LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Omeprazol Zentiva k.s.
(omeprazole)

SE/H/2507/01/DC

This module reflects the scientific discussion for the approval of Omeprazol Zentiva k.s.. The procedure was finalised at 2024-01-25. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Omeprazol Zentiva k.s., 20 mg, Capsule, hard.

The active substance is omeprazole. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

This is a hybrid application, and the applied product Omeprazol Zentiva k.s. is an immediate-release formulation with Losec 20 mg hard gastro-resistance capsule as reference product. The dosage form and composition of the applied product (immediate release capsule, with sodium hydrogen carbonate as API protectant) is not similar as the reference product (enteric coated pellets in capsule). The excipient sodium hydrogen carbonate acts as API protectant in the stomach, allowing omeprazole to pass to the small intestine without being decomposed by the stomach acids.

Omeprazole is a proton pump inhibitor (ATC: A02BC01). Omeprazole is a racemic mixture of two enantiomers which reduces gastric acid secretion through specific reversible inhibition of the H^+K^+-ATPase acid pump in the parietal cell. Omeprazole inhibits both basal acid secretion and stimulated acid secretion.

Proposed indication:
Indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

Proposed posology and method of administration:
Posology
Adults
The recommended dose is 20 mg once daily for 14 days.

It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms.

The majority of patients achieve complete relief of heartburn within 7 days. Once complete relief of symptoms has occurred, treatment should be discontinued.

Special populations
Renal impairment
Dose adjustment is not needed in patients with impaired renal function.

Hepatic impairment
Patients with impaired hepatic function should be advised by a doctor before taking omeprazole.

Elderly
Dose adjustment is not needed in the elderly.

Method of administration
[Invented name] should be taken on an empty stomach, at least 30 minutes before food and at least 2 hours after last meal. The capsule should be swallowed whole with half a glass of water and must

not be chewed or opened, in order to obtain the full effect of the medicinal product.

II.2 General comments on the submitted dossier

The application for Omeprazol Zentiva k.s., 20 mg, capsule, hard, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, ES, FR, PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Losec, 20 mg, gastro-resistant capsule, hard, authorised in Austria since 1990, with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

The reference product used in the comparative bioavailability study is Losec, 20 mg, gastro-resistant capsule, hard, from Austria with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS FR: Losec, 20 mg, gastro-resistant tablet, authorised in RMS since 1997, with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted studies has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the by the CZ authority (SÚKL) in 2019, 2020 and 2021, without any critical findings. No

inspection of the submitted comparative bioavailability studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Omeprazol Zentiva k.s. are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for the drug substances are adequately drawn up.

Stability studies have been performed with the drug substances. The proposed retest period of 5 years for Zydus is justified. The proposed retest period of 36 months for Uquifa is justified.

Drug Product
The development of the product has been described, the choice of excipients is justified, and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on four batches from Zentiva and two batches from Labormed. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 2 years with storage conditions “Store below 25°C. Store in the original package in order to protect from moisture” for the drug product is considered acceptable.

III.2 Non-clinical aspects

The present procedure is a hybrid procedure where the dosage form and composition differ from the reference product (immediate release capsule, with sodium hydrogen carbonate as API protectant instead of enteric coated pellets in capsule). The pharmacodynamic, pharmacokinetic and toxicological properties of the proton-pump inhibitor (PPI) Omeprazole Zentiva are well known. As omeprazole is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate. A short overview is provided below.

Pharmacology
Omeprazole is a prodrug whose active metabolite blocks the gastric H+,K+-ATPase and thereby gastric acid secretion at the terminal stage of the acid secretory pathway, leading to reduced basal and stimulated acid secretion. Experimentally, the inhibitory effect of omeprazole on acid secretion has been mainly investigated in the dog and the rat (besides humans).

In the rat, omeprazole inhibited basal as well as stimulated acid secretion. Inhibition of the H+/K+ ATPase was correlated with inhibition of gastric acid secretion. When omeprazole is added to permeabilized isolated gastric glands, acid formation driven under anoxic conditions by the addition of ATP is inhibited. Maximum binding of omeprazole to the pump enzyme with full inhibition of acid pumping was 2.5 nmol/mg of the enzyme. Drug concentration in the blood abolished fast with the elimination half-life about 7–10 minutes in rats, while the inhibition prolonged since it was achieved

by covalent binding of activated omeprazole. The
inhibitory effect reaches its maximum at about one hour and acid secretion remains, depending on species, inhibited for up to four days.

Based on in-vitro studies, omeprazole and other PPIs, in addition to their primary inhibitory action on H+/K+ ATPase, exhibit antibacterial effect, probably due to more complex action on e.g. motility, metabolism, and the inhibition of proton pumps present in microbial membranes. Dose-related and permanent (>24 hours) growth inhibition was seen on actively growing Gram-positive cocci, i.e., *Enterococcus faecalis* and *Staphylococcus aureus*. A smaller effect (for 8 hours only) was found on Gram-negative cocci, i.e., *Escherichia coli* and *Klebsiella pneumoniae*. After 24 hours incubation of *Helicobacter pylori* in the presence of omeprazole 200μg/mL bacterial count was reduced to zero compared to 104cfu/mL in the control without omeprazole. The inhibitory effect was reduced after the addition of cysteine to the medium, suggesting omeprazole binding to SH groups in its vicinity, irrespective of the biological target. Omeprazole has also been shown to be anti-parasitic against e.g., *Candida albicans*, *Giardia intestinalis* and *lamblia*, *Schistosoma monsoni*.

In-vitro, PPIs have demonstrated anti-inflammatory effects by selectively inhibiting the tumour necrosis factor-α (TNF-α) and, remarkably, also interleukin-1β (IL-1β) secretion by Toll-like receptor (TLR)-activated human monocytes, in the absence of toxic effects. In-vivo, in a murine model of lethal endotoxic shock, single administration of PPI protected mice from death (60% survival versus 5% in untreated mice) and decreased TNF-α and IL-1β systemic production. A consistent inhibitory effect of omeprazole on the cytokine release, specifically TNF-α, IL-1β and IL-6, was also demonstrated in a study with rat neuropathic pain model.

Pharmacokinetics
Oral administration of omeprazole (single doses of 13.8 and 138.16 mg/kg) to male mice resulted in maximum plasma concentrations (Cmax) obtained in 10 minutes (first plasma sample). Omeprazole levels declined then very rapidly to minimum detectable levels at 0.5 and 2 hours after the gavage. The mean Cmax increased from 15.9 ± 5.3μmol/L after the lowest dose to 155.4 ± 24.5μmol/L after the dose of 138.16 mg/kg, i.e., the concentration increased proportionally to the amount of drug administered. Similarly in rats, oral administration of omeprazole 40mg/kg resulted in rapid absorption; omeprazole was detected in the first plasma sample (5 min) and Cmax were reached at 11.1–40.6 min. In dogs, an intraduodenal dose of omeprazole is very rapidly absorbed. Maximum concentration was already attained during the first 5 to 15 minutes post-dosage. In comparison, intragastric administration results in a lower rate of absorption and a reduction in the systemic availability. Cmax was reached after Cmax was obtained at 30–75 minutes after administration and the AUC was only about 15% of that of a corresponding i.v. dose of omeprazole. In both dogs and humans, there is a close correlation between the area under the plasma concentration curve (AUC) and the inhibitory effect.

Omeprazole is extensively bound to plasma proteins, mainly to albumin and α1-acid-glycoprotein. In comparison with 95% in human plasma, the protein binding is slightly lower in rats and dogs (90 and 87%, respectively). Following i.v. and oral administrations of 14C-labelled omeprazole in rats, the highest concentrations of radiochemical entities were found in the liver, kidneys, and duodenum. The stomach and thyroid gland also concentrated significant amount of the drug. Whole-body autoradiography in mouse showed sustained high levels of radioactivity only in the gastric mucosa. the radioactivity in the rat and mouse brain was moderate or low. Radioactivity was also demonstrated in the foetus in mouse, indicating that that placental barrier is permeable to radiolabelled omeprazole.

In humans, there are two CYP450 isoenzymes that participate in the metabolism of PPIs across species. The CYP2C19 isoenzyme primarily transforms PPIs into hydroxy metabolites, whereas CYP3A4 primarily transforms PPIs into sulfone metabolites. 5-hydroxyomeprazole is the main

metabolite. None of the metabolites contribute to the antisecretory activity of omeprazole. Omeprazole exhibits stereoselective metabolism. The sum of the intrinsic clearances of all three metabolites for S-omeprazole (esomeprazole, ESOM) is one-third of the rate for R-omeprazole. There are species differences in metabolism. For example, omeprazole is mainly metabolized by CYP1A2, CYP2D1, and CYP3A1 in rats. In dogs, the main metabolic route is aromatic hydroxylation at position 6 in the benzimidazole ring. In rat, R-isomer showed significantly higher bioavailability and more potent inhibition of acid secretion than the S-isomer and the racemate, in the dog, however, no differences could be detected between the two isomers.

Following hepatic metabolism, the ultimate excretion of most PPIs is renal. After i.v. administration 25.9 and 32.0% of the dose was excreted via the kidneys over a period of 72 hours in rats and dogs, respectively, while the average cumulative urinary recovery of the oral dose during the same period was 22.7 and 21.2%, respectively. In both rat and dog experiments, more than 90% of the total urinary recovery was excreted during the first 24 hours regardless of the route of administration. The corresponding recoveries in the faeces over the entire collection period were 71.9 and 73.1 % of the i.v. and oral doses, respectively. Less than 0.1% and 0.5% of the amount excreted via the kidneys and in faeces were due to unchanged omeprazole.

Toxicology

In an acute toxicity test in mouse and rat with orally administered omeprazole (highest dose 4g/kg, follow-up 14d after dose), there was no lethality. After i.v. exposure in mouse, the LD50 was 0.08g/kg. The minimal lethal i.v. dose of esomeprazole sodium and omeprazole sodium was 310 mg/kg and 240–310 mg/kg, respectively. The major treatment related clinical signs of toxicity in the acute toxicity studies were salivation, dyspnea, reduced motor activity, increased or decreased respiratory frequency, abdominal respiration, ataxia, tremor, convulsions, and cyanosis.

Omeprazole has been well tolerated in long-term toxicity studies in doses up to 138mg/kg orally in dogs, and 414 mg/kg orally in rats. Except for gastric ECL cell carcinoids found in the rat after life-long treatment, no significant toxicological findings of clinical importance have been observed. In female rats treated with omeprazole (max 138mg/kg) for 3 months, hypergastrinaemia induced by pharmacological inhibition of gastric acid secretion caused a hyperplasia of oxyntic mucosal cells. The hyperplastic mucosa had an increased capacity to produce acid and was functionally normal.

In a 3-month exposure study in rats, oral exposure to S-omeprazole (ESOM) at between 14 and 280 mg/kg led to at 140mg/kg decreased body weight gain (16%, 13%, 28%, in the low, mid, and high dose males, respectively), decreased haemoglobin, packed cell volume, corpuscular volume, increased platelet count and histopathological changes (high dose) in the stomach (the chief cell eosinophilia at vacuolated glandular cells, acanthosis, and hyperkeratosis) and in the kidney (basophilic cortical tubules and inflammatory cell infiltration). Decreased body weight gain (18%) and histopathological changes in the stomach and kidney were also found in the omeprazole treated animals.

Dogs orally exposed to S-omeprazole at 0.65, 5.5, and 28 mg/kg/day for 3 months. At 28 mg/kg/day, histopathological changes were observed in the stomach, and these included mucosal fibrosis, hyperplasia, chief cell atrophy, and focal necrosis in all omeprazole groups.

S-omeprazole was negative in the Ames mutation test, in the in vivo rat bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test. S-omeprazole was however positive in the in vitro human lymphocyte chromosome aberration test. Omeprazole was positive in the in vitro human lymphocyte chromosome aberration test, the in vivo mouse bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test. Omeprazole in carcinogenicity studies (18-month study in mice and a 24-month study in rats) did not generate any neoplasms in mice whereas in rats, gastric ECL cell hyperplasia was present in all treated groups and ECL cell carcinoids

(otherwise rare in controls) were also observed in a dose-related manner (doses 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day corresponding to about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis.

Some DART studies have no signs of omeprazole toxicity while other have been positive. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg (about 5.5–56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, foetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/foetal toxicity and postnatal developmental toxicities were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human doses on a body surface area basis). One study in male rats mapping the risk of sub-chronic use of PPIs (including S-omeprazole) on male fertility found alterations in the levels of hormones such as testosterone, follicle-stimulating hormone, and luteinizing hormone. 45 days oral exposure at 2.5, 5, and 10 mg/kg/day generated reduced sperm count, impaired sperm quality and abnormal sperm.

Environmental Risk Assessment (ERA)
An ERA has been submitted for omeprazole, with the justification that no Phase I assessment is necessary as there has been no significant increase in consumption the previous years (from 2019 to 2022) for the relevant RMS+CMS countries (SE, DE, ES, FR, PT). Under the present CHMP ERA guideline framework (EMEA/CHMP/SWP/4447/00 corr 2*), this is acceptable.

There are no objections to approval of Omeprazole Zentiva from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two studies evaluating pharmacokinetics, bioavailability and food effect.

Pharmacokinetic properties of the active substance
Omeprazole is acid labile and therefore the formulation of Omeprazol Zentiva k.s. contains sodium hydrogen carbonate which neutralises acid pH of the stomach and thus protects omeprazole from acid degradation, enabling absorption.

Study 838/21 (Bioavailability and food effect)
Methods
This was a single-dose, four-period study conducted in 20 healthy volunteers, comparing Omeprazole, 20 mg, capsule (test) with Losec, 20 mg, hard gastro-resistant capsule (reference) under fasting conditions in Period 1 (reference) and Period 2 (test). The study design and methodology were modified in protocol amendment 02. Period 3 was cancelled. Period 4 was conducted under fed conditions to evaluate the influence of potential food intake on the bioavailability of the test product. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of omeprazole were determined with a LC/MS-MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 25 January 2022 and 21 April 2022.

Results
The pharmacokinetic profiles and the results from the pharmacokinetic and statistical analysis are presented below.

Pharmacokinetic profile of means

Figure 1: Mean plasma concentration-time profiles for Test 1 and Reference formulations (linear scale)

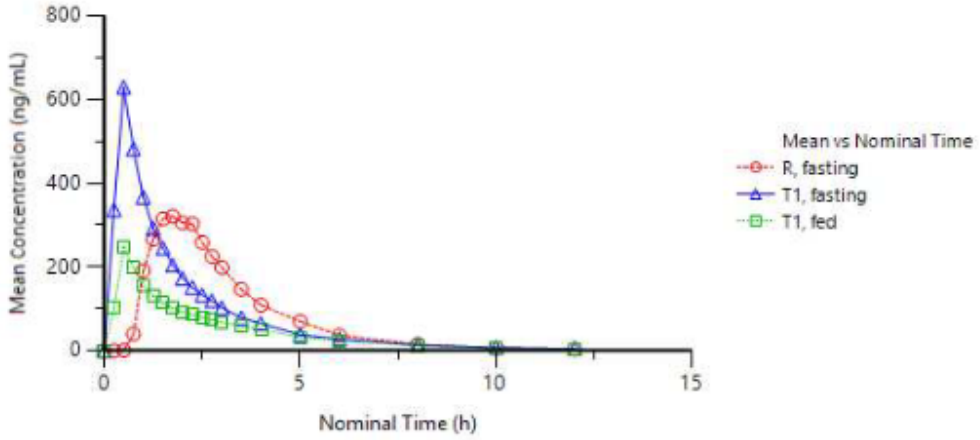
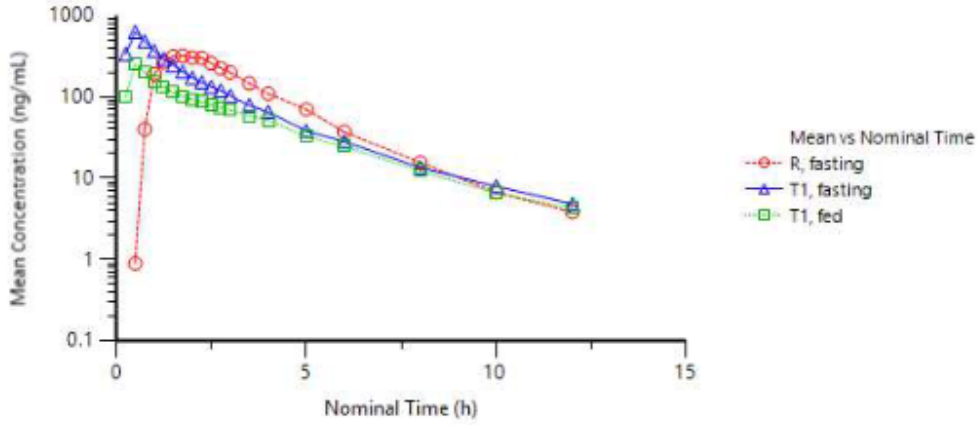


Figure 2: Mean plasma concentration-time profiles for Test 1 and Reference formulations (semi-logarithmic scale)



Test vs. Reference under fasting conditions (Stage 1)

Stage 1									
Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/R (%)	90% CONFIDENCE LIMITS (%)		BE	CV_{intra} (%)
	N	Test	N	Ref.		Lower	Upper		
$AUC_{(0-t)}$ (ng·h/mL)	18	685.7	18	658.7	104.09	96.71	112.03	YES	12.73
$AUC_{(0-\infty)}$ (ng·h/mL)	18	708.6	18	679.2	104.32	97.04	112.16	YES	12.53
C_{max} (ng/mL)	18	590.6	18	385.3	153.28	135.76	173.08	NO	21.17

Note: Subjects No. 04 and 20 were excluded from statistical assessment.

For AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. For C_{max} the 90% confidence interval for the ratio of the test and reference products fell outside the conventional acceptance range of 80.00-125.00%.

Test under fed vs. Test under fasting conditions (Stage 3)

Stage 3									
Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO $T_{fed}/T_{fasting}$ (%)	90% CONFIDENCE LIMITS (%)		BE	CV_{intra} (%)
	N	T_{fed}	N	$T_{fasting}$		Lower	Upper		
$AUC_{(0-t)}$ (ng·h/mL)	17	329.7	17	655.3	50.31	41.60	60.86	NO	32.60
$AUC_{(0-\infty)}$ (ng·h/mL)	17	363.0	17	677.4	53.58	45.51	63.08	NO	27.77
C_{max} (ng/mL)	17	225.0	17	578.5	38.90	31.07	48.70	NO	38.90

Note: Subjects No. 04, 15, and 20 were excluded from statistical assessment.

Compared to fasting conditions, a high-fat, high-calorie meal decreased the mean AUC_{0-t} and C_{max} of omeprazole by 50% and 61%, respectively.

Study 883/22 (Bioavailability)

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Omeprazole, 20 mg, hard capsule (test) with Losec, 20 mg, gastro-resistant capsule (reference) under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 10 hours post-dose. Plasma concentrations of omeprazole were determined with a LC/MS-MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 10 September 2022 and 29 September 2022.

Results

The pharmacokinetic profiles and the results from the pharmacokinetic and statistical analysis are presented below.

Pharmacokinetic profile of means

Figure 1: Mean OML plasma concentration-time profiles for Test and Reference formulations (linear scale)

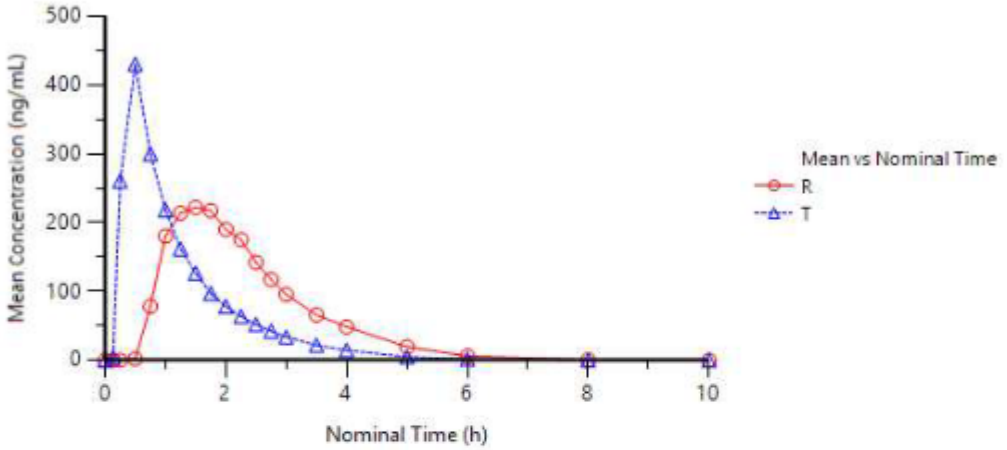
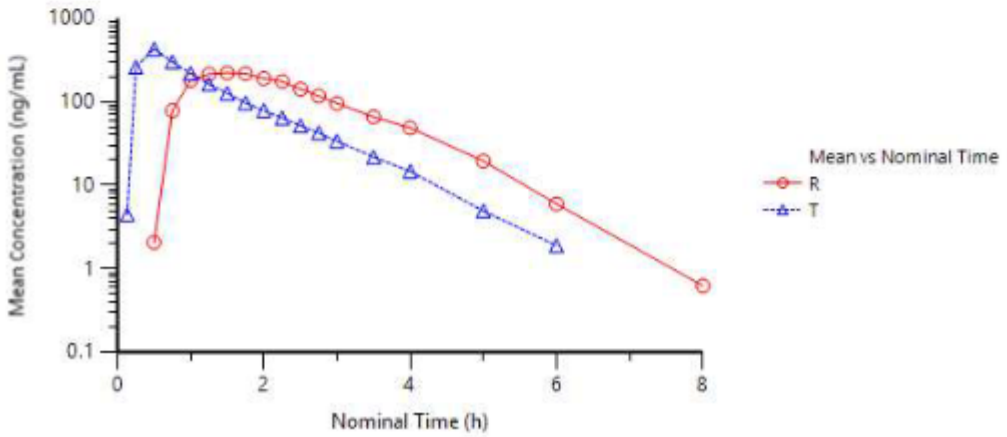


Figure 2: Mean OML plasma concentration-time profiles for Test and Reference formulations (semi-logarithmic scale)



Summary tables of arithmetic means and comparative bioavailability data

Table 6 Summary Table of Arithmetic Means

Parameter	TEST			REFERENCE			RATIO T/R (%)
	N	MEAN	± SD	N	MEAN	± SD	
$AUC_{(0-t)}$ (ng·h/mL)	23	477.9	296.3	23	509.2	302.2	93.86
$AUC_{(0-\infty)}$ (ng·h/mL)	23	494.0	298.8	21	557.5	300.8	88.60
C_{max} (ng/mL)	23	445.8	221.6	23	345.8	213.7	128.94
t_{max} (h)	23	0.47	0.11	23	1.75	0.79	26.71
λ_z (h^{-1})	23	0.84523	0.15061	21	0.88141	0.16255	95.90
$t_{1/2}$ (h)	23	0.85	0.17	21	0.81	0.16	104.26

N = Number of observations

Table 8 Confidence Intervals
(ln-transformed Distribution)

Parameter	GEOMETRIC LEAST SQUARES MEANS				RATIO T/R (%)	90% CONFIDENCE LIMITS (%)		BE	CV_{intra} (%)
	N	Test	N	Ref.		Lower	Upper		
$AUC_{(0-t)}$ (ng·h/mL)	23	396.3	23	422.0	93.90	86.34	102.12	YES	16.64
$AUC_{(0-\infty)}$ (ng·h/mL)	23	413.9	21	451.4	91.70	84.64	99.34	–	15.08
C_{max} (ng/mL)	23	388.1	23	284.3	136.53	117.63	158.46	–	29.97

Note: Subject No. **17** was excluded from statistical assessment; N = Number of subjects

For AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. For C_{max} the 90% confidence interval for the ratio of the test and reference products fell outside the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The applied product is an immediate-release formulation. In general, the clinical program appears sufficient to characterise the new formulation. A single-dose bioavailability study is adequate. As the SmPC of the reference product recommends administration with or without food a study in the fasting state is appropriate. A study comparing the food-effect of the test formulation is also adequate.

The submitted bioavailability and food effect studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The bioanalytical methods were adequately validated.

Study 883/22: After administration of the test product, earlier t_{max} values were observed compared to the Losec capsules. Median t_{max} values were earlier (0.50 vs. 1.50 h). As expected, C_{max} values were higher after administration of the test formulation. This indicates the immediate release behaviour of the test product compared to the modified-release characteristics of the reference product.

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. Literature data was provided to support that the efficacy can be considered similar with similar AUC levels and that the safety was not a concern with the higher C_{max}. For AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The results from study 838/21 indicate that the extent of omeprazole absorption was significantly reduced when the test formulation was administered under fed conditions. Compared to fasting conditions, a high-fat, high-calorie meal decreased the mean $AUC_{(0-t)}$ and C_{max} of omeprazole by 50% and 61%, respectively.

Omeprazol Zentiva k.s. should be taken on an empty stomach due to the significant food effect. The recommendation to take the product at least 30 minutes before food and at least 2 hours after last meal is considered acceptable. It is described in the package leaflet that the product can be taken in the morning before breakfast. This is considered sufficient to keep the fasted state before intake of omeprazole.

Pharmacodynamics
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

Clinical efficacy
The omeprazole reference product has been registered for decades and its clinical effects are well-known. The applicant has submitted several publications of studies on the effects of omeprazole.

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

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

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease. 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.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) and not to the actual plasma concentration at a given time. Hence, the higher C_{max} observed for the test product will not compromise the efficacy of the product.

The peak plasma levels after absorption of Omeprazol Zentiva is occurring approximately 30 min after dose. In the standard preparation (Losec) the peak occurs 1-2 hours after dose. As described in the posology section, it might be necessary to take the capsules for 2-3 consecutive days to achieve

improvement of symptoms. In the 883/22 study presented in the pharmacokinetic section, gastric pH was measured, and an early slight increase of pH is observed shortly after intake of the test item. This increase is likely due to the excipient bicarbonate which aims to protect the omeprazole in the acidic milieu. No clinically relevant benefit from the faster absorption is assumed and no such claims are put forward by the applicant.

Clinical safety
Omeprazole in proposed omeprazole formulation is released immediately, whereas the omeprazole in the omeprazole reference product is released by modified-release characteristics. In line with this, C_{max} of proposed omeprazole formulation is achieved earlier with a higher amplitude compared to the C_{max} after administration of the reference product Losec (see pharmacokinetics section).

The applicant has provided a justification regarding the higher C_{max}, mainly referring to the C_{max} for approved products of higher strength. It is acknowledged that higher doses of omeprazole are approved with no additional safety concerns. Further, intravenous formulations leading to higher peak C_{max} are also approved. Comparison of C_{max} with 40 mg omeprazole immediate release suspension and delayed-release omeprazole capsule are presented, but no data is presented on the frequency of reported adverse event at the higher doses. The clinical experience with omeprazole at higher doses and intravenous formulation is extensive and no significant safety concerns due to the higher C_{max} of the 20 mg immediate release formulation is expected.

There are no objections to approval of Omeprazole Zentiva from a clinical point of view.

Pharmacovigilance system

Proposed MAH: Zentiva k.s., Zentiva France, Zentiva Portugal Lda.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Proposed MAH: Cassella-med GmbH & Co. KG.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Omeprazol Zentiva k.s..

Part II Safety specification

Summary of safety concerns	
Important identified risks	None.
Important potential risks	None.
Missing information	None.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 1.0 signed 20 Sep 2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

To support the application, the applicant has submitted two clinical studies evaluating the pharmacokinetics, bioavailability and food effect. No further clinical studies were conducted. The application contains a sufficient review of published clinical data.

After administration of Omeprazol Zentiva k.s. (test), earlier t_{max} values were observed compared to the reference Losec capsules. Median t_{max} values were earlier (0.50 vs. 1.50 h). As expected, C_{max} values were higher after administration of the test formulation. This indicates the immediate release behaviour of the test product compared to the modified-release characteristics of the reference product.

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. Literature data was provided to support that the efficacy can be considered similar with similar AUC levels and that the safety was not a concern with the higher C_{max}. For AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The results also indicate that the extent of omeprazole absorption was significantly reduced when the test formulation was administered under fed conditions. Compared to fasting conditions, a high-fat, high-calorie meal decreased the mean $AUC_{(0-t)}$ and C_{max} of omeprazole by 50% and 61%, respectively.

Omeprazol Zentiva k.s. should be taken on an empty stomach due to the significant food effect. The recommendation to take Omeprazol Zentiva k.s. at least 30 minutes before food and at least 2 hours after last meal is considered acceptable. It is described in the package leaflet that the product can be taken in the morning before breakfast. This is considered sufficient to keep the fasted state before intake of omeprazole.

The applicant has provided a justification regarding the higher C_{max}, mainly referring to the C_{max} for approved products of higher strength. It is acknowledged that higher doses of omeprazole are approved with no additional safety concerns. Further, intravenous formulations leading to higher peak C_{max} are also approved. Comparison of C_{max} with 40 mg omeprazole immediate release suspension and delayed-release omeprazole capsule are presented, but no data is presented on the frequency of reported adverse event at the higher doses. The clinical experience with omeprazole at higher doses and intravenous formulation is extensive and no significant safety concerns due to the higher C_{max} of the 20 mg immediate release formulation is expected.

The quality of the generic product, Omeprazol Zentiva k.s., is found adequate. There are no objections to approval of Omeprazol Zentiva k.s., from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The user test was assessed and accepted at day 70.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-