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CIN NO: U24231GJ1992PLC018237

MEGASTROLE 40 INJ - SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product

Generic Name/INN Name: Omeprazole for Injection 40 mg

Trade Name: MEGASTROLE 40 INJ

Strength:

Each vial contains:
Omeprazole Sodium BP eq. to
Omeprazole 40 mg

2. Qualitative and Quantitative composition:

Sr. No	Ingredients	Spec	Label claim (mg/Vial)	Std. Qty. mg/Vial	Function
1.	Sterile Omeprazole Sodium (Lyophilized) equivalent to Omeprazole*	BP	40.00 mg	123.00 mg	Active

* Add the calculated quantity based on the Assay (potency) and Water content of sterile Omeprazole Sodium BP.

3. Pharmaceutical form:

Dosage Form: Powder for Injection

Visual & Physical characteristics of the product: A white or almost white, hygroscopic powder filled in intactly sealed Amber glass vial.

4. Clinical particulars

4.1. Therapeutic indications:

As alternative treatment of the oral formulation where fast and pronounced acidity inhibition is required for:

Duodenal ulcer

Benign gastric ulcer

Reflux oesophagitis

Zollinger-Ellison syndrome

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4.2. Posology and method of administration:

Dosage

Route of administration: I.V. use.

Omeprazole 40 mg as once daily intravenous application is only recommended in those incidental cases where oral therapy is inappropriate and pronounced acidity inhibition is essential. The mean reduction of acid production in the stomach during 24 hours is circa 90%. With Zollinger-Ellison patients the recommended initial dosage is 60 mg Omeprazole per day. For a 60 mg dose an additional half (5 ml) of the reconstituted solution should be given as an intravenous injection. Any unused solution should be discarded. Higher dosages can be necessary and the dosage should be individually adjusted. With a total dosage of more than 60 mg per day the administration of the daily dosage should be spread out over the day. A one week treatment is usually sufficient.

Reduced renal or hepatic function

The dosage does not need to be adjusted for renal function. In patients with hepatic function disorders the biological availability can be enhanced and the plasma half-life of Omeprazole can increase. In these patients a daily dosage of 10-20 mg can be sufficient.

Children

There is limited experience of use in children. Therefore Omeprazole injection is not recommended in children.

The elderly

Omeprazole can be administered to the elderly without adjustment of the dosage.

Method of administration:

Omeprazole injection solution may only be administered as an intravenous injection. The solution must not be added to an infusion solution. After preparation the injection must be administered slowly with a maximum speed of 2 ml/minute (over a period of at least 5 minutes, or 2.5 minutes when half of the reconstituted solution is given). After reconstitution, the preparation should be used within 4 hours and any unused portion should be discarded.

4.3. Contraindications:

Omeprazole is contraindicated in patients with hypersensitivity to Omeprazole.

Omeprazole like other proton pump inhibitors should not be administered with Atazanavir.

4.4. Special warnings and precautions for use:

In patients with peptic ulcer disease Helicobacter pylori-status should be determined if relevant. In patients who are shown to be Helicobacter pylori-positive, the elimination of the bacterium by eradication therapy should be aimed wherever possible.

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

The diagnosis of reflux oesophagitis should be confirmed endoscopically.

Decreased gastric acidity, due to any means – including proton-pump inhibitors – increases gastric counts of bacteria normally present in the gastro-intestinal tract. Treatment with acid-reducing medicinal products leads to a slightly increased risk of gastrointestinal infections, such as Salmonella and Campylobacter.

In patients with severe impaired hepatic function, liver enzyme values should be checked periodically during treatment with Omeprazole.

During combination treatment caution should also be exercised in patients with severe renal and hepatic dysfunction.

Blindness and deafness have been reported in the use of the injection form of Omeprazole; therefore, in severely ill patients the monitoring of visual and auditory senses is recommended.

This medicinal product is essentially 'sodium- free'. The total amount of sodium (Na+) in the reconstituted solution is less than 1 mmol (23 mg) per 40 mg dose.

4.5. Interaction with other medicinal products and other forms of interaction:

As Omeprazole is metabolised in the liver through cytochrome P450 isoforms (mainly CYP 2C19, S-mephenytoin hydroxylase) and inhibits enzymes of the CYP2C subfamily (CYP 2C19 and CYP 2C9) it can delay the elimination of other active substances metabolised by

these enzymes. This has been observed for diazepam (and also of other benzodiazepines as triazolam or flurazepam), phenytoin and warfarin.

In patients under continuous treatment with phenytoin, the concomitant treatment with 20 mg daily of Omeprazole orally did not modify the phenytoin plasma concentration. In the same way, the concomitant treatment with 20 mg daily of Omeprazole orally did not cause a modification in the coagulation time in patients under continuous treatment with warfarin. Periodic monitoring of patients receiving warfarin or phenytoin is recommended and a reduction of warfarin or phenytoin dose may be necessary.

Other active substances that could be affected are hexabarbital, citalopram, imipramine, clomipramine etc.

Omeprazole may inhibit the hepatic metabolism of disulfiram. After concomitant oral use, some possibly related cases of muscular rigidity have been reported.

There are contradictionary data on the interaction of orally administered Omeprazole with ciclosporin. Therefore, the plasma levels of ciclosporin should be monitored in those patients treated with Omeprazole, because an increase in ciclosporin levels is possible.

Plasma concentrations of Omeprazole and clarithromycin are increased during concomitant oral administration. Although, there is no interaction with metronidazole or amoxicillin, these antimicrobial agents are used concomitantly with Omeprazole in order to eradicate Helicobacter pylori.

Due to the decreased intragastric acidity, the absorption of ketoconazole or itraconazole may be reduced during Omeprazole treatment as it is with other acid secretion inhibitors and antacids.

Simultaneous treatment with Omeprazole and digoxin in healthy subjects lead to a 10 % increase in the bioavailability of digoxin as a consequence of the increased gastric pH.

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, Cmax, and Cmin). Increasing the atazanavir dose to 400 mg did not compensate for the impact of Omeprazole on atazanavir exposure. Proton pump inhibitors including Omeprazole should not be co-administered with atazanavir (see section 4.3).

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Omeprazole may reduce the oral absorption of vitamin B12. This should be taken into account in those patients with low basal levels who undergo a long-term treatment with Omeprazole.

Because of potential clinically significant interaction St. John's wort should not be used concomitantly with Omeprazole.

There is no evidence of an interaction with caffeine, propranolol, theophylline, metoprolol, lidocaine, quinidine, phenacetin, estradiol, amoxicillin, budesonide, diclofenac, metronidazole, naproxen, piroxicam, or antacids when Omeprazole is given orally.

4.6. Pregnancy and lactation:

There is limited experience on the use of Omeprazole in pregnant women. Experience to date indicates no increased risk of congenital malformations or other adverse effects of Omeprazole on pregnancy or the unborn child. Animal studies do not indicate direct or indirect harmful effects with respect to reproduction.

Omeprazole Injection should only be prescribed during pregnancy when strictly indicated.

Omeprazole is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Omeprazole Injection should be made taken into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

4.7. Effects on ability to drive and use machines:

No studies on the ability to drive and use machines have been performed. However, apart from side effects affecting the CNS or visual abilities, no effects on the ability to drive are expected from the intake of Omeprazole.

4.8. Undesirable effects:

Omeprazole is well tolerated, in general, undesirable effects are mild and reversible. In clinical trials performed and post-authorisation follow up, the following undesirable effects have been notified, although in most cases a casual relationship could not be established between such reactions and Omeprazole treatment. In order to classify them the following frequencies definition have been followed:

- very common (≥1/10)
- common (≥1/100, ≥1/1,000, ≥1/10,000, ≤1/1,000)

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- very rare (≤1/10,000 including isolated reports)

Blood and the lymphatic system disorders	Rare: leucopenia, thrombocytopenia, agranulocytosis and pancytopenia. Very rare: changes in blood count
Immune system disorders	Uncommon: urticaria. Rare: hypersensitivity reactions e.g. fever, angioedema, bronchospasm and anaphylatic shock, allergic vasculitis.
Nervous system disorders	Common: somnolence, sleep disturbances (insomnia), vertigo, headaches and drowsiness. These complaints usually improve during continued therapy. Uncommon: paresthesia. Rare: light headedness. Reversible mental confusion, agitation, aggression, depression and hallucinations in predominantly severely ill or elderly patients.
Eye disorders	Uncommon: visual disturbances (blurred vision, loss of visual acuity or reduced field of vision). These conditions usually resolve on cessation of therapy.
Ear and labyrinth disorders	Uncommon: auditory dysfunction (e.g. tinnitus). These conditions usually resolve on cessation of therapy.
Gastrointestinal disorders	Common: diarrhoea, constipation, flatulence (possibly with abdominal pain), nausea and vomiting. In the majority of these cases the symptoms improve if the therapy is continued. Uncommon: taste disturbances. This condition usually resolves on cessation of therapy. Rare: brownish-black discoloration of the tongue during concomitant administration of clarithromycin and benign glandular cysts: both were reversible after cessation of treatment, dryness of the mouth, stomatitis, candidiasis or pancreatitis.
Hepato-biliary disorders	Uncommon: increrase of liver enzyme values (which resolve after discontinuation of therapy). Rare: hepatitis with or without jaundice, hepatic failure and encephalopathy in patients with pre-existing severe liver disease.
Skin and subcutaneous tissue disorders:	Uncommon: pruritus, skin eruptions, alopecia, erythema multiforme or photosensitivity and increased tendency to sweat.

In an acid environment at a pH of less than 4 the protonised Omeprazole is converted to Omeprazole sulphenamide, the active substance proper.

Compared to the plasma half-life of the Omeprazole base, Omeprazole sulphenamide remains in the cell for a longer period of time. Thus the duration of the inhibition of acid secretion is substantially longer than the period in which Omeprazole-base is present in plasma. The degree of inhibition of acid secretion is directly correlated to the area under the plasma concentration-time curve (AUC) but not to the plasma concentration at any given time. A sufficiently low pH-value is only found in the gastic parietal cells; this explains the high specificity of Omeprazole. It is the Omeprazole sulphenamide that binds to the enzyme and inhibits its activity.

If the enzyme-system is inhibited, the pH-value increases and less Omeprazole accumulates or is converted in the gastric parietal cells. Consequently, the accumulation of Omeprazole is regulated by a kind of feedback-mechanism.

Intravenous administration of Omeprazole affords a quick and effecting inhibition of gastric acid production. With duodenal ulcer patients the mean reduction of basal and stimulated acid production during 24 hours is circa 90%.

A single intravenous injection of 40 mg has, over a period of 24 hours, almost the same effect on acid production as an oral dose of 80 mg.

5.2. Pharmacokinetic properties:

Distribution

The distribution volume of Omeprazole in the body is relatively small (0.3 l/kg of body weight) and corresponds to that of the extracellular fluid. Approximately 95% is protein bound.

Metabolism and excretion

Omeprazole is entirely metabolised, mainly in the liver by CYP 2C19. The plasma half-life is about 40 minutes, and the total plasma clearance is 0.3 to 0.6 l/min. A small percentage of het patients lack a functional CYP2C19 enzyme and have reduced elimination rate of Omeprazole. In these cases, the terminal elimination half-life can be approximately 3 times as

	Rare: Stevens-Johnson-syndrome or toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Rare: muscle weakness, myalgia and joint pain.
Renal and urinary disorders	Rare: nephritis (interstitial nephritis)
Other adverse effects:	Uncommon: malaise, peripheral oedema (which resolved on cessation of therapy) Rare: hyponatremia, gynaecomastia.

In sporadic cases irreversible visual disorders have been reported with very seriously ill patients who were treated with intravenous injections of Omeprazole and then, in particular, with high dosages. A causal link has however not been established.

4.9. Overdose:

5. Pharmacological properties:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors

ATC-code: A02B C01

Omeprazole, a substituted benzimidazole, is a gastric proton pump inhibitor, i.e. Omeprazole directly and dose-dependently inhibits the enzyme H+,K+-ATPase, which is responsible for the gastric acid secretion in the gastric parietal cells. Due to this selective intracellular mode of action and the low affinity for other membrane-bound receptors (such as the histamine H2, muscarine M1 or gastrinergic receptors), Omeprazole has been assigned to a separate class of acid-inhibiting agents, which block the final step of acid production.

As a consequence of its mode of action, Omeprazole leads to an inhibition of both basal and stimulable acid secretion, irrespective of the stimulus type.

Thus, Omeprazole increases the pH-value and reduces the volume of gastric acid secretion.

As a weak base the prodrug Omeprazole accumulates in the acid environment of the parietal cells and will only become effective as an inhibitor of the H+, K+-ATPase after being protonised and rearranged.

long as the normal value, and the area under the plasma concentration-time curve (AUC) of orally administered Omeprazole can increase by up to 10 times. The sulphone, sulphide and hydroxy-Omeprazole are found in plasma. These metabolites have no significant effect on acid secretion.

About 20% of administered dose is excreted in faeces and the remaining 80% is excreted in urine as metabolites. The two major urinary metabolites are hydroxy-Omeprazole and the corresponding carboxylic acid.

Special patient populations

In patients with renal impairment the systematic availability of Omeprazole was very similar to that in healthy subjects.

In patients with chronic hepatic disease the clearance of Omeprazole is reduced, and the plasma half-life can increase up to approximately 3 hours. The systemic bioavailability can then be enhanced in these patients.

The bioavailability of Omeprazole is slightly elevated in the elderly, and the elimination rate is slightly diminished. But the individual values are nearly equal to that of young healthy subjects, and there is no indication that the tolerance in elderly patients treated with normal doses of Omeprazole is reduced.

5.3. Preclinical safety data

Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6. Pharmaceutical particulars:

6.1. List of Excipients:

None

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

24 months

6.4. Special precautions for storage:

Do not store above 25°C. Store in the original package in order to protect from light.

6.5. Nature and contents of container:

10 ml amber color glass vial, USP Type-I.

6.6. Special precautions for disposal:

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Applicant:

Name and Address of Applicant

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