg/day) | 15 | Adult patients with Barrett's esophagus | 21-28 days | 40mg unit dose sachet containing 40mg omeprazole and 1680mg sodium bicarbonate |
| **Conrad (2005)**[41] | Randomised, multicentre, double-blind, study | Efficacy (control of upper GI bleeding) | 40mg unit dose suspension (Zegerid) | 359 | Critically ill patients at risk of gastrointestinal bleeding | Up to 14 days | 40mg unit dose sachet containing 40mg omeprazole and 1680mg sodium bicarbonate |
| **Castell (2005)**[42] | Open-label, randomised, two period crossover study | Efficacy (control of nocturnal gastric acidity) | 40mg unit dose suspension | 36 | GERD patients with nocturnal acid breakthrough | 6-8 day periods | 20mg unit dose sachet containing 20mg omeprazole and 1680mg sodium bicarbonate |

**MODULE 2.5 – CLINICAL OVERVIEW**

# 2.5.5 OVERVIEW OF SAFETY

**Safety profile of omeprazole - General**

The safety database reflects exposure to omeprazole in >3000 adult patients from worldwide clinical trials in addition to extensive post-marketing experience since approval and launch in 1988, together with available data for the paediatric population.

Summary of the safety profile

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

**Table** 2.5.5.1 | List of identified or suspected adverse drug reactions for omeprazole

| SOC/frequency | Adverse reaction |
|---|---|
| **Blood and lymphatic system disorders** | |
| Rare: | Leukopenia, thrombocytopenia |
| Very rare: | Agranulocytosis, pancytopenia |
| **Immune system disorders** | |
| Rare: | Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock |
| **Metabolism and nutrition disorders** | |
| Rare: | Hyponatraemia |
| Not known: | Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia. |
| ***Psychiatric disorders*** | |
| Uncommon: | Insomnia |
| Rare: | Agitation, confusion, depression |
| Very rare: | Aggression, hallucinations |
| **Nervous system disorders** | |
| Common: | Headache |
| Uncommon: | Dizziness, paraesthesia, somnolence |
| Rare: | Taste disturbance |
| **Eye disorders** | |
| Rare: | Blurred vision |
| **Ear and labyrinth disorders** | |
| Uncommon: | Vertigo |
| **Respiratory, thoracic and mediastinal disorders** | |
| Rare: | Bronchospasm |
| **Gastrointestinal disorders** | |
| Common: | Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting |
| Rare: | Dry mouth, stomatitis, gastrointestinal candidiasis |
| Not known: | Microscopic colitis |
| **Hepatobiliary disorders** | |

| SOC/frequency | Adverse reaction |
|---|---|
| Uncommon: | Increased liver enzymes |
| **Hepatobiliary Disorders** | |
| Uncommon | Increased liver enzymes |
| Rare: | Hepatitis with or without jaundice |
| Very rare: | Hepatic failure, encephalopathy in patients with pre-existing liver disease |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon: | Dermatitis, pruritus, rash, urticaria |
| Rare: | Alopecia, photosensitivity |
| Very rare: | Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) |
| Not known: | Subacute cutaneous lupus erythematosus |
| **Musculoskeletal and connective tissue disorders** | |
| Uncommon: | Fracture of the hip, wrist or spine |
| Rare: | Arthralgia, myalgia |
| Very rare: | Muscular weakness |
| **Renal and urinary disorders** | |
| Rare: | Interstitial nephritis |
| **Reproductive system and breast disorders** | |
| Very rare: | Gynaecomastia |
| **General disorders and administration site conditions** | |
| Uncommon: | Malaise, peripheral oedema |
| Rare: | Increased sweating |

## Safety profile of Omeprazole Oral Suspension in the applicant studies

In the applicant submitted clinical studies, Omeprazole Oral Suspension was administered to 117 across five studies.

The reported adverse events are summarised in Table 2.5.5.2. There were no serious adverse events. All adverse events reported were mild. Omeprazole Oral Suspension was well tolerated.

**Table** 2.5.5.2 | Display of Adverse events reported after administration of Omeprazole Oral Suspension (Test Product) in the applicant submitted clinical studies

| **Study No.** 0104-16 (Adults) | | | **Dose:** 20mg (20mg/5ml) | | | | **Doses:** 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Type:** Comparative bioavailability | | | **Subjects:** 27 (26 completed) | | | | | | |
| **Adverse event (Preferred Term)** | **Mild** | | **Moderate** | | **Severe** | | **Total** | | **Total** |
| | R | NR | R | NR | R | NR | R | NR | R+NR |
| **Infections and infestations** | | | | | | | | | |
| Upper respiratory tract infection | | 1 | | | | | | 1 | 1 |
| ***Eye disorders*** | | | | | | | | | |
| Eye discharge | | 1 | | | | | | 1 | 1 |
| **Gastrointestinal disorders** | | | | | | | | | |
| Diarrhoea | 1 | | | | | | 1 | | 1 |
| Mouth ulceration | | 2 | | | | | | 2 | 2 |
| **Investigations** | | | | | | | | | |
| High Eosinophils count | | 1 | | | | | | 1 | 1 |

| **Study No.** 376-15 (Adults) | | | **Dose:** 20mg (20mg/5ml) | | | | **Doses:** 1 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Type:** Comparative bioavailability | | | **Subjects:** 28 (27 completed) | | | | | | |
| **Adverse event (Preferred Term)** | **Mild** | | **Moderate** | | **Severe** | | **Total** | | **Total** |
| | R | NR | R | NR | R | NR | R | NR | R+NR |
| - There were no Adverse events reported in this study - | | | | | | | | | |

| **Study No.** 375-15 (Adults) | | | **Dose:** 20mg (20mg/5ml) | | | | **Doses:** 1 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Type:** Comparative bioavailability | | | **Subjects:** 28 (28 completed) | | | | | | |
| **Adverse event (Preferred Term)** | **Mild** | | **Moderate** | | **Severe** | | **Total** | | **Total** |
| | R | NR | R | NR | R | NR | R | NR | R+NR |
| - There were no Adverse events reported in this study - | | | | | | | | | |

| **Study No.** 454-14 (Adults) | | | **Dose:** 10mg (10mg/5ml) | | | | **Doses:** 1 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Type:** Comparative bioavailability | | | **Subjects:** 24 (22 completed) | | | | | | |
| **Adverse event (Preferred Term)** | **Mild** | | **Moderate** | | **Severe** | | **Total** | | **Total** |
| | R | NR | R | NR | R | NR | R | NR | R+NR |
| **General disorders and administration site conditions** | | | | | | | | | |
| Pyrexia | | 1 | | | | | | 1 | 1 |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | | | | |
| Oropharyngeal pain | | 1 | | | | | | 1 | 1 |

| **Study No.** BA 04/07 (Children) | | | **Dose:** 1.5mg/kg/day | | | | **Doses:** 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Type:** Efficacy | | | **Subjects:** 12 (9 completed) | | | | | | |
| **Adverse event (Preferred Term)** | **Mild** | | **Moderate** | | **Severe** | | **Total** | | **Total** |
| | R | NR | R | NR | R | NR | R | NR | R+NR |
| - There were no Adverse events reported in this study - | | | | | | | | | |

R=Related, NR=Not-Related (according to Investigator)

In relation to omeprazole suspension formulations, two strengths of Zegerid Powder for Suspension (unit dose sachet containing either 20 mg or 40 mg omeprazole and 1680 mg sodium bicarbonate) have been marketed in the USA since 2004 (lower strength) / 2005 (higher strength). In addition, two strengths of Zegerid Caps (capsule product containing either 20 mg or 40 mg omeprazole and 1100 mg sodium bicarbonate) have been marketed in the USA since 2006. No specific safety issues have been raised and the adverse event profile (as reflected in the labelling) is in line with that of Prilosec (which was the reference product against which Zegerid was approved) in the USA. Zegerid OTC (capsule product containing omeprazole 20 mg and 1100 mg sodium bicarbonate) has been marketed in the USA since 2010.

The safety experience with Zegerid is particularly relevant in the context of Omeprazole Oral Suspension. The applicant's Omeprazole Oral Suspension [Studies 376-15, 375-15, 454-14], Zegerid Powder for Suspension [Study OSB-IR-06][25] and Zegerid Caps [Studies OME-IR (CAP)-CO1, OME-IR (CAP)-C02][26] have each been shown to be equivalent to Losec / Prilosec in terms of the extent of omeprazole absorption after single dose administration. However, in each of these studies the Cmax of the Omeprazole Oral Suspension test product / the Zegerid test product was higher than that of Losec / Prilosec after single dose administration. A comparison of the Cmax ratios of the investigational and reference products after single dose administration to fasting volunteers in Studies 376-15, 375-15, OSB-IR-06 and OME-IR(CAP)-C01 is of particular value as in each of these studies 20 mg doses of omeprazole were administered to the volunteers.

| Study | Test Product | Reference Product | % Mean Ratio (T/R) of ln (Cmax) (Least Square Means) | 90 % Confidence Interval |
|---|---|---|---|---|
| 376-15 | Omeprazole 4 mg/ml Oral Suspension (5 ml) | Losec Capsules 20 mg | 137.9 | 122.79 - 154.98 |
| 375-15 | Omeprazole 4 mg/ml Oral Suspension (5 ml) | Losec Capsules 20 mg | 144.9 | 128.30 - 163.69 |
| OSB-IR-06 | Omeprazole Sodium Bicarbonate Immediate Release 20 mg Suspension | Prilosec Delayed Release Capsules 20 mg | 160.44 | 140.41 - 183.33 |
| OME-IR(CAP)-C01 | Zegerid Immediate Release Capsules 20 mg | Prilosec Delayed Release Capsules 20 mg | 148.49 | 129.16 – 170.72 |

**Table** 2.5.5.3 | A comparison of the % Mean Ratios (T/R) of Ln (Cmax) of the investigational and reference products in Studies 376-15, 375-15, OSB-IR-06 and OME-IR(CAP)-C01

The summary presented in Table 2.5.5.3 suggests that the Xeolas Omeprazole Oral Suspension test products and the Zegerid test products evaluated in Studies 376-15, 375-15, OSB-IR-06 and OME-IR(CAP)-C01 have similar % mean ratios of Ln(Cmax) *vis a vis* Losec / Prilosec.

**Safety profile of omeprazole in children**

The safety database in children <1 year comprises Xeolas study BA 04/07 (short-term), AstraZeneca study 251 (the main safety/tolerability/efficacy study in this population) along with published studies, together with available post-marketing data.

**Study 251** was a randomized, single-blind, 56 day, safety/efficacy study in paediatric GERD patients 0 – 2 years. This study included patients with a 2-month history of clinically diagnosed GERD-related symptoms. Of the 115 patients randomized, 98 were < 1yr. Patients were randomized to an omeprazole dose of 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg, with omeprazole administered as a bicarbonate suspension. The safety variables included adverse events (AE), clinical laboratory results and physical examinations.

The mean age was 6.3 months and the distribution of males and females at baseline were 43.5% and 56.5%, respectively. ~85% of patients were < 1 year and ~ 59 % of patients were < 6 months.

| | Children Age | | |
|---|---|---|---|
| | 0-6 months | 6-12 months | 12-24 months |
| n = | 68 | 30 | 17 |

**Table** 2.5.5.4 | Summary of Exposure to Study Medication and Demographics in Study 251

| | Patients Randomized into Study (n=115) | | |
|---|---|---|---|
| Dose of study medication | Ome 0.5 mg/kg n=37 | Ome 1.0 mg/kg n=38 | Ome 1.5 mg/kg n=40 |
| Total number of patients exposed to one dose of study medication | 35 | 35 | 36 |
| Maximum number of doses any one patient took | 63 | 61 | 61 |
| Baseline characteristics | | | |
| Mean age (months) | **7.0** | **6.2** | **5.8** |
| Minimum age (months) | 1.1 | 1.3 | 0.7 |
| Maximum age (months) | 21.8 | 20.2 | 17.6 |

106 (92.2%) patients took at least one dose of study medication and are included in the safety analysis. Of this safety population, 83 (78.3%) patients experienced one or more adverse events during the study. 26 of those patients (31.3%) were dosed with omeprazole 0.5 mg/kg, 26 (31.3%) were dosed with omeprazole 1.0 mg/kg, and 31 (37.3%) were dosed with omeprazole 1.5 mg/kg.

There were a total of 215 adverse events in any category and 2 serious adverse events.

Table 2.5.5.5 presents a summary of incidence rates, according to body system classification for an adverse event (AE).

**Table** 2.5.5.5 | Number (%) of Patients with Adverse Events by Body System in Study 251

| Body System | 0.5 mg/kg (n=35) | 1.0 mg/kg (n=35) | 1.5 mg/kg (n=36) | Total (n=106) |
|---|---|---|---|---|
| Patients with >1 Adverse Event | 26 (74.3%) | 26 (74.3%) | 31 (86.1%) | 83 (78.3%) |
| Respiratory System Disorder | 14 (40.0%) | 14 (40.0 %) | 21 (58.3%) | 49 (46.2%) |
| GI System Disorder | 12 (34.3%) | 16 (45.7%) | 18 (50.0%) | 46 (43.4%) |
| Resistance Mechanism Disorder | 10 (28.6%) | 9 (25.7%) | 10 (27.8%) | 29 (27.4%) |
| Skin Appendage Disorder | 7 (20.0%) | 9 (25.7%) | 8 (22.2%) | 24 (22.6%) |
| Body as a Whole | 10 (28.6%) | 7 (20.0%) | 5 (13.9%) | 22 (20.8%) |
| Psychiatric Disorder | 3 (8.6%) | 8 (22.9%) | 3 (8.3%) | 14 (13.2%) |
| Hearing Vestibule Disorder | 2 (5.7%) | 1 (2.9%) | 2 (5.6%) | 5 (4.7%) |
| Central Peripheral Nervous System | 1 (2.9%) | 1 (2.9%) | 0(0.0%) | 2 (1.9%) |
| Platelet Bleed Clot | 1 (2.9%) | 1 (2.9%) | 0(0.0%) | 2 (1.9%) |
| Urinary System Disorder | 1 (2.9%) | 0(0.0%) | 1 (2.8%) | 2 (1.9%) |
| Cardiovascular Disorder | 0(0.0%) | 0(0.0%) | 1 (2.8%) | 1 (0.9%) |
| Liver Biliary System Disorder | 0(0.0%) | 0(0.0%) | 1 (2.8%) | 1 (0.9%) |
| Metabolism Nutrition Disorder | 1 (2.9%) | 0(0.0%) | 0(0.0%) | 1 (0.9%) |
| Muscular Skeletal System Disorder | 0(0.0 %) | 0(0.0%) | 1 (2.8%) | 1 (0.9%) |
| Myo, Endo, Pericardial Valve Disorder | 0(0.0%) | 0(0.0%) | 1 (2.8%) | 1 (0.9%) |
| Neonate Infant Disorder | 0(0.0%) | 1 (2.9%) | 0(0.0%) | 1 (0.9%) |
| Neoplasms | 0(0.0%) | 1 (2.9%) | 0(0.0%) | 1 (0.9%) |
| Vision Disorder | 0(0.0%) | 2 (5.7%) | 2 (5.6%) | 4 (3.8%) |
| WBC & Resistance Disorder | 0(0.0%) | 1 (2.9%) | 0(0.0%) | 1 (0.9%) |

The most frequently occurring AEs were related to the Respiratory System, the Gastrointestinal System (GI), and the Resistance Mechanism System with total percentages of 46.2%,43.4%, and 27.4%, respectively (Table 2.5.5.5). Respiratory infection (23.6%,25 out of 106 patients) and rhinitis (14.2%, 15 out of 106 patients) were the most frequently occurring AEs within the Respiratory System. In the GI System, diarrhoea (22.6%, 24 out of 106 patients) and constipation (12:3%, 13 out of 106 patients) were the most frequently occurring AEs. Otitis media (22.6%, 24 out of 106 patients) was the most frequent AE in the Resistance Mechanism System.

Five patients (two patients who were less than 12 months old) reported SAEs. These were all infections; urinary tract infection, pneumonia, pertussis, lymphadenitis, bronchiolitis with croup. The investigators considered the SAEs were unlikely to be related to the study drug but were probably related to the natural history and/or disease related events in this population. In addition, all SAEs were either mild or moderate in intensity.

A total of 6 patients discontinued from the study because of adverse events. The 6 patients had 11 adverse events: 10 of the 11 adverse events were considered possibly treatment related. The adverse events included exacerbation of GERD symptoms, increased irritability, vomiting, rash, repetitive motion behaviour, and abnormal crying.

No deaths occurred during this study. There were no clinically important findings or trends in haematology, clinical chemistry, urinalysis, vital signs, or physical examination (including medical history) observed across or within the omeprazole treatment groups.

The majority of the AEs were either mild or moderate in intensity and there was no apparent dose relationship to occurrence of AEs. The AEs that occurred most frequently were considered similar to typical symptoms observed in a general population of paediatric patients.

**Study 250** was a pharmacokinetic single dose study in 25 paediatric patients aged 0.5 – 24 months in need of acid suppression therapy. The mean age was 8.7 months. 12 patients were < 6 months and 17 patients were < 12 months. Doses used were 0.5 mg/kg-1.5 mg/kg with omeprazole administered as a bicarbonate suspension (i.e. same formulation as study 251).

Nineteen patients were included in the safety population. During the treatment period, there was a total of 18 AEs in any category. Accordingly, the overall safety database for the main studies conducted with the reference product administered as a bicarbonate suspension involved 131 patients (106 in Study 251 and 19 in Study 250) who were 0.5 to 24 months old and took at least one dose of study medication. For Studies 250/251, the maximum exposure was 1.5 mg / Kg omeprazole P.O. once daily for 8 weeks in 36 subjects. In general the AEs reported from this population were consistent with the known safety profile of omeprazole in the adult population. No new safety signals were identified in the paediatric population of 0 to 2 years old. Based upon these results, it was concluded that omeprazole administered as a bicarbonate suspension was generally well tolerated in the 0 - 24 months paediatric population.

**Study I-678**Error! Bookmark not defined. was a long-term study. Sixty-five patients were enrolled, all were treated with omeprazole, and are included in the safety analysis. In this study (healing plus long-term treatment up to 24 months) 472 Adverse Events (AE) were reported in 55 patients. Various infections (respiratory infection, otitis media, pharyngitis etc.) and gastrointestinal symptoms were the most commonly reported events.

63 serious adverse events (SAEs) in 26 patients were recorded during the study. There were 28 reports of SAE during the healing phase and 35 (one of them fatal) during the maintenance phase. Pneumonia, haematemesis, convulsions/convulsions aggravated, gastroenteritis and vomiting were reported for three or more of the patients. None of these episodes were considered to be related to omeprazole treatment.

One patient died of cardiac arrest, but this serious adverse event was not considered causally related to omeprazole therapy. This study provides information about iron absorption, gastrin levels, vitamin B12 levels and the histopathology of the ventricular mucosa besides the reported adverse events. The PdAR compared the AEs reported in the studies performed in children 2-16 years with those performed in children 0-2 years, commenting that the only apparent difference was the absence of reports of headache in the younger patients, possibly due to the difficulty reporting such AEs in the youngest, including pre-verbal patients.

For study HASSALL/I-678 the AE information is presented by age group (<2 years and >2 years) and by treatment phase (healing or maintenance phase). There was no apparent difference between the two age groups in number or category of reported AEs during the healing or maintenance phase.

Four SOCs (System Organ Class) seem to be more common in the youngest age group when comparing to older children and adults. These four SOCs are: Congenital, familial and genetic disorders, pregnancy, puerperium and perinatal conditions, Surgical and medical procedures and Psychiatric disorders. For the SOCs Ear and labyrinth disorders, Musculoskeletal and connective tissue disorders, Reproductive system and breast disorders, Skin and subcutaneous tissue disorders and vascular disorders, there seems to be fewer events in both the youngest age groups and children of all ages when comparing to adults.

In summary, no apparent safety concerns have been identified in the pediatric population, but the number of small children, and the duration of the studies, is limited.

***Hassal*** et al [50] reported on a cohort of 166 paediatric patients who received long term (>9 months) PPI treatment (predominantly omeprazole) for severe reflux, generally associated with GERD-predisposing conditions. The mean age at initial prescription was 7.8 years. Approximately 13% of the patients were < 2 years at index prescription. The median duration of treatment was 3 years and one patient had a treatment duration of 11 years. Most children had underlying GERD-predisposing disorders such as cerebral palsy and other neurological

disorders or syndromes. The authors noted that PPIs were highly efficacious in these severely affected patients as confirmed by symptom resolution or significant decrease in symptom frequency. There were only 6 AEs reported judged as potentially related to PPI treatment and these occurred in only 4 patients (2.4% of treated patients, 6/528 patient years). No serious adverse reactions were reported and for omeprazole diarrhoea, skin rash, agitation/irritability and nausea/vomiting were reported (all in children aged 12-16).

None of the other studies discussed in the PdAR reported any safety signals or special concerns relating to omeprazole in the paediatric setting.

**Specific Paediatric Adverse Events from the literature: Omeprazole and discolouration of the gastric contents**

A Lareb publication[Error! Bookmark not defined.] describes a small number of reports from the Netherlands of gastric content discolouration in children (< 1 year) associated with the use of omeprazole. The stability of omeprazole is pH dependent. Below pH 4 omeprazole degrades rapidly to a number of compounds, including red/dark purple materials. It is for this reason that omeprazole is formulated as a buffered suspension in the current application.

A number of the cases related to the insertion of beads (after opening of the capsules) into the buccal space of the infant or dissolving MUPS tablets in water to facilitate administration. Lareb concluded that dispersion in water or insertion of the coated pellets can lead to degradation of the enteric coat rendering the omeprazole available for degradation. The phenomenon might be compounded by delayed gastric emptying of pellets in critically ill children. Apart from highlighting the real problems for parents/carers of administering current formulations (capsules/tablets) to children, the gastric content discolouration is evidence of pre-absorption omeprazole degradation which would result in lower bioavailability and reduced effectiveness of the treatment[51]. The Lareb report highlights that similar problems are likely with extemporaneous liquid formulations prepared from solid dose formulation of omeprazole.

Omeprazole Oral Suspension is a buffered oral suspension. Comparative bioavailability testing has shown equivalent bioavailability to capsules containing enteric coated granules / pellets, confirming that the formulation provides protection from degradation. Similarly, the formulation does not involve pellets/beads that can be retained in the stomach. Accordingly, the potential for gastric content discolouration with omeprazole oral suspension is considered to be low.

**Post-marketing experience in children**

As the PdAR mentions, the total number of exposed children is not known and cannot readily be estimated using sales or consumption data. From a review of publications, including dispensing data, it is apparent that the requirements for liquid formulations is largely met by the use of extemporaneous formulations via manipulation of existing formulations and by the use of unlicensed medicines or "specials".

The use of omeprazole in children began in cases of emergency and severely ill children a long time ago. In the USA, a 2010 FDA review of PPI utilization concluded that between 2002 - 2009 in the age group 0-17 years, except for classically neonatal diseases, there were no major differences in AEs between the paediatric age groups, also when compared with adult AEs. Similarly, another FDA review was carried out in 2013 in the ≤ 1 year paediatric age subgroup. Table 2.5.5.6 below lists the most commonly reported AEs (≥ 5 patients). With the exception of "Off label Use", the review concluded that most of these common AEs were most likely to be related to the natural history and/or disease-related events in the patient population. The FDA

review concluded that no new safety concerns were raised during the review of the post-marketing safety data.

**Table** 2.5.5.6 | FDA Post Marketing Reports: Most frequently Reported AEs in Children ≤1 year [n >5]

| Preferred Term | No. of patients |
|---|---|
| Vomiting | 34 |
| Off label use | 25 |
| Diarrhoea | 12 |
| Drug ineffective | 12 |
| Neutropenia | 8 |
| Regurgitation | 8 |
| Faeces discoloured | 7 |
| Wrong technique in drug usage process | 7 |
| GERD | 5 |
| Rash | 5 |

According to the PdAR, most of the spontaneously reported adverse events were non-serious. A majority of all reports, where outcome is known, were either resolved or improved. The types of events and the relative number of events were similar in children and in adults for most of the SOCs. However, nervous system disorders and psychiatric disorders for example seem to be more common in children. Also, these two types of disorders seem to be slightly more common in the youngest children (0 - 2 yrs). Skin events seem to be less common in children.

The overall conclusion is that omeprazole is safe to use in children but that dose recommendations should be followed, particularly in young children.

**Special warnings and precautions for use**

The SmPC for the reference product includes the following warnings that are generally related to the PPI class, together with appropriate precautions:

- Exclusion of malignancy in the presence of any alarm symptoms, as PPI treatment may alleviate symptoms and delay diagnosis.
- Co-administration of atazanavir with proton pump inhibitors is not recommended.
- As with all acid-blocking medicines, potential for reduced absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria.
- Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered.
- An interaction is observed between clopidogrel and omeprazole: concomitant use of omeprazole and clopidogrel should be discouraged.
- Hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics).
- Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors.
- Subacute cutaneous lupus erythematosus (SCLE): PPIs are associated with very infrequent cases of SCLE.
- Interference with laboratory tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole

treatment should be stopped for at least 5 days before CgA measurements (see Section 2.5.3).
- Although some children with chronic illnesses may require long-term treatment, it is not recommended.
- Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.
- As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

**Summary of safety of omeprazole in children and adults – SmPC recommendations**

Omeprazole is one of the most widely prescribed and used molecules world-wide, with more than 25 years experience in the clinic. The safety database is considerable including extensive clinical studies and post-marketing data. In adults, the availability of omeprazole as an OTC product in Europe/US is testament to its established safety profile. There are no particular safety concerns.

With respect to adults, the safety information included in the reference product SmPC is comprehensive and up-to-date.

With respect to the paediatric population, the following text is currently included in the SmPC of the reference product, and refers to the 250, 251, I-678 and Hassal studies covering the span of children's ages:

*"The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long term data regarding the effects of omeprazole treatment on puberty and growth."*

It is considered that the above text is satisfactory with respect to the paediatric population and no changes are proposed.

## MODULE 2.5 – CLINICAL OVERVIEW

### 2.5.6 BENEFITS AND RISKS CONCLUSIONS

Omeprazole is a well-established active substance and has been approved in Europe since 1988. Extensive clinical experience with omeprazole is considered to have demonstrated the therapeutic value of the active substance.

GERD is a condition with similar pathophysiology across all age groups. The course of GERD and the effects of omeprazole are similar in adults and paediatric patients. Omeprazole, the most commonly prescribed treatment for GERD, is well established as an effective treatment option for both adults and children.

*Omeprazole Oral Suspension 2mg/ml and 4mg/ml* is an adapted galenical form especially suited to paediatric patients and has been specifically designed as a dosage form for patients who are unable to readily take solid dosage forms. An important feature of the formulation is that it is suitable for dose titration on a weight-adjusted basis, and can facilitate the administration of doses less than 10mg. In the development of the formulation, the requirements and features appropriate to the paediatric population have been taken into account, including a low dosing volume.

The pharmacokinetics and pharmacodynamics of omeprazole have been well characterized in adults and in the paediatric setting. A well-designed and executed relative bioavailability study has confirmed that *Omeprazole Oral Suspension* can be considered to have comparable bioavailability to the reference product, *Losec capsules*; Omeprazole Oral Suspension was equivalent to Losec capsules in terms of extent of absorption/availability of omeprazole. Furthermore, the application includes a small clinical study showing efficacy in infants < 3 months old, and comparable bioavailability has been shown to the clinical formulation used in the main paediatric clinical studies; Omeprazole Oral Suspension was equivalent to Losec capsules in terms of $C_{max}$ and extent of absorption/availability of omeprazole. The application contains an adequate review of published clinical data including data on similar formulations.

The pharmaceutical and PK/clinical data presented in the application fulfils many of the missing requirements outlined in a previous review of omeprazole in the paediatric setting. The bridging pharmacokinetic and clinical data provided enables the translation of existing evidence into clinical practice.

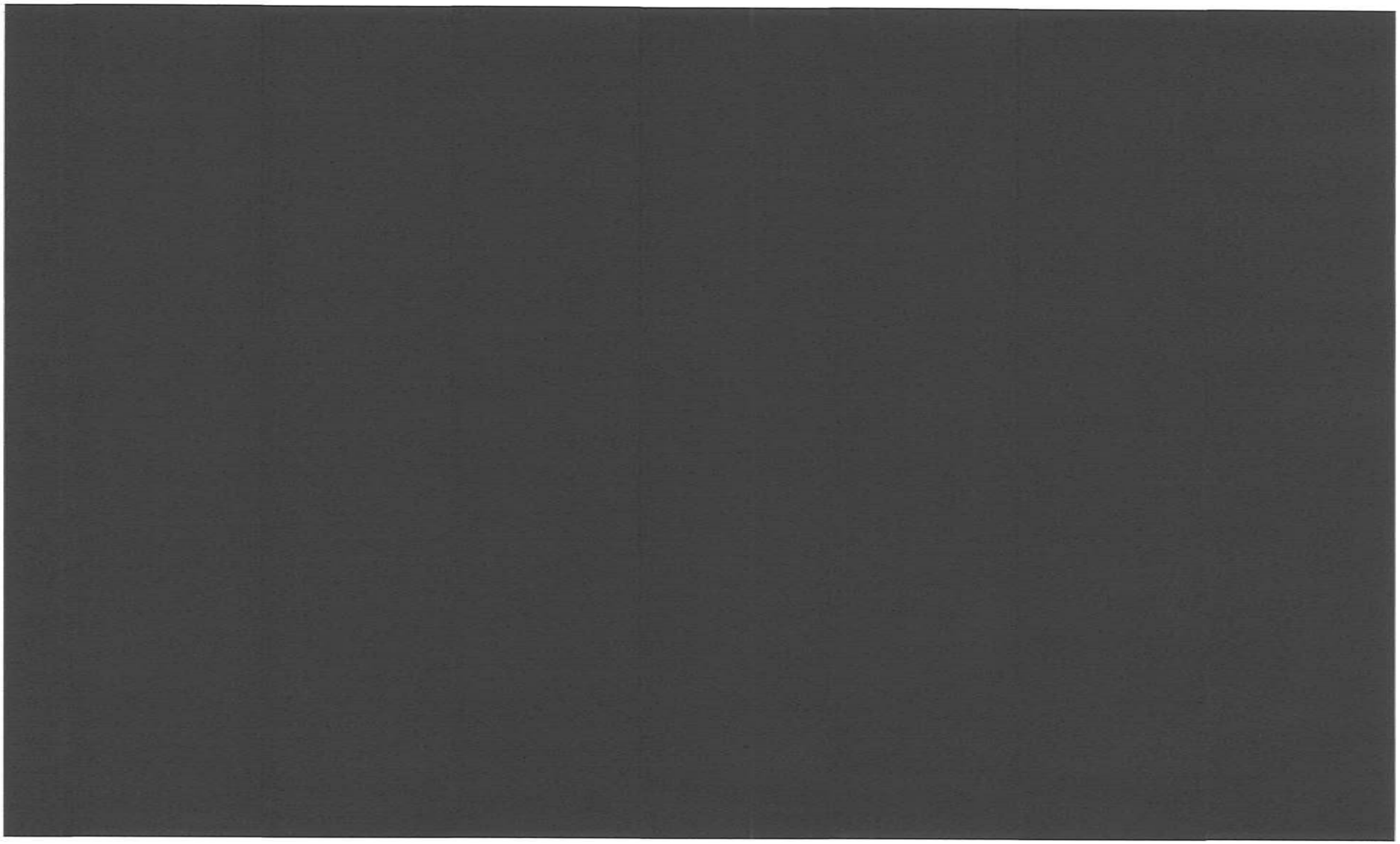
Extensive long-term experience with the molecule in a variety of formulations and including OTC use (in adults) have not revealed any special concerns in either adults or children. The safety profile of omeprazole is well established.

In conclusion, the availability of an instant release oral suspension formulation of omeprazole offers important potential benefits for patients, carers and physicians. Firstly, the dosage form is suitable for patients that are unable to take capsules/tablets. Secondly, the availability of the new dosage form extends the range of patients that can benefit from treatment with the molecule, including children requiring a dose < 10mg and tube fed patients. Finally, Omeprazole Oral Suspension represents a product with established stability, suitable organoleptic characteristics, an appropriate presentation and proven bioavailability, so that patients, carers and physicians do not need to rely on extemporaneous or manipulated formulations with uncertain quality or bioavailability. The risk benefit is, therefore, considered to be positive.

***Omeprazole Oral Suspension 1mg/ml*** is an additional strength especially suited to younger paediatric patients. [redacted]. In the development of the formulation, the requirements and features appropriate to this paediatric sub-set population have been taken into account, including a low dosing volume. This new strength extends the range of patients that can benefit from Omeprazole Oral Suspension.

**MODULE 2.5 – CLINICAL OVERVIEW**

# 2.5.7 APPENDICES



**MODULE 2.5 – CLINICAL OVERVIEW**

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