1.3.1 Summary Product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

JAWAPRAZOLE (Omeprazole capsules USP 20 mg), 20 mg per capsule, hard gelatin capsule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains

Omeprazole USP	20 mg
(As enteric coated pellets)	
Excipients	Q.S.

Kindly refer section 6.1 for full list of Excipients.

3 PHARMACEUTICAL FORM

Pink/Transparent Hard gelatin capsules size "2" printed "JAWA" & "PRAZOLE " on capsule which containing white enteric coated pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of oesophageal reflux disease. In reflux oesophagitis the majority of patients are healed after 4 weeks. Symptom relief is rapid. Treatment of duodenal and benign gastric ulcers including those complication NSAID therapy. Relief of reflux-like symptoms (e.g. heartburn) and or ulcer-like symptoms (eg. epigastric pain) associated with add-related dyspepsia. Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment. Relief of associated dyspeptic symptoms. Helicobacter pylori eradication: Omeprazole should be used in combination with antibiotics for eradication of Helicobacter pylori (Hp) in peptic ulcer disease. Relief of associated dyspeptic symptoms. Prophylaxis of acid aspiration. Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology

Oesophageal reflux disease including reflux oesophagitis: The usual dosage is 20 mg Jawaprazole once daily. The majority of patients are healed after 4 weeks. For those patients not fully healed after the initial course, healing usually occurs during a further 4-8 weeks treatment. Jawaprazole has also been used in a dose of 40mg once daily in patients with reflux oesophagitis refractory to other therapy. Healing usually occurred within 8 weeks. Patients can be continued at dosage of 20 mg once daily.

Acid reflux disease: For long-term management Jawaprazole 20 mg once daily is recommended, increasing to 20 mg if symptoms return.

Duodenal and benign gastric ulcers: The usual dose is 20 mg Jawaprazole once daily. The majority of patients with duodenal ulcer are healed after 4 weeks. The majority of patients with benign gastric ulcer are healed after 8 weeks. In severe or recurrent cases the dose may be increased to 40 mg Jawaprazole daily. Long-term therapy for patients with a history of recurrent duodenal ulcer is recommended at a dosage of 20mg Jawaprazole once daily. For prevention of relapse in patients with duodenal ulcer the recommended dose is Jawaprazole 10 mg, once daily increasing to 20 mg, once daily if symptoms return. The following groups are at risk from recurrent ulcer relapse; those with Helicobacter pylori infection, younger patients (<60 years), those whose symptoms persist for more than one year and smokers. These patients will require initial long-term therapy. Jawaprazole 20 mg once daily, reducing to 10 mg once daily if necessary.

4.3 Contraindications

Omeprazole delayed-release capsules are contraindicated in patients with known hypersensitivity to any component of the formulation stated in section 6.1. When gastric ulcer is suspected, the possibility of malignancy should be excluded before treatment with Jawaprazole is instituted, as treatment may alleviate symptoms and delay diagnosis.

4.4 Special warnings and precautions for use

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the decreased intragastric acidity the absorption of ketoconazole or itraconazole maybe reduced during omeprazole treatment as It is during treatment with other secretion inhibitors. As Jawaprazole is metabolized in the liver through cytochrome P450. It can delay the elimination of diazepam, phenytoin and warfarin. Monitoring of patients having warfarin or phenytoin is recommended and a reduction of warfarin or phenytoin dose may be necessary. However concomitant treatment with Jawaprazole 20mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. Similarly, concomitant treatment with Jawaprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin. Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration. This is considered to be a useful interaction during H. pylori eradication. There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, cyclosporin, lidocaine, quinidine, oestradiol. amoxicillin or antacids. The absorption of Jawaprazole is not affected by alcohol or food. There is no evidence of an interaction with piroxicam, diclofenac or naproxen. This is considered useful when patients are required to continue these treatments. Simultaneous treatment with omeprazole and digoxin in healthy subjects to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric pH.

4.6 Pregnancy and lactation

There is no evidence on the safety of Jawaprazole in human pregnancy. Animal studies have revealed no teratogenic effect, but reproduction study have revealed reduced litter weights. Avoid in pregnancy unless there is no safer alternative. There is no information available on the passage of Jawaprazole into breast milk or its effects on the neonate. Breast feeding should therefore be discontinued unless the use of Jawaprazole is considered essential.

4.7 Effects on ability to drive and use machines

No effects are foreseen.

4.8 Undesirable effects

Jawaprazole is well tolerated and adverse reactions have generally been mild and reversible. The following have been reported as adverse events in clinical trials or reported from routine use but in many cases a relationship to treatment with omeprazole has not been established. Skin rash, urticaria and pruritus have been reported, usually resolving after discontinuation of treatment. In addition, photosensitivity, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epdenmalnecrolysis, angioedema and alopecia have been reported in isolated cases. Diarrhoea and headache have been reported and maybe severe enough to require discontinuation of therapy in a small number of patients. In a majority of cases, the symptoms resolved after discontinuation of therapy. Other gastrointestinal reactions have included constipation, nausea/vomiting, flatulence and abdominal pain. Dry mouth, stomatitis and candidiasis have been reported as isolated cases. Paraesthesia has been reported. dizziness, light-headedness and feeling faint have been associated with treatment, but al usually resolve on cessation of therapy. Also reported are somnolence, insomnia and vertigo. Reversible mental confusion, agitation, depression and hallucination have occurred predominantly in severely ill patients. Arthritic and myalgic symptoms have been reported and have usually resolved when therapy stopped. In isolated cases, the following have been reported: blurred vision, taste disturbance, aggression, peripheral oedema, hyponatraemia, increased sweating, gynaecomastia, impotence, leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, anaphylactic shock, malaise, fever, bronchospasm, encephalopathy in patients with pre-existing severe liver disease, hepatitis with or with or without jaundice, rarely hepatic failure and interstitial nephritis which has resulted in acute renal failure. Increases in liver enzymes have been observed.

4.9 Overdose

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also, apathy, depression and confusion have been described in single cases.

The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

Mechanism of action

Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamic effects

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion

Oral dosing with omeprazole once daily provides for rapid and effective 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 esophagus in patients with gastro-esophageal 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.

No tachyphylaxis has been observed during treatment with omeprazole.

Effect on H. pylori

H. pylori is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. H. pylori is a major factor in the development of gastritis. H. pylori together with gastric acid are major factors in the development of peptic ulcer disease. H. pylori is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.

Eradication of H. pylori with omeprazole and antimicrobials is associated with, high rates of healing and long-term remission of peptic ulcers.
Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.

Other effects related to acid inhibition
During long-term treatment gastric glandular cysts have been reported in 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 acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.
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 tumours.
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.
Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Paediatric population
In a non-controlled study in children (1 to 16 years of age) with severe reflux esophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved esophagitis level in 90% of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0–24 months with clinically diagnosed gastroesophageal reflux disease were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased by 50% after 8 weeks of treatment irrespective of the dose.

Eradication of H. pylori in children
A randomised, double blind clinical study (Heliot study) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of H. pylori infection in children age 4 years old and above with gastritis: H. pylori eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years.

5.2 Pharmacokinetic properties

Absorption

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Metabolism

Biotransformation Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxy omeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Elimination

The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-linearity

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship 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 omeprazole and/or its metabolites (e.g. the sulfone). No metabolite has been found to have any effect on gastric acid secretion.

Special populations
Hepatic impairment: The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.
Renal impairment: The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

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

5.3 Preclinical safety data
No inhouse preclinical safety data is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Talcum Powder
Dummy Pellets
Empty Gelatin Cap.Pink/Clear Trans Size "2"

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Store in a dark, dry place, Not exceeding 30°C temp. Keep out of the reach and sight of children.

6.5 Nature and contents of container <and special equipment for use, administration, orimplantation>

2 X 7 Capsules Alu-Alu Pack, 1 X 14 and 10 X 14 Strip Pack

6.6 Special precautions for disposal <and other handling>

No Special Requirements

7 <APPLICANT/MANUFACTURER>

APPLICANT

M/s. JAWA INTERNATIONAL LIMITED

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