

**Paediatric Public Assessment Report
EU Worksharing Project**

**Losec/Losec MUPS
(omeprazole)**

Marketing Authorisation Holder: AstraZeneca

Rapporteur:	Sweden
Co-Rapporteur:	Portugal
Paediatric assessment Procedure start date:	February 9, 2007
End of procedure	November 1, 2007

I. ABBREVIATIONS

AE	Adverse Event
AUC	Area under the curve
AUC(0-t)	Area under the plasma concentration-time curve to the last detected value
CL	Clearance
CL _R	Renal clearance
C _{max}	Maximum plasma concentration
EU	European Union
FDA	Food and Drug Administration
Helicobacter	
Pylori	HP
MAH	Market Authorisation Holder
MPA	Medical Products Agency (Sweden)
PK/PD	Pharmacokinetics/Pharmacodynamics
PP	Per protocol
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time to maximum plasma concentration

SCOPE OF THE ASSESSMENT

This is a paediatric data assessment for Losec through worksharing with Sweden as Rapporteur and Portugal as Co-Rapporteur.

The MAH of Losec was requested to submit paediatric data available which had not been submitted to all EU member states.

The MAH was also asked to propose a SPC text supported by the new data.

Some of the submitted documentation might have been submitted to some of the EU member states before.

The goal of the worksharing is to agree on an SPC text. The MAH is thereafter asked to submit national type II variations to all member states to change the national SPCs in the agreed way. If suitable, the SPC of generic products should in addition be changed accordingly.

FINAL RECOMMENDATION OF THE PROCEDURE

Based on the review of the paediatric data on pharmacokinetics, safety and efficacy, for Losec (omeprazole), approval is recommended from the age of one year in children weighing at least 10 kgs as well as eradication of helicobacter pylori from the age of four. As a result of the response assessment round, the following text is proposed for inclusion in the national SmPCs through variation procedures.

Final agreed SPC text:

Section 4.1 Indications

Children over 1 year of age and ≥ 10 kg: Reflux oesophagitis. Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

Section 4.2 Posology and method of administration

Reflux oesophagitis

The treatment time is 4-8 weeks

Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease

The treatment time is 2-4 weeks. If symptom control has not been achieved after 2-4 weeks the patient should be investigated further.

The dosage recommendations are as follows:

Age	Weight	Dosage
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≥ 1 year of age	10-20 kg	10 mg once daily.
<i>The dosage can be increased to 20 mg once daily if needed.</i>		

≥ 2 years of age	> 20 kg	20 mg once daily.
<i>The dosage can be increased to 40 mg once daily if needed.</i>		

Children over 4 years of age

In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori.

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

The treatment should be supervised by a specialist.

Weight

Dosage

15-≤30 kg

Combination with two antibiotics: Losec Mups 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7,5 mg/kg body weight are all administrated together 2 times daily for 1 week

30-≤40 kg

Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated 2 times daily for 1 week.

>40 kg

Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated 2 times daily for 1 week.

Section 4.4 Special warnings and precautions for use

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Section 4.8 Undesirable effects

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 yrs 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.

Section 5.1 Pharmacodynamic properties

Paediatric data: In a non-controlled study in children (1 to 16 yrs of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0-24 months with clinically diagnosed GERD 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.

Eradication of Helicobacter pylori in children:

A randomised, double blind clinical study (Héliot study) has concluded to the efficacy and an acceptable safety for omeprazole associated to two antibiotics (amoxicilline and clarithromycine) in the treatment of Helicobacter pylori infection in children of 4 years old and above with a gastritis: Helicobacter pylori eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicilline + clarithromycine versus 9.4% (3/32 patients) with amoxicilline + clarithromycine. However, there was no evidence of clinical benefit demonstrated regarding dyspeptic symptoms. This study does not support any information for children aged less than 4 years old.

Section 5.2 Pharmacokinetic properties

During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

II. FIRST ROUND, DRAFT ASSESSMENT REPORT (PPDAR)

II.1 Recommendation

Based on the review of the paediatric data on pharmacokinetics, safety and efficacy, for Losec (omeprazole), approval is recommended from the age of one year in children weighing at least 10 kgs as well as eradication of helicobacter pylori from the age of four.

Scope of the assessment

Losec is authorised in most countries in Europe for treatment of severe reflux oesophagitis from age one year. The documentation assessed considers available data to support inclusion of

- Extension of dose recommendation in children to less than one year.
- Helicobacter pylori eradication for children from four years
- Oral solution prepared from Losec iv for infusion or injection 40 mg

The applicant proposes the following SPC text:

“LOSEC MUPS tablets are recommended to be given in the morning and swallowed whole with half a glass of water. The tablets/capsules must not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food

LOSEC MUPS tablets

Break the MUPS tablet and disperse it in a spoonful of non-carbonated water - if so wished, mix with some fruit juices or applesauce. The dispersion should be taken immediately (or within 30 minutes). Always stir just before drinking. Rinse it down with half a glass of water. DO NOT USE milk or carbonated water. Ingest without chewing the enteric-coated pellets.

LOSEC capsules

The capsule can be opened and the contents swallowed directly with half a glass of water or after mixing the contents in a slightly acidic fluid eg, fruit juice or applesauce, or in non-carbonated water. The dispersion should be taken immediately (or within 30 minutes). Always stir just before drinking. Rinse it down with half a glass of water. Alternatively patients can suck the capsule and swallow the pellets with half a glass of water. Ingest without chewing the enteric-coated pellets.

For patients who cannot drink or swallow semi-solid food and for intubated patients

It is recommended to use an oral solution prepared from Losec IV for infusion or injection 40 mg.

Solution for oral use

Oral use of Losec IV for infusion or injection is recommended for children who require a lower dose than 10 mg, for patients who cannot use Losec capsules or dispersed Losec MUPS tablets and for intubated patients. For practical information regarding preparation and handling of solution for oral administration, see separate handling instructions.

Children

For use in children 2 years and older the recommended dose is:

Weight	Dosage
10-20 kg	LOSEC/LOSEC MUPS 10 mg once daily
>20 kg	LOSEC/LOSEC MUPS 20 mg once daily

If needed the dose may be increased to 20 mg and 40 mg respectively.

For use in children 0-24 months the recommended dose is:

Weight	Dosage
10-20 kg	LOSEC/LOSEC MUPS 10 mg once daily

If needed the dose may be increased to 20 mg

<10 kg	1 mg/kg/day
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For children 0-3 months a dose of 0.5 mg/kg/day may be sufficient

Helicobacter pylori eradication for children from 4 years

Weight	Dosage
15-30 kg	LOSEC/LOSEC MUPS 10 mg, amoxicillin 25 mg/kg, and clarithromycin 7,5 mg/kg, all twice a day for one week.
30-40 kg	LOSEC/LOSEC MUPS 20 mg, amoxicillin 750 mg and clarithromycin 7,5 mg/kg, all twice a day for one week.
>40 kg	Dosage as in adults”

II.2 Scientific discussion

II.2.1 Quality aspects

Stability data generated on Losec powder for solution for infusion is presented. The drug product was reconstituted with purified water and stored in a refrigerator for 8 days followed by six hours storage at room temperature in a syringe. The samples were then diluted with a 5% sodium bicarbonate solution (final concentrations of 0.38 mg/ml and 0.67 mg/ml) and then analysed after storage at room temperature for 1 hour. Results from visual inspection, pH measurements, HPLC assay and -related substances analysis demonstrates a good stability. It is concluded that Losec powder for solution for infusion is stable under the conditions described in the report: Losec powder for solution for infusion can be stored in a refrigerator for up to 8 days and after that stored at room temperature for up to 6 hours. This solution must be used within one hour after

dilution with 5% sodium bicarbonate solution and stored at ambient room temperature exposed to normal indoor light.

In addition a study on acid resistance after dispersion of Losec capsules, Prilosec capsules and Losec MUPS tablets in various fluids is presented. In the study gastro-resistant pellets and Losec MUPS were studied for the enteric coating function after dispersion in different fluids (e.g. different fruit juices, apple sauce, tap water, milk, spring water and carbonated water). The functionality of the gastro-resistant coating was found acceptable in acidic fruit juices, apple sauce and non-carbonated water.

Assessor's comment: *There are two separate issues to consider.*

The first issue considers the pharmaceutical stability.

The second issue concerns the principal question whether it is acceptable to have the same labelling for an oral and a parenteral drug product.

- 1. In Sweden two different parenteral products are approved with slightly different formulations. It is not apparent which formulation the stability was conducted on. The stability data presented is acceptable, however microbiological data is missing and the effect of "normal indoor light" has not been demonstrated as presented in the report. No formal handling instructions are provided in the core SmPC presented. However it is assumed that the handling instruction presented in the stability report is applicable. It is stated that the reconstitution of the product shall be conducted using a syringe to inject the purified water in order to protect the drug product from the carbon dioxide content in the air.*
- 2. In the previous national procedure for oral use of the parenteral formulation it was considered not acceptable to have an oral and parenteral product with the same label. On the contrary, it is very important that the labelling for the different pharmaceutical forms is clearly distinguishable. A reconstituted vial with oral solution must not be mistaken for a reconstituted vial with solution for infusion. The proposed handling instructions would allow an un-sterile product to be stored for a period of more than a week with a label which also states it to be a parenteral product. This proposed variation has not provided any new information compared to the previous variation submitted to the Swedish MPA and based on the submitted information the conclusion remain that a drug product which is labelled for both parenteral and oral use is not acceptable. This is a major deficiency.*

It should be clarified which drug product was included in the oral solution stability study. Microbiological data for the storage time of the re-constituted solution should be provided. The light conditions for the product in the syringe and the final sodium bicarbonate solution during the study should be described. Additional data supporting the statement regarding exposure to normal indoor light should be submitted if applicable. A clarification regarding the carbon dioxide effect on the reconstituted product shall be provided, especially in the view that the solution is further diluted with sodium carbonate solution prior to administration.

II.2.2 Non-clinical aspects

Not applicable

II.2.3 Clinical aspects

II.2.3.1 Clinical pharmacology

Pharmacodynamics

Study Q1 (Study 292) (included in previous submission)

This was a multicenter, retrospective, multiple dose study and the purpose was to determine the esophageal and/or gastric pH profile after multiple doses of omeprazole in neonates and infants, aged 0 months to 24 months at the time of the 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. The formulation used was mainly omeprazole enteric coated granulae from the capsule suspended in 8.4 sodium bicarbonate solution. The mean time between first and second pH assessment was 8.2 weeks.

TABLE 4
Summary Statistics on the Fraction (%) of Time pH<4.0 in Esophageal pH
All Esophageal Patients

	At 1 st pH Assessment	At 2 nd pH Assessment	Change in the Fraction of Time pH<4.0
n	43	43	43
Mean	12.5	3.8	-8.7
p-value ^a	--	--	≤0.001
Median	10.8	1.5	-6.8
SD	9.3	5.7	11.2
Minimum	2.8	0.0	-50.6
Maximum	50.8	30.0	24.4

^a Obtained from paired t-test comparing the values of the 1st pH assessment to the value of the 2nd pH assessment

Reference: Section 14.2, Table 14.2.1 and Table 14.2.2.

The conclusion from this study was that omeprazole was effective in treating acid reflux in this population. No safety data was collected.

Assessors comment: *Although poorly designed, this study clearly indicates that omeprazole is effective in raising the intra-esophageal pH in this population. This is in line with data from older children, adolescents and adults. However, the formulation used was mainly omeprazole enteric coated granulae from the capsule suspended in 8.4 sodium bicarbonate solution, which is questioned in this AR.*

Study A3 (protocol 250)

This was a single-dose pharmacokinetic study where a few patients (n=12) was assessed for pharmaco-dynamic parameters as well. From the pH assessment prior to dosing, the fraction of time esophageal pH was less than 4.0 decreased on average from 4.8% to 2.7%, and from 13.2% to 6.8%, for the 1.0 mg/kg and 1.5 mg/kg treatment group, respectively. However, only a third of the patients had evidence of GERD, defined as the fraction of time esophageal pH was less than 4.0 for more than 6% of the time, indicating that the average may not be clinically meaningful. Similarly, the fraction of time gastric pH was less than 4.0 decreased on average from 64.2% to 42.4%, and from 58.0% to 46.2%, for the 1.0 mg/kg and 1.5 mg/kg treatment group, respectively. Statistical significance was observed only for the 1.0 mg/kg treatment group ($p \leq 0.2$)

Assessors comment: *The result indicates that omeprazole raises intra-esophageal pH although in this study only significant for the 1.0 mg/kg treatment group.*

Pharmacokinetics

General Pharmacokinetic properties of omeprazole

Omeprazol is a racemic drug where both enantiomers are active. The pharmacokinetics is stereoselective and dose-dependent. The S-enantiomer (=esomeprazole) is metabolised by CYP3A4 and CYP2C19 (approximately 1:1 during 40 mg qd treatment). S-omeprazol inhibits its own CYP2C19 catalysed metabolism. Thus, under single-dose conditions the contribution of CYP2C19 is higher. The R-enantiomer appears to be metabolised to a relatively higher extent by CYP2C19 but in presence of the S- and especially at multiple dose conditions, this contribution may be less than earlier thought. CYP2C19 is absent in 3% of Caucasians and 15% of Asian origin.

Comparison between clinical study formulations and other formulation issues

Study 213 – Comparison between modes of administration used in clinical studies

This study was a bioequivalence study of a single 20 mg dose administered as an intact capsule and an open capsule mixed with one tablespoon of applesauce. The capsules contain enteric coated granules of omeprazole. The study was performed in **adult** healthy volunteers under fasting conditions. Blood samples were drawn 0-12 hours post-dose. Plasma was analysed for omeprazole using LC/MS/MS by MSD Harris, Lincoln, Nebraska. The performance of the method appears satisfactory according to the original method validation. No within-study validation was presented. The treatments were bioequivalent with respect to $AUC_{0-\infty}$ but C_{max} was somewhat lower for the open capsules (Table 4).

Table 4 Results of the bioequivalence study

	$AUC_{0-\infty}$ ng*h/ml	C_{max} (ng/ml)	T_{max} (h)	$T_{1/2}$ (h)	90%CI $AUC_{0-\infty}$	90%CI C_{max}
Intact capsule	603±892	282±208	1.50 (0.75-6.00)	0.97±0.52	0.96 (0.91-1.02)	0.75 (0.67-0.84)
Open capsule	610±900	229±200	2.00 (0.75-4.50)	0.97±0.49	-	-

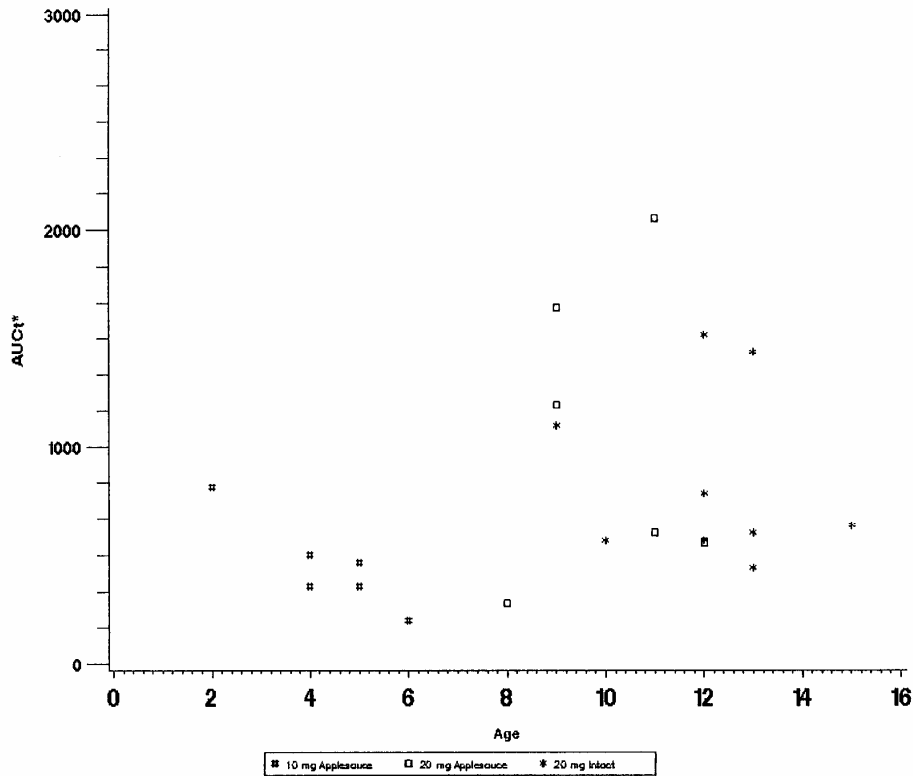
Clinical pharmacokinetic studies in paediatric patients

No new pharmacokinetic studies have been submitted since the national application in 2003. The studies submitted are described below.

Study A1 (Protocol 212).

In this study the pharmacokinetics of omeprazol was studied after a single dose of 10 and 20 mg as capsules in patients weighing ≤ 20 kg and >20 kg respectively. Twenty-four patients aged from **2 to 15** years were included in the study. The gender-distribution was 1:1. The 10 mg dose was administered as granules from opened capsule mixed with applesauce. The 20 mg dose was administered as intact capsules (n=10) or as granules from an opened capsule mixed with applesauce. Blood samples were taken for 6 hours post-dose. In total 8 samples were drawn. The concentration was measured with LC/LS/LS. A plot of the observed dose and weight normalised AUC_{0-t} vs. age is presented below. In this figure, two patients with higher AUCs than the others were excluded as they were considered to be "outliers". These patients had an AUC_{0-t} of 5451 and 7916 $ng \cdot h/ml$ and were 8 and 2 years old, respectively, and should be taken into consideration.

Figure 1 AUC_{0-t} normalized for dose and bodyweight vs. age



A summary of the pharmacokinetic parameters is presented in table 1 below:

Table 1

	Weight kg	Age yrs	mg/kg	AUC_{0-t} $ng \cdot h/ml$	$AUC_{0-\infty}$ $ng \cdot h/ml$	AUC_{0-t}^*	$AUC_{0-\infty}^*$	Cmax ng/ml	$T_{1/2}$ hrs
N ^a	23	23	23	23	16	23	16	23	16
Mean	35	9.4	0.55	709	759	1308	1199	354	0.94
SD	16	3.6	0.16	1001	1063	1801	1303	394	0.25
Median	33	10.0	0.53	366	405	605	746	198	0.91
Min	11	2.0	0.27	106	111	202	211	92	0.55
Max	75	15.0	0.91	4361	4551	7916	5689	1813	1.45

^a it was only possible to calculate $t_{1/2}$ in 16 subjects

* AUC_{0-t} and $AUC_{0-\infty}$ denotes dose and weight normalised values ie $AUC/dose(mg)/weight$ (kg)

Assessors comment:

In this study and in study A2 a total of 11 children were younger than 8 years and 9 patients weighed less than 20 kg. Judging from the scatter plot, it seems that younger children (2- 6 years of age) may have higher clearance per weight (or lower bioavailability) of omeprazole than older children. This is as expected. As the doses used in this study were the ones applied for, it is useful to have a figure presenting the individual non-normalised exposure vs. age. Such a plot was submitted in the response round of the national procedure. The plots indicated that the exposure (AUC and Cmax) was similar over the studied age/weight range (2-15 years and 11-75 kg). However, it should be remembered that only 2 patients (and only one in the plot) was <4 years. The applicant is asked to submit the plots requested to the MS of this procedure.

Study A2 (protocol no 245)

Study A2 was a multiple-dose study in 38 paediatric **healthy volunteers** from **2 to 16** years of age. The study was performed in a CRO, MTRA in Natrick, Massachusetts. Informed consent was obtained from the parent/guardian as well as assent from the child "when appropriate". Omeprazole 10 or 20 mg q.d. depending on bodyweight (10 mg to patients weighing ≤20 kg and 20 mg to patients weighing >20kg), was administered as a capsule or as open capsule in apple sauce (depending on the child's ability to swallow capsules) for 5 days. Blood samples were drawn for 6 hours post-dose on the first and last treatment day. The subjects were fasting or roughly fasting (if necessary a liquid low-fat meal was given at least 2 hours before dosing) until 2 hours after drug administration. The analysis of omeprazole was performed by MDS Harris laboratories. Omeprazol was again analysed with LC/MS/MS. Prestudy validation results for the analysis was submitted. The performance of the method appears satisfactory. The majority of subjects received a 20 mg dose. Only 5 of 38 subjects received 10 mg q.d. Two subjects were excluded from the pharmacokinetic calculations due to uncertainties in the sample IDs. The results are presented in table 2 below.

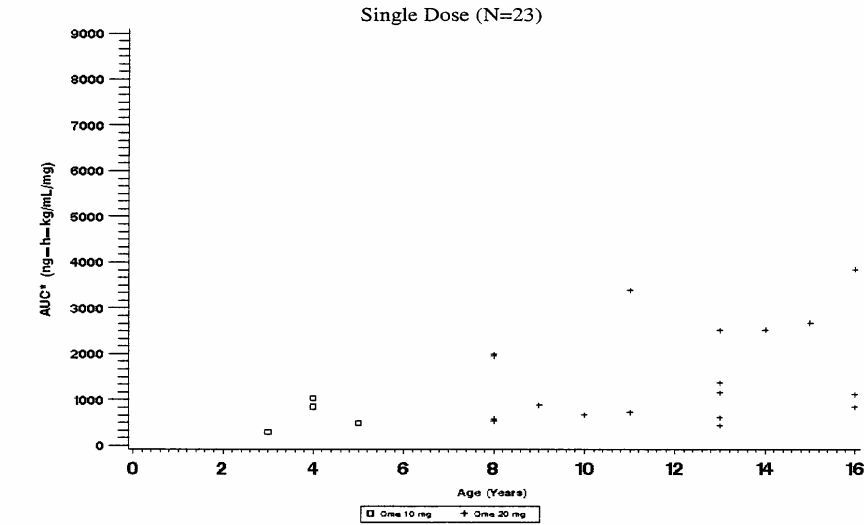
Table 2

	Single dose				Multiple dose			
	<i>AUC_{0-∞}</i> ng/ml	AUC _{0-t} ng/ml	Cmax ng/ml	T1/2 hrs	<i>AUC_{0-∞}</i> ng/ml	AUC _{0-t} ng/ml	Cmax ng/ml	T1/2 hrs
10 mg								
N	4	4	4	4	2	4	4	2
Mean	675	385	222	1.09	1185	538	328	0.62
SD	331	224	130	0.22	169	263	191	0.21
Median	674	368	174	1.09	1185	544	360	0.62
Min	312	158	131	0.89	1065	227	181	0.48
Max	1038	647	408	1.29	1304	837	412	0.77
20 mg								
N	19	32	32	19	23	32	32	23
Mean	1515	507	275	1.04	2952	996	500	1.03
SD	1040	373	197	0.36	2170	814	368	0.24
Median	1115	386	215	1.00	2371	633	374	0.97
Min	436	63	21	0.65	555	143	89	0.64
Max	3853	1251	886	2.27	8468	3134	1412	1.56

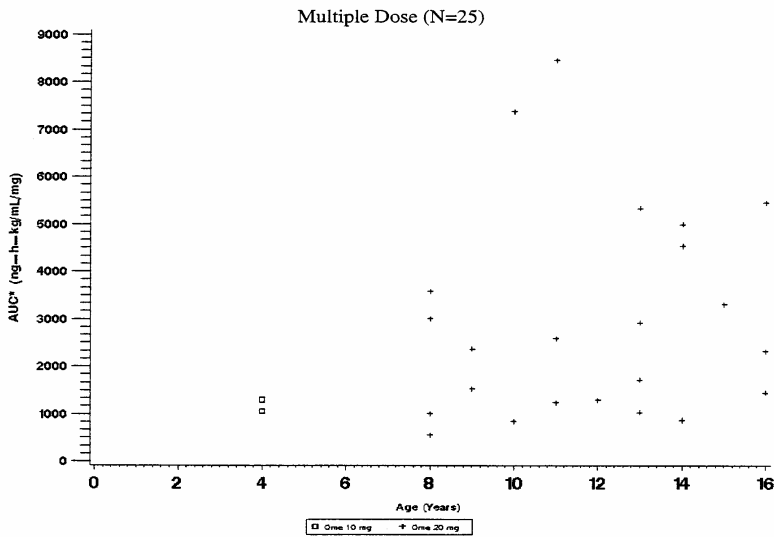
AUC_{0-∞} (in italics) denotes dose and weight normalised values ie AUC/dose(mg)/weight (kg)
This should reflect 1/CL_{oral}/kg.

Scatterplots of dose and weight normalised AUC_{0-t} are presented below.

Figure 2a,b Dose and weight normalised AUC versus age - single and multiple dose



There are 2 AUC+ values for age 9.



Assessors comment:

The inter-individual variability appears very high in this study. As before, plots of actual AUCs obtained with the different doses were requested in the national procedure and the applicant is asked to also submit the plots to the MS of the present procedure. The plots indicated that the exposure (AUC and Cmax) is similar over the studied age/weight range. It is noted that only very few children below eight years of age were included in the plots. Judging by the tabulated individual AUC_{0-t} values, the exposure was slightly lower in the two children not included in the plot.

Study A3 (Protocol 250)

Study A3 was a randomised 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. The omeprazole dose was 0.5 (n=2), 1.0 (n=13) or 1.5 (n=15) mg/kg and was administered (with a syringe) as an **open capsule suspended in 8.4% sodium bicarbonate** (2 mg/ml in 8.4% sodium bicarbonate solution). The maximum dose was 20 mg. Blood samples were drawn prior to dosing and for 6 hours (7 samples) post-dose. The children were fasting for 1 hour before dose and were allowed to eat 30 minutes post-dose. A subgroup of the patients was monitored for gastric and/or esophageal pH, apnea and bradycardia. Four of the patients received an additional treatment of 0.5 mg/kg for up to 5 days. Six patients had one or more missing blood samples and of these six, one patient had 4 missing samples. In one patient, high omeprazole concentration was measured in the pre-dose sample and no explanation for this could be found. This concentration was included in the PK calculations. One patient had a second omeprazole dose after having quickly regurgitated the first dose.

The observed/calculated pharmacokinetic parameters are shown in table 3 below. A scatter plot of dose and weight normalised AUC_{0-t} versus age showed that the exposure is markedly increased in some patients younger than 5 months but in older patients the exposure is quite similar in the full age range (Fig 3). In general, the exposure was highly variable between individuals.

Only a third of the patients had evidence of GERD (esophageal pH < 4 for $\geq 6\%$ of the time). In these patients the mean decrease of % time with esophageal pH<4 was 1.4-24.9%. If all patients were included the mean change was -2.1 to -6.4%. Plots of change in % time with esophageal and gastric pH <4 vs AUC_{0-t} were presented. No clear relationship was observed.

Table 3

	$AUC_{0-\infty}$ ng/ml	$AUC_{0-\infty}$ ng/ml	AUC_{0-t} ng/ml	Cmax ng/ml	T1/2 hrs
0.5 mg/kg (n=1) age 1.2 months, weight 4.8 kh					
N	1	1	1	1	1
	1809	3619	1594	698	2.05
1.0 mg/kg age 7.8±6.4 (range 0.5-21.5) months weight 6.7±2.6 (range 3.3-10.6) kg					
N	7	7	12	12	7
Mean	1705	1705	1083	636	1.15
SD	1543	1547	519	557	0.16
Median	1412	1412	1251	392	1.12
Min	436	436	113	99	0.92
Max	4932	4932	4554	1798	1.39
1.5 mg/kg age 10.2±7.7 (range 2.1-24.0) months weight 8.4±3.4 (range 3.3-13.8) kg					
N	9	9	12	12	9
Mean	1431	954	1114	789	1.43
SD	1628	1085	1454	1107	0.64
Median	752	501	684	485	1.18
Min	188	125	86	20	0.85
Max	4261	2841	4208	3740	2.73

$AUC_{0-\infty}$ denotes $AUC_{0-\infty}$ / dose (mg/kg)

Figure 3 Dose and weight normalised AUC_{0-t} versus age after a 1 or 1.5 mg/kg oral single dose

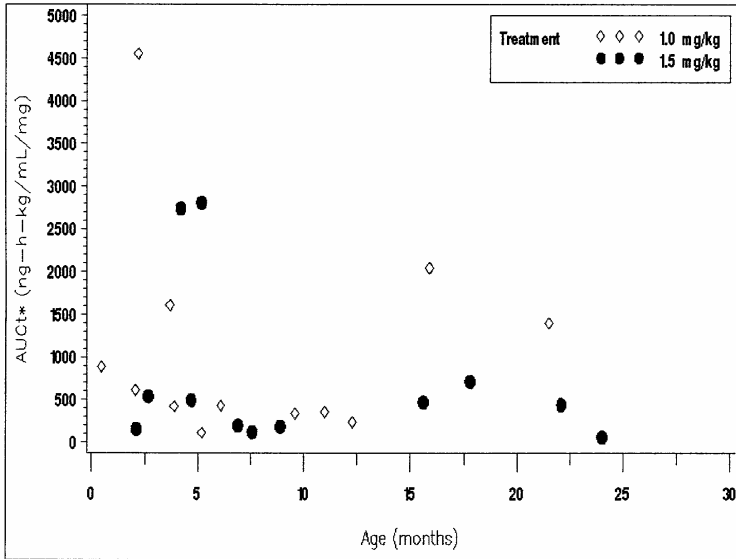
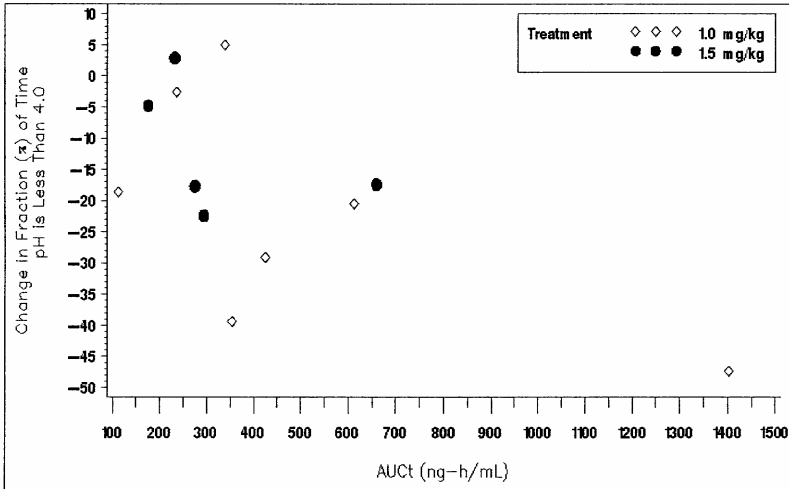


Figure 4 AUC_{0-t} vs. change of time with gastric pH <4



Assessors comment:

The actual, non-normalised AUC and C_{max} values versus age were requested in the national procedure. In general, a lower clearance is expected the first months of life than in older children. Indeed, in the very young children, the exposure appears higher. However, there are also older children with high exposure. One patient had very high exposure (up to 9-fold the "normal" exposure) and four more patients had high exposure (3-4-fold the "normal" exposure). It should be noted that also in study A2, the exposure was very variable. In the national variation application, the applicant presented non-adjusted AUC but did not divide the results with respect to dosing group, as would have preferred. However, the AUCs in three patients aged 5, 4 and 2 months were several-fold higher than the average exposure and this is not likely to be caused by

differences in dose. The higher exposure may be related to individual hepatic maturation or to genetic polymorphisms. We ask the applicant to present the earlier submitted plots to the MS.

No relationship between AUC and time with pH <4 was seen although there seem to be a tendency to a relationship between AUC and change in gastric pH (Fig 4). This kind of relationship has been shown for adults. The drug was suspended in bicarbonate. The effect of the "vehicle" on the intragastric pH is unknown.

Study B3 (Study no I-678)

The pharmacokinetics of omeprazole was studied in 25 paediatric patients in a branch of a dose titration study when the full therapeutic dose was reached. The dose was increased in 0.7 mg increments every 5-14 days until pH below 4 for $\leq 6\%$ of 24 hrs was achieved. Omeprazole was administered as capsules. Children who had difficulties in swallowing capsules could mix the granules of open capsules with a weak acidic vehicle such as yoghurt, apple sauce, juice and take the mixture either by mouth or by gastroscopy tube. The granules were dissolved in bicarbonate in patients with jejunum tubes. The granules could also be swallowed directly with a glass of water. Blood samples were collected for 6 hours. The plasma samples were analysed at Astra Hässle using LC. There was no information on how long the current dose regimen had been administered. The study included two 1-year olds, one 2-, 3- and 4- year old, two 5-year olds, five 6-10-year olds and ten children older than 10 years. Nine of the patients weighed less than 20 kg. The therapeutic doses reached were 0.7-3.5 mg/kg corresponding to 7-109 mg. The dose normalised AUC_{0-t} (to 1 mg/kg) versus age is presented below (Fig 5). Oral clearance appears to be higher in younger children. The relationship between age and half-life was less clear. (Fig 6).

Fig 5 Dose normalised AUC_{0-t} versus age after individual dose titration to therapeutic response

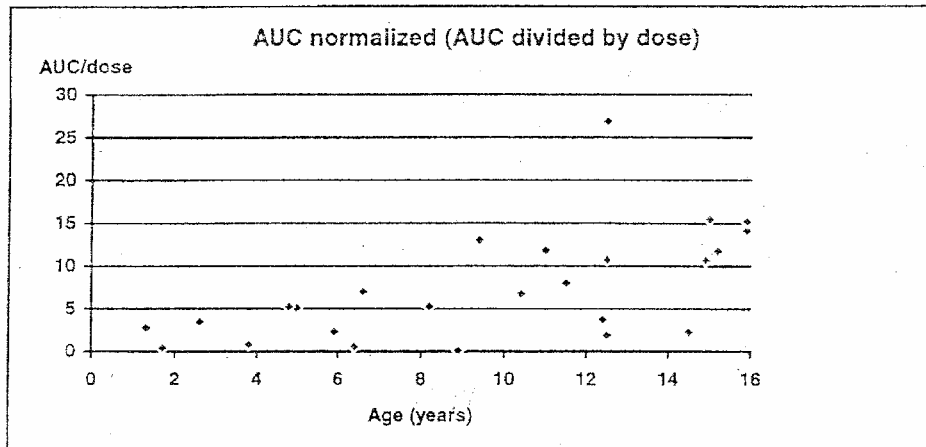


Figure 3 AUC values normalised by first healing dose (AUC/dose (mg/kg)), plotted against age.

Figure 6 The half-life of omeprazole versus age after individual dose titration to therapeutic response

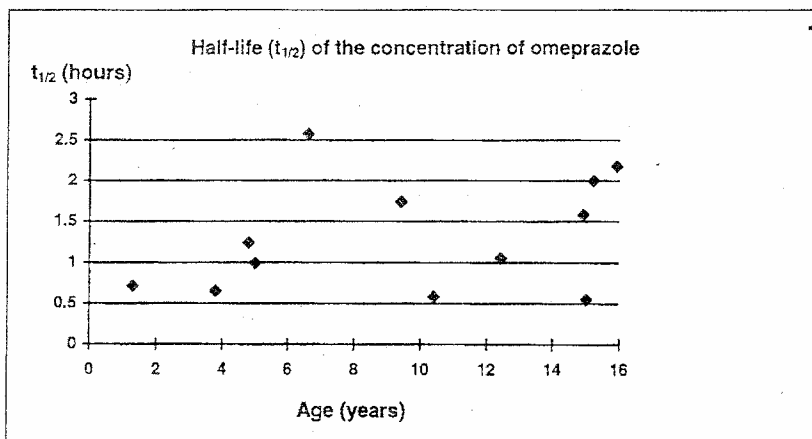


Figure 4 Half-life of the concentration of omeprazole, plotted against age.

Assessor's comments:

The applicant was earlier asked to present the available data on non-normalised AUC as mean and SD, median and range. This data is interesting as it shows where the exposure corresponding to therapeutic response. They were also asked to also show a plot of actual AUC versus age. The applicant is asked to submit these plots also to the MS to this procedure.

One of the subjects was treated with phenobarbital. This child had the lowest AUC of omeprazole observed in the study (0.3 umol*h/ or 0.1 if dosenormalised) suggesting induction of the metabolism of omeprazole.

Published pharmacokinetic studies

Jacqs -Aigrain et al 1994

This study investigated the pharmacokinetics of omeprazole in 13 children in the age range **0.3-19 years**. The dose administered ranged from 39.6-139mg/1.73m². Blood was collected until 12 hours post-dose and omeprazole, the sulphone and the sulphide metabolites were measured in plasma. Three patients were below 1 year and one was below 2 years old. CL in the 3 one year old patients was 0.18, 0.45 and 0.68 L/h/kg and in the 1 year old it was 0.18L/h/kg. These figures did not differ much from the individual CL values in the other part of the population and the mean CL was 0.23±0.32 L/h/kg. There was no plot of exposure vs. age but looking at the table of results there were no clear trends in that respect. This was also true for the Cmax and AUC of the sulphone metabolite.

Faure et al 2001

In this study the pharmacokinetics of omeprazole was investigated in 9 children between **4.5 and 27 months** of age. Three patients were younger than one year and 5 patients were less than 2 year old.. Omeprazole had been given as a daily 1-hour infusion of 20 mg/1.73m² or 40 mg/1.73m² for 3-5 days at the time of sampling. It is noted that steady state may not have been fully reached at this time due to the time dependency in omeprazole pharmacokinetics. Systemic clearance was 0.68 and 0.42 L/kg/h at the 20 and 40 mg regimens, respectively. There was no presentation of exposure vs. age but no clear trend was visible looking at the table of results.

Kearns et al 2003

The pharmacokinetics of omeprazole was investigated after a single oral dose of 10 or 20 mg in 23 **2-16 year**-old patients weighing ≤ 20 kg and >20 kg, respectively. Ten of the patients were ≤ 5 years old. Omeprazole was administered as capsules, whole or sprinkled on applesauce. Mean AUC normalised for dose in mg/kg was stated to be similar over the age range studied. However, data supporting this statement was not shown. A plot of terminal elimination constant vs. age showed no clear age association. However, the number of patients (with available data?) in the lower end of the age range was low ($n=4 \leq 5$ years old).

Marier et al 2004

The pharmacokinetics of omeprazol was studied after a 20 mg single dose in 18 healthy **adult** men and in 12 **children** with GERD (mean age 6.1 ± 4.4 , range **0.5-13 yrs**, mean weight 24.2 ± 16.5 (range 6-64) kg). Blood samples were collected over 5 hours and data was analysed by population PK analysis. The obtained plasma concentration-time courses and a plot over CL/F normalised for bodyweight vs. age are presented below. Bodyweight normalised oral clearance in children was not significantly different from that observed in adults (0.51 ± 0.34 vs. 0.62 ± 0.27 L/h/kg).

Figures 7 and 8

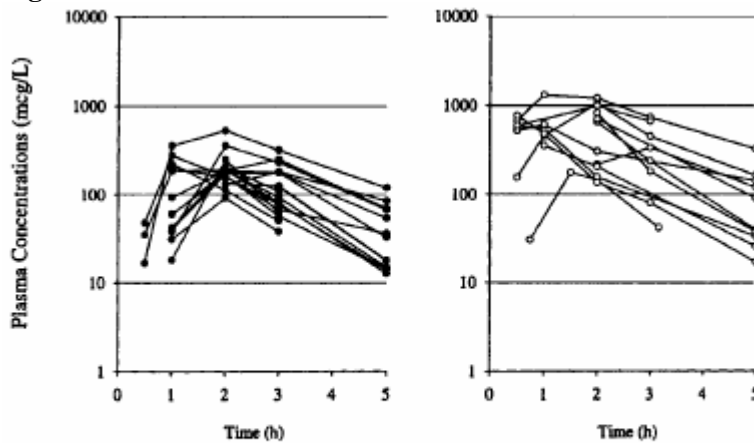
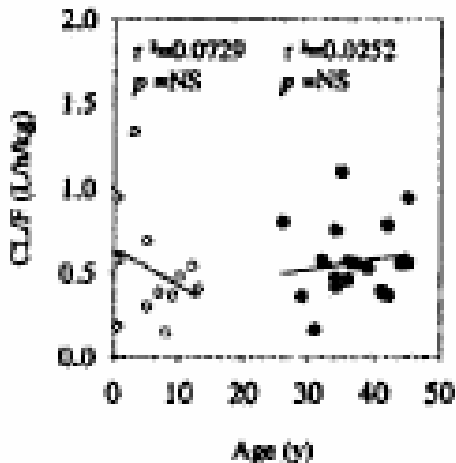


FIGURE 1. Individual pharmacokinetic profiles of omeprazole after multiple doses in healthy adults (●) and children with GERD (○).



Pharmacokinetic summary

The applicant has shown that the intact and opened capsules as included in the clinical studies give equivalent total exposure (AUC). No comparison is made with the Losec MUPS tablet formulation.

Omeprazole is acid-labile and is therefore approved for oral use as enteric coated tablets. No pharmacokinetic study is available showing that orally administered i.v. solution give equivalent exposure as the same dose administered in an enterocoated formulation. This is a deficiency. If pharmaceutical documentation can show that the granules were dissolved at the time of administration and that buffering capacity of the oral solution is equal to the buffer administered in the clinical studies, this could support efficacy in children weighing less than 10 kg (and are at least 1 year old) as the clinical documentation then could be extrapolated to the clinical situation.

The actual exposures at the recommended therapeutic doses have not been well described as well as how it relates to observed exposure in adult patients.

Omeprazol is presently not approved below the age of 2 years in Sweden. In our national assessment we concluded that the proposed dose appears to give an exposure of omeprazole which is similar over the age range 2-16 years. As marked pharmacokinetic differences between teenagers and adults are rare, it is likely that the exposure also is similar to adult exposure during treatment with 20 mg q.d.

Clinical efficacy and safety data support an approval in children from the age of 1 year weighing ≥ 10 kg for which an appropriate formulation is available. The pharmacokinetic data in children under the age of 2 is sparse. The gathered data in children up to 2 years old indicate that clearance is reduced in children under the age of 6 months.

II.2.3.2 Clinical efficacy

In Sweden Losec MUPS is nationally approved for children for the indications reflux esophagitis and symptomatic treatment of heartburn and acid in children above the age of 2. Furthermore, Losec MUPS is approved for treatment of Helicobacter pylori associated duodenal ulcers in children from 4 years. All clinical data submitted in this procedure was included in the previous variation application. For an overview of the different approvals and dosing in the EU please see attached Appendix.

Below a summary from the AR on which this approval was based:

There are four clinical studies, B1 – B4, documenting the effect of omeprazole in various gastrointestinal conditions. Summary data on studies B1-B4 are shown in table 5.

Table 5 – Summary data on patients included in studies B1 – B4

(GERD=Gastro Esophageal Reflux Disease, EE=erosive esophagitis, DU=duodenal ulcer, GU=gastric ulcer, PU=peptic ulcer, OAC=omeprazole/amoxicillin/clarithromycin, AC=amoxicillin/clarithromycin)

Study	Safety population	Patients available for efficacy evaluation	Age range
B1	130	GERD 115 <i>H.pylori</i> negative EE 3 <i>H.pylori</i> negative DU 4 <i>H.pylori</i> negative GU 3 <i>H.pylori</i> positive/non PU 5	2-16 years
B2	106	106	0.7-22 months
B3	65	Healing part 65 Maintenance part 46	0.5-18 years 1-18 years
B4	73 OAC 35 AC 38	OAC 31 AC 32	3-15 years

Main study(ies)

Study B1 (CSR 214)

This was a multi-center, open-label study which enrolled 131 patients. Of these, 130 patients were included in the safety analysis and 122 patients were included in the efficacy analysis. The age range was 2-16 years. There were approximately an equal number of males and females with an average age of 9.7 years. The subjects were assigned to one of five treatment arms.

Primary objective: to investigate whether once daily treatment with omeprazole, 20 mg capsules for subjects >20 kg and 10 mg capsules for subjects ≤20 kg, safely and effectively relieved pain-related and regurgitation-related symptoms of GERD as a primary disorder in pediatric subjects with clinically or endoscopically diagnosed nonerosive GERD (defined as no esophageal mucosal breaks: less than Grade 2 esophagitis).

Secondary objective: to investigate whether once daily treatment regimens with omeprazole safely and effectively treated subjects who were clinically and endoscopically diagnosed with DU, GU, EE or *H.pylori* infection in pediatric subjects.

Main criteria for inclusion: children with a history of symptoms suggestive of nonerosive GERD for at least 2 months.

Primary Efficacy Variables:

Non-erosive GERD subjects:

The primary efficacy variable was the proportion of subjects successfully treated, defined as no moderate or severe episodes of either pain-related symptoms or vomiting/regurgitation during the last 4 days of treatment (i.e. days 25 through 28, inclusive).

DU, GU and EE subjects:

The proportion of subjects who successfully healed their mucosal lesions based on end-of-treatment endoscopy.

Table 1 - Summary of exposure to study medication

Dose of study medication	Ome 10 mg n=17	Ome 20 mg n=111	Ome 40 mg n=3
Total number of subjects exposed to one dose of study medication	17	110	3
Maximum number of doses any one subject took	33	48	31

Results:

For subjects in all 5 treatment arms, the physician's global assessment indicates that omeprazole improved overall GERD-related symptoms. 83% of subjects improved, 17% of subjects remained the same. No subjects worsened.

For nonerosive GERD subjects, the observed success rate was of 59.3%, defined as no moderate or severe episodes of either pain-related symptoms or vomiting/regurgitation during the last 4 days of treatment

For subjects diagnosed with DU, GU and EE, 9 out of 10 subjects healed their mucosal lesions. 4 out of 4 subjects in the group *H.pylori* subjects, had *H.pylori* eradicated based on histology.

Assessors comment:

The vast majority of patients had GERD. There were very few patients in the four groups with other diagnoses.

No placebo group was included, and it is therefore not possible to know the frequency of spontaneous improvement. Hence, it can be concluded that omeprazole was effective but the magnitude of the effect can not be estimated.

Study B2(CSR 251)

This was a multi-center, randomized, single-blind, study. A total of 115 patients were randomized to 1 of 3 treatment groups, with 79 patients completing the study. Of these, 106 patients were included in the safety analysis and 100 were included in the efficacy analysis.

The age range was age 0.7 months to 21.8 months with a mean age of 6.3 months.

Table 2. Age distribution of children in study B2

Children 0-6 months	Children 6-12 months	Children 12-24 months
68	30	17

Primary objective: to investigate whether once daily treatment with omeprazole safely and effectively reduces the number of regurgitation episodes related to gastroesophageal reflux disease (GERD) in pediatric patients ages 0 months through 24 months, inclusive.

Main criteria for inclusion: patients between the ages of 2 months and 24 months with at least a 2-months history of clinically diagnosed GERD-related symptoms. Depending on the randomization schedule the patients were dosed with 0.5 mg/kg, 1.0 mg/kg or 1.5 mg/kg of omeprazole.

The duration of treatment was approximately 56 days.

Primary efficacy variable: the average number of vomiting/regurgitation episodes per day in the last 72 hours of treatment was evaluated.

Results:

The average actual dose of omeprazole was 4.0 mg, 7.3 mg and 9.7 mg, respectively, for 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg treatment groups. Patients in the treatment group 1.5 mg/kg weighed slightly less than average.

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.

Primary efficacy variable:

At baseline patients reported approximately 9.4 vomiting/regurgitation episodes per day during the last 72 hours. The number of vomiting/regurgitation decreased by 50 % after 8 weeks of treatment with omeprazole. No statistical difference were detected between any treatment groups. A summary of the approximate decrease in vomiting/regurgitation episodes is shown in table 7.

Table 3 - summary of the approximately decrease in vomiting/regurgitation episodes

Omeprazole dosage	Approximately decrease in vomiting/regurgitation episodes per day during the last 72 hours
1.5 mg/kg	- 4.35 (95 % CI: (- 8.2, - 0.46)
1.0 mg/kg	- 2.97 (95 % CI: (- 7.0, 1.06)
0.5 mg/kg	- 4.34 (95 % CI: (- 8.5, - 0.15)

A sensitivity analysis removing three patients with extreme values showed a trend towards a greater reduction in vomiting/regurgitation episodes with each increasing dose group of omeprazole.

A graphical analysis on the average number of vomiting/regurgitation episodes per day illustrates that larger doses (1.0 mg/kg and 1.5 mg/kg) show effect at week 1 while the lowest dose (0.5 mg/kg) shows effect at week 3.

Assessors comment: *The results were similar for all three dose groups, with no clear dose-effect relationship. The onset of effect of the lowest dose was, however, delayed compared to the higher doses.*

The used formulation was Prilosec Delayed-Release Capsules, 20 mg (Bulk Lot #J0968), suspended in an 8.4% sodium bicarbonate solution (Bulk Lot #56-537-DK) and administered once daily via a syringe or, in some instances, via nasogastric or percutaneous gastrostomy tube. Depending on the randomization schedule, each patient was randomized to 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg and dosed accordingly based on weight.

Since this is a suspension it is not fully understood how the dose calculations can be so exact.

Study B3 (CSR I-678)

This was a multicenter, open, uncontrolled, study which enrolled 65 patients. The study was divided into two phases; a dose finding and healing phase and a maintenance phase.

An interim report from the healing phase of this study has constituted the pivotal study in the first application for pediatric dosing.

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.

The age of inclusion was 1 to 16 years. The children were required to have endoscopically verified esophagitis of at least Grade 2 (Savary-Miller) and could be either previously untreated or failures following H2 receptor antagonists/prokinetic therapy or surgery. Intra-esophageal pH was to remain below 4.0 for more than 6 % of a 24h monitoring period for inclusion in the study. Patients in whom esophagitis had healed during the healing phase could enter maintenance treatment if clinically indicated.

Endoscopy, symptom relief, routine laboratory tests, fasting gastrin measurements and histopathological assessment of endocrine cells, gastritis and *H.pylori* were used to assess the efficacy and safety of omeprazole.

Information about iron absorption and vitamin B12 levels are provided in the study.

Many of the children in this study were severely, often multiple, sick patients with other, potent, concomitant drugs.

Healing phase: 65 patients were included in the study and all are included in the report. See age distribution below:

Table 4. Age distribution in study B3

Children <2 years	Children 2-6 years	Children 6-12 years	Children >12 years
6	21	21	17

The therapeutic goal was intraesophageal pH below 4.0 for no more than 6 % of 24 hours.

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 maximum dose allowed was 3.5 mg/kg or the total daily dose not exceeding 80 mg. 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.

Sixty five patients entered the dose-finding part but 8 of them discontinued during that period, thus 57 patients started the healing treatment.

Maintenance phase: 46 of the 54 patients that were healed decided to enter the maintenance phase. Twenty children were in the age group <7 years, 16 in the age group 7-12 years and 10 in the age group >12 years.

The initial daily dose of omeprazole corresponded to half of their individual healing dose. If symptom recurrence occurred during the maintenance phase, the dose was increased back to the healing dose.

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

Results of the healing phase

In the healing phase data from 65 children were available for an All Patients Treated analysis.

There were 29 children aged < 7 years, 24 aged 7 – 12 years and 12 aged > 12 years. Of the 57 patients that entered the healing part, 29 children had gastroesophageal reflux symptoms without

any other disease as the cause of their symptoms, 21 children with cerebral palsy or another neurologic condition and 7 with esophageal atresia.

Table 5 – The dosages needed to achieve the therapeutic goal (pH below 4 for ≤ 6 % of 24hr)

Number of patients	Dosage needed to achieve the therapeutic goal
24	0.7 mg/kg
15	1.4 mg/kg
7	2.1 mg/kg
6	2.8 mg/kg
2	3.5 mg/kg

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. At entry, 82 % of the children had moderate or severe overall symptoms. At the last visit in the healing phase, 33 % had no overall symptoms, 57 % had mild overall symptoms and 10 % still had moderate or severe symptoms. No patient had severe heartburn/epigastric pain and one patient had severe dysphagia/odynophagia. Regurgitation/vomiting was still present in 40 % of the patients, though with considerably less frequency. Irritability with meals was absent or markedly improved by the end of the healing phase.

Most patients gained weight during the healing phase of the study.

Results of the maintenance phase:

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 month 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 %. Eight patients reported irritability with meals and seven reported coughing/wheezing spells.

Assessors comment: *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 to evaluate the effect. Only 6 patients were below the age of 2 which makes the data difficult to interpret for this age group. The results shows highly clinically relevant efficacy of omeprazole.*

Study B4

This was a multicenter, double-blind, randomised, controlled, parallel group study.

The study was designed to evaluate omeprazole in combination with amoxicillin and clarithromycin (OAC) in pediatric patients with dyspeptic symptoms and *H.pylori* associated histological gastritis. Seventy-three patients were enrolled in the study and randomized to either the omeprazole group (omeprazole and antibiotics) 35 patients, or to the placebo group (antibiotics) 38 patients. The age ranged from 3 to 15 years and the mean (SD) ages were 11.7 (2.9) years in the omeprazole group and 10.0 (3.8) years in the placebo group. The primary analysis according to intention to treat (ITT) approach comprised 63 patients with positive baseline HP status, i.e. diagnosed *H.pylori* positive with the ¹³C-urea breath test at entry, 31 patients in the omeprazole group and 32 patients in the placebo group. The secondary analysis according to the per protocol (PP) approach consisted 25 patients in the omeprazole group and 28 patients in the placebo group.

The safety population consisted of 35 and 38 patients in the omeprazole and placebo groups respectively.

The treatment period was 7 days and *H.pylori* status (eradication follow-up) was assessed at 4-5 weeks after end of treatment by means of ¹³C Urea Breath Test. Omeprazole was given in a dose of 10 mg bid (body weight 15-30 kg) or 20 mg (body weight >30 kg).

Main criteria for inclusion: children with *H.pylori* associated gastritis, age under 15 years and 3 months, *H.pylori* infection confirmed at initial endoscopy by a rapid urease test at the time of enrolment or before enrolment by a valid test provided that there has been no attempt at eradication since, patients with a gastritis assessed by histology and dyspeptic symptoms.

Primary objective: to compare *H.pylori* eradication rates in children with gastritis treated with amoxicillin and clarithromycin, combined or not with omeprazole.

Secondary objectives: evaluation of primary susceptibility of *H.pylori* to amoxicillin and clarithromycin; evaluation of improvement in abdominal pain between the two treatment groups using a visual analogue scale (VAS); evaluation of the safety/acceptability of omeprazole and document the incidence of adverse events in the two treatment groups.

Primary efficacy variable: eradication rate of *H.pylori* as assessed with ¹³C Urea Breath test 4 to 5 weeks after the end of the one-week study treatment.

Results:

The *H.pylori* eradication rate was significantly higher in the omeprazole group as compared to the placebo group ($p < 0.001$), 74.2% [58.7-89.6] in the omeprazole plus antibiotics group as compared to 9.4 % [-0.7-19.5] in the placebo plus antibiotics group.

Results were similar in the PP analysis ($p < 0.001$).

No significant differences in the evolution of digestive symptoms from baseline were found between the treatment groups ($p > 0.05$) at the end of the treatment and after the follow-up period. The digestive symptoms were graded as none, mild, moderate or severe.

VAS score at baseline as well as evolution of VAS score from baseline were not significantly different between treatment groups. The mean score was 5.3 for both groups at baseline, 2.9 at the end of the treatment period and 2.3 at the end of the follow-up period.

Assessors comment:

*The study demonstrated a significantly higher *H.pylori* eradication rate in the omeprazole group compared with the placebo group. However, no difference was observed with regard to digestive symptoms or abdominal pain.*

II.2.3.3 Clinical safety

Below a summary from the AR on which this approval was based: Study B1

Omeprazole in three doses, 10 mg, 20 mg and 40 mg, was reported to be well tolerated in the pediatric subjects 2 through 16 years, inclusive. Seventy-two subjects reported at least one adverse event during the study. The AEs that occurred most frequently were related to the Respiratory System (18.5%), the Central Nervous System (13.8%) and the Body as a Whole (12.3%). The most common AEs within the Respiratory system were coughing, pharyngitis and respiratory infection and within the Central Nervous system headaches. Accidents/injuries were the most common AEs associated with the Body as a Whole. All AEs were either mild or moderate. No severe AEs were reported.

Two subjects experienced a serious adverse event during the course of this study (one case of viral gastroenteritis and one of persisting vomiting following endoscopic investigation) and one subject discontinued from the study prior to starting study medication due to an adverse event. The relationships of the study medication to these adverse events were attributed as unlikely.

Study B2

83 patients out of 106, that took at least one dose of study medication, reported one or more adverse events. There were no apparent dose relationship to occurrence of AEs. The majority of the AEs were either mild or moderate in intensity. The AEs that occurred most frequently were related to the Respiratory System (respiratory infection, rhinitis), the Gastrointestinal system (diarrhea, constipation) and the Resistance Mechanism System (otitis media). The majority of the AEs were either mild or moderate.

Five patients reported SAEs. These were all infections; urinary tract infection, pneumonia, pertussis, lymphadenitis, bronchiolitis with croup. The investigators considered the SAEs to be unlikely related to the study drug. Six patients discontinued the study due to an AE.

Study B3

This study was the only 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.

Sixtythree 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 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 casually related to omeprazole therapy.

Study B4

The most common adverse events during the course of the study were diarrhoea (2 patients in the omeprazole group, 5 in the placebo group), abdominal pain (2 patients in the omeprazole group, 3 in the placebo group) which are expected adverse events with all three study medications. Three patients in the placebo group reported headache.

Six serious adverse events were reported, which are described below, 1 in the omeprazole group and 5 in the placebo group.

During the treatment period, one patient in the omeprazole group reported 1 SAE, diarrhoea (considered as possibly related to study drug) and 2 patients of the 38 patients in the placebo group reported 1 SAE each, suspected haematemesis (considered unlikely related to study drugs by the investigator) and melaena (causal relationship not assessed by the investigator).

During the follow-up period, 3 patients in the placebo group reported 3 SAEs: abdominal pain for two patients (causality assessed as unlikely for both patients) and one was a severe cutaneous allergic reaction (considered as possibly related to study drug).

None of these reported adverse events was an unexpected adverse drug reaction for the study medications. All SAEs resolved.

Two patients in the placebo group discontinued the treatment because of adverse events, one patient for diarrhoea and epigastric pain, and the other patient for allergy. One patient in the omeprazole group discontinued the treatment temporarily for fever and coughing.

When comparing the AEs reported in study **B1** (children 2 through 16 years) and study **B2** (children 0-24 months) the only apparent difference is the absence of reports of headache in study **B2**. For study **B3** 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 the pharmacokinetic study A3, four children aged 5 months and below had high exposure. There is no evident explanation for the high exposures observed in these children, although in some instances simultaneous disease may be a contributing factor. Two of these children were treated with multiple drugs, but none of them are documented to interfere with the disposition of omeprazole.

The exposure observed in these children is compared with the exposure observed in another group of twenty-three paediatric patients treated with intravenous omeprazole. These children were born with oesophageal atresia and were post surgery treated with iv omeprazole in order to prevent oesophageal ulcer. The highest AUC observed in these children was 38.80 µmol/h/L. Nine further children had 24 hour AUC values between 10.00 and 22.20 µmol/h/L achieved at iv doses between 0.5 mg/kg once daily and 1.15 mg/kg twice daily. There were no adverse drug reactions associated with omeprazole treatment reported in these or any of the other patients. Thus, the high exposure reported in study A3 for some patients given 1 mg/kg or 1.5 mg/kg orally has also been observed in a clinical setting where children have been given omeprazole iv in

order to prevent the development of oesophageal ulcers. Omeprazole has been well tolerated in all these children.

Assessor's comments:

The difference between the reported AEs when comparing study B1 and B2 was the absence of headaches reported in study B2. A difficulty for the patients/caregivers to report such AEs in the youngest patients has been presented as a possible explanation, which is endorsed by the assessor.

In study B3 the age group <2 years only comprises of 6 patients in the healing phase and 3 patients in the maintenance phase. There was no obvious trend among the age groups in number or category of AE reported during the two phases of the study.

Four SOCs, where the frequency of reported events seemed to be higher in the youngest age group than in older children and adults, are discussed in the response document. As stated in the response this could be expected. In summary, no apparent safety concerns has been identified in the pediatric population, but the number of small children, and the duration of the studies, is limited.

There was no safety issues reported for the very small children in study A3 who had an increased exposure of omeprazole. There were 2 patients in the iv study who had similar AUCs (19.5 uM/h and 10.5 uM/l) as the 3 children in study A3 with high drug exposure (ca 12 uM/h).

Patient exposure

The total number of exposed children is unknown. The use of omeprazole in children started in emergency cases and other severely ill children a long time ago. This was before the first Agency approvals for pediatric use of omeprazole, which came in May 1997 (Denmark and the UK followed by many other countries). It is not possible to estimate any number of exposed children based on sales figures or e.g. incoming PMS AE/SAE reports. Although no total exposure data exists, the following information based on IMS, NDTI (National Disease & Therapeutic Index) and NPA Audits from the US (see table 1)

Table 1. Annual usage of omeprazole in the U.S. among children (0 - 16 yrs of age) and adults (>17 yrs) from 1998 to 2001.

Prilosec Usage (TRxs)	1998	1999	2000	2001
Age 17 and Over	25 044 783	29 113 215	29 869 311	27 061 057
Age 0-16	551 927	936 690	1 058 946	1 910 365

TRxs = Number of prescriptions/treatment courses

Table 2. Number of Patients and Medically Confirmed AE/SAEs, corresponding Number of Consumer AE/SAEs and Total Number of AE/SAEs in Children

Report type	No. of	0-2*	>2-18**	0-18***
Medically confirmed	Patients	105	301	406
	Non-Serious AE	118	437	555
	Serious AE	53	105	158
	Total AE	171	542	713
Consumer etc.	Patients	43	108	151
	Non-Serious AE	71	203	275
	Serious AE	3	37	39
	Total AE	74	240	314
Total	Patients	148	409	557
	Non-Serious AE	189	641	830
	Serious AE	56	141	197
	Total AE	245	782	1027

* Age group 0-2 yrs, includes also cases where age was only specified as neonates or infants.

** Age group >2-18 yrs, include also cases where age was specified as child, adolescent etc. or not specified at all.

*** Age group 0-18 yrs includes all cases in children.

Table 2 shows that the majority of the reported events were non-serious in both age groups and that the patients in the 0-2 yrs group does not seem to have an increased number of events. However, the exact exposure figures are unknown.

In many of the reports the dose information is missing. The dose ranges per age in both medically confirmed and spontaneous reports were:

- 0 - 2 yrs: 3 - 40 mg
- >2 - 18 yrs: 6 - 120 mg (200 mg, intentional overdose in an 18 year old female patient)
- 0 - 18 yrs: 3 - 120 mg (200 mg, intentional overdose in an 18 year old female patient)

Adverse events

Serious adverse events and deaths

Laboratory findings

Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition Study B3 is the only long-term studying the submission. This study provides information about iron absorption, gastrin levels, vitamin B₁₂ levels and the histopathology of the ventricular mucosa besides the reported adverse events.

Anaemia was reported in 12 children during the healing plus maintenance phases of the study. However, 4 of these patients had low serum Fe⁺⁺ at baseline, one child had iron therapy due to known anaemia and 2 two children with missing levels at baseline but showed low levels at next visit. The remaining 5 children suffered from cerebral palsy and mental retardation (one had Barrett's esophagus and esophagitis grade III and one had proteinuria).

Children with erosive esophagitis are known to be at risk for developing iron deficiency.

Fasting serum gastrin levels were measured in 20 patients at baseline and at each visit, i.e. during a 24-month study period. The median gastrin levels were normal for the group at all visits despite a few patients with elevated levels. Some patients showed a considerable increase in serum gastrin levels during the healing phase but no further increase during the remaining part of the study.

Biopsies taken from corpus and antrum before and at the end of study did not show any changes of concern with respect to signs of inflammation, activity or atrophy. Two children had simple (diffuse) argyrophil cell hyperplasia and two had linear chain-forming hyperplasia.

A retrospective analysis of vitamin B₁₂ levels in serum was performed. The B₁₂ levels differed among the patients who had received omeprazole for more than 15 months. The values decreased in some patients and increased in some. The decrease in B₁₂ levels did not reach below the lower limit of normal.

According to the expert report, it may be advised to monitor serum B₁₂ during long term treatment with a PPI since severely ill pediatric patients, in need of this kind of medication, may have levels or stores of vitamin B₁₂ at the lower limit.

On DDW 2005 there was a report on long-term of PPI use in children by Hassal et al where the authors had retrospectively screened databases from BC Children's hospital in Vancouver for long-term (>9 months) PPI-use. They found 166 patients, mean age 7.8 years. The median duration of treatment was 2.5 years and one patient had treatment duration of 11 years. Most children had underlying diseases such as cerebral palsy and other major motor disorders. There were 6 AEs reported judged as potentially related to PPI treatment, diarrhoea and nausea was the most common but also skin rash and agitation/irritability was reported.

Post-marketing Safety conclusion

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 seem to be similar in children and in adults for most of the SOCs. 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.

Eight cases were reported as fatal. There were, however, only seven SAEs with fatal outcome. One of the eight cases (1996AH00598) recovered from the event and died from an unknown cause six months later. All but one of the seven fatal events took place in children already seriously ill before the omeprazole therapy was started.

From the clinical trials included in the "Summary of Safety Results" submitted to the FDA December 22, 2000, and the data from the two additional studies, B4 and A3, as well as from the new PMS review, the overall conclusion is that omeprazole is safe to use also in children. Dose recommendations should be followed, particularly in neonates and infants.

Assessors comment:

The safety profile of omeprazole is favourable and no safety concerns has evoked during the post-marketing period.

II.2.3.4. Summary of Product Characteristics

Assessor's comments:

The MAH has proposed to include also newborn children in the submitted SPC proposal. The use in this age group was rejected in the national procedure in Sweden because the formulation that was proposed to be used was not accepted. The formulation used in the two clinical studies in children 0-24 months was an oral solution or suspension comprised of omeprazole/sodium bicarbonate. The use of the i.v. formulation for oral use is not supported by MPA for several reasons including differences in stability depending on use, lack of evidence of stability of the acid-labile omeprazole in the stomach etc. In the earlier European submission a solution prepared from the intravenous formulation was used. This was not accepted in Sweden and many other European countries but is approved in Denmark and Portugal.

However, as Losec MUPS can be suspended in a fluid and most children above the age of 1 weighs approximately 10 kg it may be acceptable to use this formulation in children from the age of 1 year under the condition that they weigh at least 10 kg. The applicant is recommended to submit an application for a variation to include children from 1 year of age weighing at least 10 kg and moreover to describe the findings in the lower age group population in sections 5.1 and 5.2 of the SmPC.

II.3 OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT>

Acid peptic disease is a common problem in the pediatric population as well as in adults with a similar prevalence of troublesome GERD (gastroesophageal reflux disease) ranging from 5-8%. The symptom of GERD in infants and children varies from crying, irritability or sleep disturbances to feeding difficulties and/or vomiting.

Several groups of children are particularly likely to have pathological reflux, for example children with neurologically impairment, cystic fibrosis and children with repaired esophageal atresia. Omeprazole has been used in for several years in pediatrics especially in these vulnerable patients groups as stated above. Omeprazole is considered to be an effective and safe drug in the pediatric population as well as in the adult population. However, since it may be of more importance to not over-treat children it is recommended that pediatricians is mainly responsible to initiate this kind of treatment especially in children below the age of 12, even though recommendations is not imperative in all EU countries.

In Sweden Losec MUPS is approved for children from the age of 2 as well but in a number of other EU countries Losec MUPS is approved from the age of one year. In two countries, Denmark and Portugal. Losec MUPS is approved from newborn. See Appendix. Since the dose 1mg/kg appears to be safe to use in children it would be possible to approve Losec MUPS from 10 kg which is the usual weight of a 1-year old infant. Losec MUPS is available in the 10 mg strength and can be suspended in water or fruit juice. Therefore Losec MUPS can be approvable from the age of 1 year if the infant weighs at least 10 kg. Furthermore data indicates that the same pharmacodynamic effect in smaller infants as well as in children over the age of 2 and adults and no other or more serious safety concerns has evoked. It is recommended to submit a application for a variation to change the dosing of Losec MUPS to include children from age 1 year and with weight at least 10 kg and moreover to describe the findings in the lower age group population in sections 5.1 and 5.2 of the SmPC.

It is not accepted to use Losec MUPS in children below the age of 1 and/or below 10 kg because of the lack of an appropriate formulation. Furthermore, the kinetic data implies that some children below 6 months may have high exposure why safety in this population is insecure due to sparse clinical data.

Omeprazole is acid-labile and is therefore approved for oral use as enteric coated tablets. No pharmacokinetic study is available showing that orally administered i.v. solution give equivalent exposure as the same dose administered in an enterocoated formulation. This is a major deficiency.

Furthermore the use of both oral and parenteral administration in the same label is not acceptable, especially as the drug needs reconstitution prior to the administration. This is a major deficiency as well.

As there are pharmacokinetic data (including a population analysis and plots (visualising the exposure obtained in different age groups) which has not been submitted in this procedure but which were submitted nationally earlier, the applicant is asked to submit this information and to discuss the exposure obtained in the different age/weight groups with the proposed dosing in relation to the observed exposure in adults during treatment with therapeutic doses.

II.4 REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RAPPORTEUR

Major objections

I. Quality

The use of both oral and parenteral administration in the same label is not acceptable, especially as the drug needs reconstitution prior to the administration.

II. Clinical efficacy

It is not accepted to use Losec MUPS in children below the age of 1 and/or below 10 kg because of the lack of an appropriate formulation.

Omeprazole is acid-labile and is therefore approved for oral use as enteric coated tablets. No pharmacokinetic study is available showing that orally administered i.v. solution give equivalent exposure as the same dose administered in an enterocoated formulation. This is a deficiency.

Other concerns

I. Quality

1. It should be clarified which drug product was included in the oral solution stability study.
2. Microbiological data for the storage time of the re-constituted solution should be provided.
3. The light conditions for the product in the syringe and the final sodium bicarbonate solution during the study should be described. Additional data supporting the statement regarding exposure to normal indoor light should be submitted if applicable.

4. A clarification regarding the carbon dioxide effect on the reconstituted product shall be provided, especially in the view that the solution is further diluted with sodium carbonate solution prior to administration.

II. Pharmacokinetics

5. The applicant is asked to submit the plots requested in our national application for the observed non-normalised exposures to be shown (Studies A1, A2, A3 and B3) as well as the population PK/PD study report and to discuss the likely exposures obtained with the suggested doses in different paediatric age groups in comparison to exposure in adults at recommended doses.

II.5 **PROPOSED CHANGES TO THE SPC, ANNOTATED WITH THE RAPPORTEUR'S COMMENTS AFTER EACH SECTION**

Marketing authorisation holders are requested to submit a text proposal for inclusion in the SPC.

Section 4.1 Therapeutic indications or, where relevant in section 4.2. When data are considered insufficient to allow information in 4.1 and/or 4.2 a text proposal for inclusion in Section 5.1 Pharmacodynamic properties should be considered.

Section 4.2 Posology and method of administration: different age categories and/or a lower cut-off age should be mentioned

It is proposed to use the in Sweden nationally approved wording, except for the change to 1 year and $\geq 10\text{kg}$: See below:

Children over ≥ 1 year of age and $\geq 10\text{ kg}$

Reflux oesophagitis. Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

For the indication reflux oesophagitis and symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

Age	Weight	Dosage
$> \geq 1$ year of age	10-20 kg	10 mg once daily. The dosage can be increased to 20 mg once daily if needed.
> 2 years of age	$> 20\text{ kg}$	20 mg once daily. The dosage can be increased to 40 mg once daily if needed.

If symptom control has not been achieved after 2-4 weeks the patient should be investigated further.

Children over 4 years of age

In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori.

Weight	Dosage
15-30 kg	Combination with two antibiotics: Losec Mups 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are administered together 2 times daily for 1 week.

30-40 kg	Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are administered 2 times daily for 1 week.
> 40 kg	Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 1 g and clarithromycin 500 mg are administered 2 times daily for 1 week.

Section 4.8 Undesirable effects: specific heading when relevant

It is proposed to add short information about two of the submitted studies in children in section 5.1.

Section 5.1: It is suggested to include:

Pediatric data:

“In a non-controlled study in children (from one year to 16 years of age) with severe reflux oesophagitis, in 90% of the cases a significant improvement was obtained in the oesophagitis level after a three-month treatment with oral omeprazole at doses ranging from 0.7 to 1.4 mg/kg/day (children weighing over 20 kg, 20 mg; from 10 to 20 kg of weight, 10 mg). Treatment substantially reduced reflux symptoms, though 40% of the patients still had regurgitation and/or vomiting at the end of the healing period.”

In a single-blind study, children aged 0-24 months with clinically diagnosed GERD 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. The result was similar for all three dose groups but with a delay of effect in the lowest dosing group. There was no apparent dose relationship to occurrence of AEs and most AEs were mild or moderate in intensity.

Section 5.2:

This text is approved in Sweden:

“During treatment with the recommended doses to children from the age of 2 years, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.”

The applicant is asked to propose a similar text reflecting the available data in children down to 1 year of age.

II.6 ADDITIONAL COMMENTS FROM MEMBER STATES ON DRAFT ASSESSMENT REPORT

Most member states agreed that oral use of the i.v. solution was not acceptable and agreed with the conclusions of the rapporteur and co-rapporteur.

The indication for *Helicobacter pylori* eradication in children from 4 years was extensively discussed during the procedure as some member states thought that this part of the indication should be refused. Furthermore, it was proposed that omeprazole should only be prescribed in children under the supervision of a specialist and that the effects noted during the long term study on vitamin B12 and serum gastrin levels should be included in the SPC as well as that there are no long term data regarding the effects of omeprazole treatment on puberty and growth. The treatment durations were discussed as well as the description of the available clinical data in sections 4.8 and 5.1.

III. SECOND ROUND

III.1 RESPONSE ASSESSMENT.

Pharmacokinetics

The response provided to requested data. It appears that roughly similar exposure is obtained down to the age of 1 year/ bodyweight 10 kgs.

Clinical efficacy and safety

Most of the issues raised during the first round were solved and the SPC was changed accordingly. The discussion regarding the Helicobacter indication was continued. It was the opinion of the Rapporteur that it is clinical practise to eradicate the Helicobacter pylori in these situations with a combination therapy of Omeprazole and two antibiotics. To remove this indication, (in countries that already approved this indication) could send signals that may give rise to confusion in the profession. However, it was suggested to include a more general wording regarding national guidance on for example bacterial resistance pattern.

IV. THIRD ROUND

IV.1 DAY 115 COMMENTS FROM MEMBER STATES AND FINAL DISCUSSIONS

There was still disagreement concerning the indication for eradication of Helicobacter Pylori. It was finally agreed that Omeprazole should obtain this indication for children older than four years of age if used in combination with antibiotics for treatment of duodenal ulcer caused by Helicobacter pylori. When selecting appropriate combination therapy consideration should be given to official local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

V. FINAL RECOMMENDATION

The applicant is requested to submit a type II variation to include the following text as national type II variations in all member states.

Section 4.1 Indications

Children over 1 year of age and ≥ 10 kg: Reflux oesophagitis. Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

Section 4.2 Posology and method of administration

Reflux oesophagitis

The treatment time is 4-8 weeks

Symptomatic treatment of heartburn and acid regurgitation in gastrooesophageal reflux disease

The treatment time is 2-4 weeks. If symptom control has not been achieved after 2-4 weeks the patient should be investigated further.

The dosage recommendations are as follows:

Age	Weight	Dosage
≥ 1 year of age	10-20 kg	10 mg once daily. <i>The dosage can be increased to 20 mg once daily if needed.</i>
≥ 2 years of age	> 20 kg	20 mg once daily. <i>The dosage can be increased to 40 mg once daily if needed.</i>

Children over 4 years of age

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

Weight	Dosage
15- \leq 30 kg	<i>Combination with two antibiotics: Losec Mups 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7,5 mg/kg body weight are all administrated together 2 times daily for 1 week</i>
30- \leq 40 kg	<i>Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated 2 times daily for 1 week.</i>
>40 kg	<i>Combination with two antibiotics: Losec Mups 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated 2 times daily for 1 week.</i>

Section 4.4 Special warnings and precautions for use

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Section 4.8 Undesirable effects

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 yrs 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.

Section 5.1 Pharmacodynamic properties

Paediatric data: In a non-controlled study in children (1 to 16 yrs of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90 % of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0-24 months with clinically diagnosed GERD 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.

Eradication of Helicobacter pylori in children:

A randomised, double blind clinical study (Héliot study) has concluded to the efficacy and an acceptable safety for omeprazole associated to two antibiotics (amoxicilline and clarithromycine) in the treatment of Helicobacter pylori infection in children of 4 years old and above with a gastritis: Helicobacter pylori eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicilline + clarithromycine versus 9.4% (3/32 patients) with amoxicilline + clarithromycine. However, there was no evidence of clinical benefit demonstrated regarding dyspeptic symptoms. This study does not support any information for children aged less than 4 years old.

Section 5.2 Pharmacokinetic properties

During treatment with the recommended doses to children from the age of 1 year ,similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.