1.3

PRODUCT INFORMATION

1.3.1

Summary Of Product Characteristics (SPC)

1.17.1.1 Product information for health professionals

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented Name of the Medicinal Product

ULCERTRET-20

Gastro-resistant Omeprazole Capsules BP 20 mg

1.2 Strength

Gastro-resistant Omeprazole Capsules BP 20 mg

1.3 Pharmaceutical Form

Hard Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard Gelatin Capsule Contains:

Omeprazole BP ……..…20 mg.

Excipients…….…. q.s.

(As enteric coated granules)

Approved Colours are added in Capsule Shells

3. PHARMACEUTICAL FORM

Hard gelatin capsule

Pink / Colourless Transparent sealed, hard gelatin capsules containing almost white enteric coated pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ULCERTRET-20 is indicated in:

1. Treatment of reflux oesophagitis disease. In reflux oesophagitis the majority of patients are healed after 4 weeks. Symptom relief is rapid.

2. Treatment of duodenal and benign gastric ulcers including complicating NSAID therapy.
3. Relief of reflux-like symptoms (e.g. heartburn) and/or ulcer-like symptoms (e.g. epigastric pain) associated with acid-related dyspepsia.
4. 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.
5. Relief of associated dyspeptic symptoms.
6. *Helicobacter pylori* eradication: When used with in combination with antibiotics, Omeprazole proves effective in the eradication of *Helicobacter pylori* (*Hp*) in peptic ulcer disease.
7. Prophylaxis of acid aspiration.
8. Zollinger-Ellison syndrome.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration: Oral

Posology:

Oesophageal reflux disease including reflux oesophagitis:

The usual starting dose is 20 mg omeprazole taken once a day for 4 weeks. For those patients not fully healed after the initial 4 week course, healing usually occurs during a further 4-8 weeks treatment.

Omeprazole has also been used in a dose of 40mg once a day in patients with reflux oesophagitis refractory to other therapy. Healing usually occurred within 8 weeks. Continuation of therapy can be considered at a dosage of 20 mg once daily.

Acid reflux disease:

For long-term management, a dose of 10 mg once daily is recommended, increasing to 20 mg if symptoms return.

Duodenal and benign gastric ulcers:

The usual dose is 20 mg Omeprazole once daily. With duodenal ulcers, the majority of patients usually are healed after 4 weeks of treatment. 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 Omeprazole daily. For patients with a history of recurrent duodenal ulcer, long term therapy is recommended at a dosage of 20 mg Omeprazole once daily.

To prevent recurrence, in patients with duodenal ulcer, the recommended dose is Omeprazole 10 mg, once daily, increasing to 20 mg, once daily if symptoms return.

The following groups of patients 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 with Omeprazole 20 mg once daily, reducing to 10 mg once daily, if necessary.

Acid-related dyspepsia:

Usual dosage is 10 mg or 20 mg Omeprazole once daily for 2 – 4 weeks depending on the severity and persistence of symptoms.

If the patient does not respond to treatment after 4 weeks or who relapse shortly after treatment, then the patient should be investigated.

For the treatment of NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions:

The recommended dosage of Omeprazole is 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment.

For the prophylaxis of NSAID-associated gastric ulcers, duodenal ulcers, gastroduodenal

erosions and dyspeptic symptoms in patients with a previous history of gastroduodenal lesions who require continued NSAID treatment:

The recommended dosage is 20 mg Omeprazole taken once a day.

Helicobacter pylori (Hp) eradication regimens in peptic ulcer disease:

Omeprazole is recommended at a dose of 40 mg once daily or 20 mg twice daily concomitant with antimicrobial agents as detailed below:

Triple therapy regimens in duodenal ulcer disease:

Omeprazole and the following antimicrobial combinations;

Amoxicillin 500 mg and metronidazole 400 mg both three times a day for one week.

or

Clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) both twice a day for one week.

or

Amoxicillin 1 g and clarithromycin 500 mg both twice a day for one week.

Dual therapy regimens in duodenal ulcer disease

Omeprazole and amoxicillin 750 mg to 1 g twice daily for two weeks. Alternatively, omeprazole and clarithromycin 500 mg three times a day for two weeks.

Dual therapy regimens in gastric ulcer disease:

Omeprazole and amoxicillin 750 mg to 1 g twice daily for two weeks.

In each regimen if symptoms return and the patient tests positive for *Hp*, therapy may be repeated or one of the alternative regimens can be used; if the patient is *Hp* negative then see dosage instructions for acid reflux disease.

To ensure healing in patients with active peptic ulcer disease, see further dosage recommendations for duodenal and benign gastric ulcer.

Prophylaxis of acid aspiration:

For patients considered to be at risk of aspiration of the gastric contents during general anaesthesia, the recommended dosage is omeprazole 40 mg on the evening before surgery followed by a further 40 mg 2 – 6 hours prior to surgery.

Zollinger-Ellison syndrome:

The initial starting dose is omeprazole 60 mg once a day. The dosage should be adjusted individually and treatment continued as long as clinically indicated. More than 90% of patients with severe disease and inadequate response to other therapies have been effectively controlled on doses of 20 – 120 mg daily. With doses above 80 mg daily, the dose should be divided and given twice daily.

Elderly:

Dose adjustment is not required in the elderly.

Children

Reflux oesophagitis

The treatment time is 4–8 weeks.

Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux Disease

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

The dosage recommendations are as follows:		
Age	**Weight**	**Dosage**
≥ 1 year of age	10-20 kg	10 mg once daily. The dosage can be increased to 20 mg once daily if needed.
≥ 2 years of age	> 20 kg	20 mg once daily. The dosage can be increased to 40 mg once daily if needed.

Children over 4 years of age

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

Weight Dosage	
15-≤30 kg	Combination with two antibiotics: Omeprazole 10 mg, amoxicillin
25mg/kg	body weight and clarithromycin 7.5 mg/kg body weight are all administered together 2 times daily for 1 week
30-≤40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered 2 times daily for 1 week.
>40 kg	Combination with two antibiotics: Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered 2 times daily for 1 week.

Impaired renal function:

Dose adjustment is not required in patients with impaired renal function.

Impaired hepatic function:

As bioavailability and half-life can increase in patients with impaired hepatic function, the dose requires adjustment with a maximum daily dose of 20 mg.

For patients (including children aged 1 year and above who can drink or swallow semi-solid food) who are unable to swallow omeprazole Capsules:

The capsules may be opened and the contents swallowed directly with half a glass of water or suspended in 10 ml of non-carbonated water, any fruit juice with a pH less than 5 e.g. apple, orange, pineapple, or in applesauce or yoghurt and swallowed after gentle mixing. The dispersion should be taken immediately or within 30 minutes. Stir just before drinking and rinse it down with half a glass of water. Alternatively the actual capsules may be sucked and then swallowed with half a glass of water. There is no evidence to support the use of sodium bicarbonate buffer as a delivery form. It is important that the contents of the capsules should not be crushed or chewed.

Method of administration:

ULCERTRET-20 should be swallowed intact, before breakfast in the morning.

4.3 CONTRAINDICATIONS

ULCERTRET-20 is contraindicated in patients with known hypersensitivity to omeprazole, or substituted benzimidazoles or to any excipient used in the formulation.

When gastric ulcer is suspected, the possibility of malignancy should be excluded before treatment with Omeprazole 20 mg Capsules is commenced, as treatment may alleviate symptoms and delay diagnosis.

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

4.4 WARNING AND PRECAUTIONS

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 a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

This product contains sucrose and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

As omeprazole is metabolised in the liver through cytochrome P450, it can prolong the elimination of diazepam, phenytoin, warfarin and other vitamin K antagonists which are in part substrates for this enzyme. Monitoring of patients receiving warfarin or phenytoin is recommended and a reduction of warfarin or phenytoin dose may be required. However, concomitant treatment with Omeprazole 20 mg once daily did not change the blood concentration of phenytoin in patients on continuous treatment with phenytoin. Similarly, concomitant treatment with Omeprazole 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 interaction with metronidazole or amoxicillin. These antimicrobials are used concomitantly with omeprazole for the eradication of *H. pylori*.

There is no evidence of an interaction with phenacetin, theophylline, caffeine, propranolol, metoprolol, ciclosporin, lidocaine, quinidine, estradiol, or antacids. The absorption of Omeprazole 20 mg capsules 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 lead to a 10% increase in the bioavailability of digoxin as a consequence of the increased intragastric 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 400mg did not compensate for the impact of omeprazole on atazanavir exposure. PPIs including omeprazole should not be co-administered with atazanavir.

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Concomitant administration of omeprazole and a CYP2C19 and CYP3A4 inhibitor, voriconazole, resulted in more than doubling of the omeprazole exposure. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUC_{τ} by 15% and 41%, respectively. A dose adjustment of omeprazole 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.

4.6 PREGNANCY AND LACTATION

Pregnancy

Well-conducted epidemiological studies indicate no adverse effects of Omeprazole 20 mg on pregnancy or on the health of the foetus/new-born child. Omeprazole 20 mg can be used during pregnancy.

Lactation

Omeprazole is excreted into breast milk but is unlikely to influence the child when used in therapeutic doses.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ULCERTRET-20 has negligible influence on the ability to drive and use machines.

However if side effects such as dizziness and light headedness are experienced the ability to drive and use machines may be affected

4.8 UNDESIRABLE EFFECTS

Omeprazole 20 mg Capsules are 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.

The following definitions of frequencies are used:

Common ≥ 1/100 to <1/10

Uncommon ≥ 1/1000 to < 1/100

Rare ≥ 1/10, 000 to <1/1000

	Common	**Uncommon**	**Rare**
Nervous system disorders:	Headache	Dizziness, paraesthesia, light headedness, feeling faint, somnolence, insomnia and vertigo	Reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients
Gastrointestinal disorders:	Diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence		Dry mouth, stomatitis and gastrointestinal candidiasis
Hepatobiliary disorders:		Increased liver enzymes	Encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure
Skin and subcutaneous tissue		Rash and/or pruritus Urticaria	Photosensitivity, bullous eruption

disorders:			erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia
Endocrine disorders			Gynaecomastia
Blood and lymphatic system disorders:			Leukopenia, thrombocytopenia, Agranulocytosis and pancytopenia
Musculoskeletal and connective tissue disorders:			Arthritic and myalgic symptoms and muscular weakness
Reproductive system and breast disorders:			Impotence
General disorders and administration site conditions:		Malaise	Hypersensitivity reactions e.g. angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock. Increased sweating, peripheral oedema, blurred vision, taste disturbance and hyponatraemia.

4.9 OVERDOSE

Rare reports have been received of overdosage with omeprazole. Doses of up to 560 mg have been described and occasional reports have been received when single oral doses have been reached up to 2400 mg, which is 120 times the recommended clinical dose. Overdosage of omeprazole is reported to be associated with nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache. Single cases of apathy, depression and confusion have been described.

The symptoms described in connection with omeprazole overdosage have been transient and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses and no specific treatment is needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for peptic ulcers and gastro-oesophageal reflux disease (GORD) - Proton Pump inhibitors.

ATC code: A02B C01

Omeprazole reduces gastric acid secretion through a unique mechanism of action. It is a specific inhibitor of the gastric proton pump in the parietal cell. It is rapidly acting and produces reversible inhibition of gastric acid secretion with once daily dosing.

An oral dose of 20 mg once a day produces a rapid and effective inhibition of gastric acid secretion with maximum effect being achieved within 4 days of treatment. In duodenal ulcer patients, a mean decrease of approximately 80% in 24-hour intragastric acidity is then maintained, with the mean decrease in peak acid output after pentagastrin stimulation being about 70%, twenty-four hours after dosing with Omeprazole 20 mg Capsules.

Clinical data for omeprazole in the prophylaxis of NSAID induced gastroduodenal lesions are derived from clinical studies of up to 6 months duration.

Helicobacter pylori (*Hp*) is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with this bacterium. *Hp* is implicated as a major contributing factor in the development of gastritis

and ulcers in such patients. Recent evidence also suggests a causative link between *Hp* and gastric carcinoma.

Omeprazole has been shown to have a bactericidal effect on *Hp* in vitro.

Eradication of *Hp* with omeprazole and antimicrobials is associated with rapid symptom relief, high rates of healing of any mucosal lesions, and long-term remission of peptic ulcer disease thus reducing complications such as gastrointestinal bleeding as well as the need for prolonged anti-secretory treatment.

In recent clinical data in patients with acute peptic ulcer omeprazole *Hp* eradication therapy improved patients' quality of life.

During long-term treatment an increased frequency of gastric glandular cysts has been reported. These changes are a physiological consequence of pronounced inhibition of acid secretion. The cysts are benign and appear to be reversible. No other treatment related mucosal changes have been observed in patients treated continuously with omeprazole for periods up to 5 years.

Paediatric data

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

Eradication of Helicobacter pylori in children:

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

Site and mechanism of action

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

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

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole is acid labile and is administered orally as enteric-coated granules in capsules. Absorption takes place in the small intestine and is usually completed within 3 – 6 hours. The systemic bioavailability of omeprazole from a single oral dose is approximately 35%. After repeated once-daily administration, the bioavailability increases to about 60%. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

Elimination and metabolism

The average half-life of the terminal phase of the plasma concentration-time curve is approximately 40 minutes. There is no change in half-life during treatment. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) but not to the actual plasma concentration at a given time.

Omeprazole is entirely metabolised, mainly in the liver. Identified metabolites in plasma are the sulfone, the sulfide and hydroxy-omeprazole, these metabolites have no significant effect on acid secretion. About 80% of the metabolites are excreted in the urine and the rest in the faeces. The two main urinary metabolites are hydroxy-omeprazole and the corresponding carboxylic acid.

The systemic bioavailability of omeprazole is not significantly altered in patients with reduced renal function. The area under the plasma concentration-time curve is increased in patients with impaired liver function, but no tendency to accumulation of omeprazole has been found.

Children

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

Pregnancy

Well-conducted epidemiological studies indicate no adverse effects of Omeprazole 20 mg on pregnancy or on the health of the foetus/new-born child. Omeprazole 20 mg can be used during pregnancy.

Lactation

Omeprazole is excreted into breast milk but is unlikely to influence the child when used in therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar Spheres

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C. Protected from light.

6.5 Nature and contents of container

2x7’s Alu/Alu blister Pack

6.6 Special precautions for disposal and other Special handling

None

7. Marketed by:

M/s. AQUATIX PHARMACEUTICALS LIMITED,
No.14, Prince Bode Oluwo Street,
Mende, Maryland,
Lagos, Nigeria

8. Manufacturer by:

SWISS PHARMA PVT. LTD.
3709, G.I.D.C., Phase-IV, Vatva,
Ahmedabad-382 445