BIOS LAB PVT. LTD.

B-8, MILAN COMPLEX, SARKHEJ, AHMEDABAD.

QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS

See Rule 150 E (F) Under The Drugs & Cosmetic Act 1940 and The Rules there under

Report No. : F/C/20180 **Mfg. No.:** 6/UA/2019, 5/UA/SC/P-2019

Sample Name : XEOZIA™-RD CAPSULES

Generic Name : Esomeprazole (EC) 40mg + Domperidone (SR) 30mg Capsules

Product Name	**XEOZIA™-RD**	**A.R.No.**	F/C/20180	**Ref. No.**	STS/F/664/00
Batch No.	199AA01	**Batch Size**	0.60 Lacs Capsules		
Mfg. Date	JAN. 2021	**Sample Qty.**	80 Capsules		
Exp. Date	DEC. 2022	**Test as per**	Manufacturer Specification		
Date of Receipt	05-02-2021	**Date of Release**	07-02-2021		

S NO.	TEST	SPECIFICATION	RESULT
1.	Description	Green coloured cap and colourless body hard gelatin capsule contain white and orange coloured pellets	Green coloured cap and colourless body hard gelatin capsule contain white and orange coloured pellets
2.	Identification	Positive test of assay	Complies
3.	Average weight	333 mg ± 5.0%	327.79 mg
4.	Uniformity of weight	± 5.0% of average weight	Upper Limit +4.1% Lower Limit -2.7%
5.	Net content	-	270.09 mg
6.	Dissolution for Esomeprazole magnesium In Acid medium In Buffer	 NMT 15.0% NLT 70.0%	 4.25% to 6.89% 86.26% to 90.49%
7.	Dissolution for Domperidone 1st hour 4th hour 8th hour 12th hour	 NLT 15.0% - NMT 40.0% NLT 30.0% - NMT 60.0% NLT 55.0% - NMT 85.0% NLT 70.0%	 26.32% to 32.12% 40.97% to 50.68% 74.64% to 82.31% 89.46% to 98.26%
8.	ASSAY Esomeprazole magnesium trihydrate IP Eq. to Esomeprazole - 40 mg Domperidone (SR) - 10 mg	Each hard gelatin capsules contains NLT 90.0% - NMT 110.0% NLT 90.0% - NMT 110.0%	 39.624 mg (99.06%) 9.85 mg (98.50%)

Reports: The sample reffered to above is of standard quality as defined in the act and the Rules made there under

Conclusion: The above collected sample is complies as per I.H Specification.

*** Manufactured by:** SARV PHARMACEUTICALS (HARIDWAR)

XEOZIA™- RD

PRODUCT DESCRIPTION

Each XEOZIA™- RD hard gelatin capsule contains

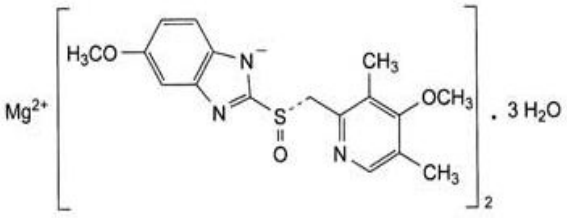
Esomeprazole magnesium trihydrate – 40 mg (As enteric coated pellets)

Domperidone IP– 30 mg (As sustained release pellets)

DESCRIPTION

Esomeprazole:

Structural formula:



Molecular formula: $(C_{17}H_{18}N_3O_3S)_2 Mg \times 3\ H_2O$

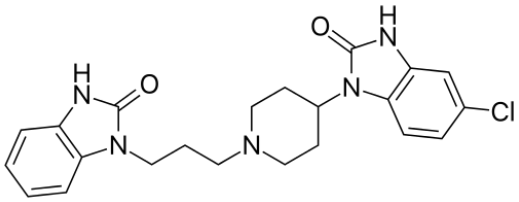
Chemical name: 5-methoxy-2-[(S)-(4-methoxy-3, 5-dimethylpyridin-2-yl) methanesulfinyl]-1H-1, 3-benzodiazole

Molecular weight: 767.2 g/mol as a trihydrate and 713.1 g/mol on an anhydrous

pKa: 4.78

Domperidone:

Structural formula:



Molecular formula: $C_{22}H_{24}ClN_5O_2$

Chemical name: 5-chloro-1-{1-[3-(2-oxo-2, 3-dihydro-1H-1, 3-benzodiazol-1-yl) propyl] piperidin-4-yl}-2, 3-dihydro-1H-1, 3-benzodiazol-2-one

Molecular weight: 425.911 g/mol

pKa: 7.9

XEOZIA™- RD is available as capsule for oral administration. It contains Esomeprazole 40 mg & Domperidone 30 mg capsule. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S-and R-isomers. Domperidone is a derivative of benzimidazole that possesses both pro-kinetic and anti-emetic properties due to its inhibitory action at dopamine D2-receptors.

PHARMACOLOGIC PROPERTIES:

Mechanism of Action

Esomeprazole:

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+- ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Domperidone:

Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. The low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

PHARMACODYNAMICS

Esomeprazole:

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After 5 days of oral dosing with 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 17 hours respectively, over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%. Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown. Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment. One week's treatment with esomeprazole 40 mg once daily and appropriate antibiotics, results in successful eradication of H. pylori in approximately 90% of patients. After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumors. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin

levels, have been observed in both children and adults during long-term treatment with esomeprazole. The findings are considered to be of no clinical significance. During long-term oral treatment with antisecretory medicinal products, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible. Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalized patients, possibly also Clostridium difficile.

Domperidone:

Domperidone is a specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in dopaminergic mechanisms.

In man, oral domperidone to increase lower esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

PHARMACOKINETICS

Esomeprazole:

Absorption

Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once daily administration. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy patients is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Metabolism

Esomeprazole is completely metabolized by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

Excretion

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolizers. Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration. The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent medicinal product is found in urine.

Linearity/non-linearity

The pharmacokinetics of esomeprazole has been doses up to 40 mg twice daily. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Domperidone:

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal patients when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and

approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy patients but is prolonged in patients with severe renal insufficiency.

NONCLINICAL PROPERTIES

Animal Toxicology or Pharmacology

Esomeprazole:

No special hazard for humans, safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. No any adverse reactions are observed and with possible relevance to clinical use were as follows: gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

Domperidone:

There is moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26-47 fold, based on IC_{50} values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered 3 times a day. Safety margins for prolongation of action potential duration in in vitro experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 45 fold. Safety margins in in vitro pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9 up to 45 fold. In in vivo models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22 fold and 435 fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3 fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day).

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3 fold. At a high, maternally toxic dose (more than 40 times the recommended human dose).

INDICATIONS

XEOZIA™-RD Capsules are indicated for the treatment of adult patients with gastroesophagal reflux disease (GERD) not responding to esomeprazole alone.

- Acid reflux (Gastroesophageal Reflux Disease/GERD)
- Dyspepsia
- Hyperacidity
- Heartburn

- Peptic ulcers

CONTRAINDICATIONS

Esomeprazole:

- Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria (see section Undesirable Effects).
- Esomeprazole should not be used concomitantly with nelfinavir.

Domperidone:

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone
- Prolactin-releasing pituitary tumor (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g. in patients with gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.
- Co-administration with QT-prolonging drugs, at the exception of apomorphine.
- Co-administration with potent CYP3A4 inhibitors.

WARNINGS & PRECAUTIONS

Esomeprazole:

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Long Term Use

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

On Demand Treatment

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.

Gastrointestinal Infections

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter (see section Pharmacodynamic Properties).

Absorption of Vitamin B_{12}

Esomeprazole, like all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption

on long-term therapy (e.g. longer than 3 years).

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of Fracture
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognized risk factors. P
Proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Subcutaneous Lupus Erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun- exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping esomeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.
The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.
Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.
Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving esomeprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Presence of Gastric Malignancy
In adults, symptomatic response to therapy with esomeprazole does not preclude the

presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

Acute Interstitial Nephritis
Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops (see section Contraindications)

Clostridium difficile-Associated Diarrhea
PPI therapy like esomeprazole may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve (see section Undesirable Effects). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole, refer to Warnings and Precautions section of the corresponding prescribing information.

Fundic Gland Polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Combination with other medicines
Co-administration of esomeprazole with atazanavir is not recommended (see section Drug Interactions). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded. Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section Drug Interactions). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.
When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see section Drug Interactions).
Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole with St. John's Wort or rifampin. Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing

information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section Pharmacodynamic Properties).

If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Domperidone:

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section Undesirable Effects).

Domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section Undesirable Effects). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section Contraindications). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine

Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the coadministration with apomorphine outweighs the risks, and only if the recommended precautions for co- administration mentioned in the apomorphine SmPC are strictly fulfilled. Please refer to the apomorphine SmPC.

Renal Impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For

repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

SPECIAL POPULATIONS

Renal Impairment

Dose adjustment is not required in all patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section Pharmacokinetic Properties).

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

Hepatic Impairment

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded (see section Pharmacokinetic Properties). Domperidone is contraindicated in moderate or severe hepatic impairment. Dose modification in mild hepatic impairment is however not needed.

Geriatric Population

Dose adjustment is not required in the elderly.

Pediatric Population

Safety and effectiveness of XEOZIA™- RD in pediatric patients have not been established

Esomeprazole:

Poor metabolizers

Approximately 2.9 ±1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolizers. In these individuals, the metabolism of esomeprazole is probably mainly catalyzed by CYP3A4. After repeated once daily administration of 40 mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolizers than in patients with a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

Gender

Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration. These findings have no implications for the posology of esomeprazole.

Hepatic Impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in

patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal Impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Geriatric Use

The metabolism of esomeprazole is not significantly changed in elderly patients (71-80 years of age). No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

No relevant data is available for esomeprazole in pediatric population.

Safety and effectiveness of esomeprazole in pediatric patients have not been established.

Pregnant Women

Data on exposed pregnancies with esomeprazole are insufficient. With the racemic mixture, omeprazole data on a larger number of exposed pregnancies. No malformative nor foetotoxic effect.

Esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. There is no direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing esomeprazole to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole. It do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section Animal Toxicology or Pharmacology).

Lactating Women

It is not known whether esomeprazole is excreted in human breast milk, there is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

Fertility

Esomeprazole oral administration do not indicate effects with respect to fertility.

Domperidone:

Hepatic Impairment

In patients with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy patients. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Patients with mild hepatic

impairment have a somewhat lower systemic exposure than healthy patients based on C_{max} and AUC, with no change in protein binding or terminal half-life. Patients with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see section Contraindications).

Renal Impairment

In patients with severe renal insufficiency (creatinine clearance <30ml/min/1.73m2) the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in healthy volunteers. Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency.
However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

Pediatric Population

No pharmacokinetic data are available in the pediatric population.

Pregnant Women

There are limited post-marketing data on the use of domperidone in pregnant women. It may have reproductive toxicity at maternally toxic doses (see section Animal Toxicology or Pharmacology). Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactating Women

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

Effects on Ability to Drive and Use Machines

Esomeprazole:

Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) have been reported (see section Undesirable Effects). If affected patients should not drive or use machines.

Domperidone:

Domperidone has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Esomeprazole:

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported. (and also from post-marketing use). In

addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse medicinal product reactions have been identified or suspected in program for esomeprazole administered orally or intravenously and post-marketing when administered orally. The reactions are classified according to frequency: very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic
	Not known	Systemic lupus erythematosus
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia (see section Special Warnings and Precautions for Use); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis, pancreatitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Not known	Subacute cutaneous lupus erythematosus (see section Special Warnings and Precautions for Use),
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist, or spine (see section Special Warnings and Precautions for Use)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis: in some patients, renal failure has been reported
	Not known	Acute kidney injury
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

Pediatrics

Safety and effectiveness of esomeprazole in pediatric patients have not been established.

Domperidone:

Tabulated list of adverse reactions

The safety of domperidone was evaluated. The patients with dyspepsia, gastro-esophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions. The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). In diabetic gastroparesis or symptoms secondary to chemotherapy or Parkinsonism were excluded.

The following terms and frequencies are applied: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), Where frequency cannot be estimated, it is recorded as "Not known".

System Organ Class	Adverse Drug Reaction Frequency		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal

Eye disorders			Oculogyric crisis
Cardiac disorders (see section Special Warnings and Precautions for Use)			Ventricular arrhythmias Sudden cardiac death QTc prolongation Torsade
Gastrointestinal	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue		Rash Pruritus	Urticaria Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain	Gynaecomastia Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

Domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. If your patient experiences any side-effects, write to info@bioslab.co.in. By reporting side-effects, you can help provide more information on the safety of this product.

DRUG INTERACTIONS

Esomeprazole:

Effects of esomeprazole on the pharmacokinetics of other medicinal products

Protease inhibitors

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir

100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36–39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section Special Warnings and Precautions for Use) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section Contraindications).
For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (with concomitant ritonavir).

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

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

Medicinal products with pH dependent absorption
Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, atazanavir, iron salts, mycophenolate mofetil (MMF), itraconazole, and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy patients increased the bioavailability of digoxin by 10% (up to 30%). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic medicinal product monitoring of digoxin should then be reinforced.
Co-administration of omeprazole in healthy patients and in transplant patients

receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution in transplant patients receiving MMF.

Medicinal products metabolized by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolizing enzyme. Thus, when esomeprazole is combined with medicinal products metabolized by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased, and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy.

Diazepam
Concomitant oral administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin
Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy patients in, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride
In healthy volunteers, concomitant oral administration of 40 mg esomeprazole and cisapride resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Warfarin
Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients showed that coagulation times were within the accepted range. However, post-marketing of oral esomeprazole, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment

during treatment with warfarin or other coumarin derivatives.

Clopidogrel
Healthy patients have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone. There was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these patients were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups. Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction Amoxicillin or quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Naproxen or Rofecoxib
Concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions.

Effects of other medicinal products on the pharmacokinetics of esomeprazole Medicinal products which inhibit CYP2C19 and/or CYP3A4
Esomeprazole is metabolized by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole.
Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4
Medicinal products known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism. Avoid concomitant use of St. John’s Wort or rifampin with esomeprazole.

Pediatricpopulation
No data available for pediatric population, Analysis have only been performed in adults.

Domperidone:

The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated QTc prolonging medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) (see section Contraindications).
- Apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SmPC. Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:
    - protease inhibitors
    - systemic azole antifungals
    - some macrolides (erythromycin, clarithromycin, telithromycin) (see section Contraindications).

Concomitant use of the following substances is not recommended Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides. (See section Contraindications)

Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

Oral ketoconazole or oral erythromycin in healthy patients confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs.

With the combination of oral domperidone 10 mg four times daily and ketoconazole 200 mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral

erythromycin 500 mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold. Domperidone monotherapy at 10 mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole) and 2.5 msec (erythromycin), while ketoconazole monotherapy (200 mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

DOSAGE AND ADMINISTRATION

Dosage: XEOZIA™- RD capsule should be taken once daily at least 1 hour before meals.

Method of Administration

- The capsules should be swallowed whole with liquid. The capsules should not be opened or chewed or crushed.
- It is recommended to take XEOZIA™- RD before meals.
- Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted, and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

OVERDOSAGE

Esomeprazole:

There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience.

Domperidone:

Symptoms

Symptoms of over dosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

INCOMPATIBILITIES: Not applicable

SHELF-LIFE: As on the pack.

STORAGE CONDITION

- Store in a cool, dark & dry place.
- Protect from direct sunlight & moisture.
- Store below 25°C.
- Keep out of reach of children.

PRESENTATION: Esomeprazole (EC) 40mg + Domperidone (SR) 30mg Capsules

PACKING: 1*10 CAP

For the use only of a Registered Medical Practitioner or Hospital or a Laboratory

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