NEW ZEALAND DATA SHEET

1. PRODUCT NAME

OMEPRAZOLE ACTAVIS 10, 20, 40, modified release capsules, 10 mg, 20 mg, 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release capsule contains omeprazole 10 mg, 20 mg or 40 mg.

For full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Modified release capsule.

Capsule 10 mg: Size 3, opaque yellow capsule, containing off-white (ivory) to cream-white spherical microgranules.

Capsule 20 mg: Size 2, opaque white capsule, containing off-white (ivory) to cream-white spherical microgranules.

Capsule 40 mg: Size 0 capsule, opaque blue cap and white body, containing off-white (ivory) to cream-white spherical microgranules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OMEPRAZOLE ACTAVIS capsules are indicated for the treatment of:

- reflux oesophagitis
- duodenal ulcer
- gastric ulcer
- NSAID-associated gastric and duodenal ulcers or erosions
- symptoms of acid related dyspepsia
- Zollinger-Ellison syndrome.

In the treatment of peptic ulceration, the eradication of *H.pylori,* as the causative organism, must be a high priority.

Accordingly, OMEPRAZOLE ACTAVIS should be used as part of combination therapy for the eradication of *H.pylori.*

Maintenance

OMEPRAZOLE ACTAVIS capsules are indicated for maintenance treatment of:

- reflux oesophagitis
- duodenal ulcer
- gastric ulcer
- Zollinger-Ellison syndrome.

4.2 Dose and method of administration

OMEPRAZOLE ACTAVIS capsules are recommended to be given in the morning and swallowed whole with half a glass of water. The contents of the capsule should not be chewed or crushed.

For patients with swallowing difficulties and for children who can drink or swallow semi-solid food

For patients with swallowing difficulties the capsule can be opened and the contents swallowed directly with half a glass of liquid or after mixing the contents in a slightly acidic fluid e.g. fruit juice,

yoghurt or in non-carbonated water. The dispersion should be taken immediately or within 30 minutes. Alternatively patients can suck the capsule and swallow the pellets with liquid. The pellets must not be chewed or crushed.

Reflux Oesophagitis
The recommended dosage is OMEPRAZOLE ACTAVIS 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 week treatment period.

In patients with severe reflux oesophagitis OMEPRAZOLE ACTAVIS 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the long-term management of patients with healed reflux oesophagitis the recommended dose is OMEPRAZOLE ACTAVIS 10 mg once daily. If needed the dose can be increased to OMEPRAZOLE ACTAVIS 20-40 mg once daily.

Severe Reflux Oesophagitis In Children From One Year And Older
The management of severe reflux oesophagitis should be diagnosed or recommended by a specialist paediatrician or gastroenterologist.

The recommended dosage regime for healing is:

Weight	Dosage
10-20 kg	OMEPRAZOLE ACTAVIS 10 mg daily
>20 kg	OMEPRAZOLE ACTAVIS 20 mg daily

If needed, dosage may be increased to 20 mg and 40 mg respectively.

Helicobacter Pylori (Hp) Eradication Regimens In Peptic Ulcer Disease
Triple therapy regimens

OMEPRAZOLE ACTAVIS 20 mg, amoxicillin 1 g and clarithromycin 500 mg, all twice a day for one week or OMEPRAZOLE ACTAVIS 20 mg, clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg), all twice a day for one week

or

OMEPRAZOLE ACTAVIS 40 mg once daily with amoxicillin 500 mg and metronidazole 400 mg both three times a day for one week.

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

In each regimen if the patient is still *Hp* positive, therapy may be repeated.

Duodenal Ulcer
The recommended dosage in patients with an active duodenal ulcer is OMEPRAZOLE ACTAVIS 20 mg once daily. Symptom resolution is rapid and in most patients healing occurs within 2 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 2 week treatment period.

In patients with poorly responsive duodenal ulcer OMEPRAZOLE ACTAVIS 40 mg once daily is recommended and healing is usually achieved within 4 weeks.

For the prevention of relapse in patients with duodenal ulcer disease the recommended dose is OMEPRAZOLE ACTAVIS 10 mg once daily. If needed the dose can be increased to OMEPRAZOLE ACTAVIS 20-40 mg once daily.

For NSAID-associated duodenal ulcers see "NSAID-Associated Gastroduodenal Lesions".

Gastric Ulcer
The recommended dosage is OMEPRAZOLE ACTAVIS 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 period.

In patients with poorly responsive gastric ulcer OMEPRAZOLE ACTAVIS 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

For the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is OMEPRAZOLE ACTAVIS 20 mg once daily. If needed the dose can be increased to OMEPRAZOLE ACTAVIS 40 mg once daily.

For NSAID-associated gastric ulcers see "NSAID-Associated Gastroduodenal Lesions".

NSAID-Associated Gastroduodenal Lesions
For NSAID-associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients with or without continued NSAID treatment, the recommended dosage of OMEPRAZOLE ACTAVIS 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 period.

For the prevention of NSAID-associated gastric ulcers, duodenal ulcers, gastroduodenal erosions and dyspeptic symptoms the recommended dosage of OMEPRAZOLE ACTAVIS is 20 mg once daily.

Symptoms Of Acid-Related Dyspepsia
For the 24-hour relief, and prevention of symptoms in patients with epigastric pain/discomfort with or without heartburn and indigestion, 20 mg OMEPRAZOLE ACTAVIS once daily in the morning for 14 - 28 days*. If symptom control has not been achieved after 4 weeks treatment with OMEPRAZOLE ACTAVIS 20 mg daily, further investigation is recommended.

*Patients may respond adequately to 10 mg daily and this dose could be considered as a starting dose.

Zollinger-Ellison Syndrome
In patients with Zollinger-Ellison syndrome the dosage should be individually adjusted and treatment continued as long as is clinically indicated. The recommended initial dosage is OMEPRAZOLE ACTAVIS 60 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of OMEPRAZOLE ACTAVIS 20-120 mg daily. When doses exceed OMEPRAZOLE ACTAVIS 80 mg daily, the dose should be divided and given twice daily.

Impaired Renal Function
Dose adjustment is not needed in patients with impaired renal function.

Impaired Hepatic Function
As bioavailability and plasma half-life of omeprazole are increased in patients with impaired hepatic function a daily dose of 10 - 20 mg may be sufficient.

Elderly
Dose adjustment is not needed in the elderly.

4.3 Contraindications
Known hypersensitivity to omeprazole, substituted benzimidazoles or any other constituent of the formulation.

4.4 Special warnings and precautions for use

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, the possibility of malignancy should be excluded as treatment may alleviate symptoms and delay diagnosis.

Concomitant administration of omeprazole and medicines such as atazanavir and nelfinavir is not recommended (see section 4.5 Interaction with other medicines and other forms of interaction).

Concomitant use of omeprazole and clopidogrel should be avoided (see section 4.5 Interaction with other medicines and other forms of interaction).

Some published studies have shown that withdrawal of long-term proton pump inhibitor (PPI) therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion. The causal relationship with omeprazole has not been fully established.

Risk Of Osteoporosis Related Fractures

Some published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with a small increased risk for osteoporosis related fractures. However, in other similar observational studies no such increased risk was found.

In randomized, double-blind and controlled clinical studies on omeprazole and esomeprazole (including two open long-term studies of up to more than 12 years) there are no indications that PPIs are associated with osteoporotic fractures.

Although a causal relationship between omeprazole/esomeprazole and osteoporotic fractures has not been established, patients at risk for developing osteoporosis or osteoporotic fractures are advised to have appropriate clinical monitoring in accordance with current clinical guidelines for these conditions.

Hypomagnesaemia

Symptomatic hypomagnesaemia has been reported rarely in patients treated with long-term PPI medication. In some severe cases hypocalcaemia was also reported. Severe hypomagnesaemia may result in serious adverse events such as tetany, seizures and potentially also arrhythmias. In some patients, treatment of hypomagnesaemia with magnesium replacement was not sufficient to correct the magnesium imbalance and discontinuation of the PPI was required. In patients later retreated with the same or different PPI, hypomagnesaemia returned within a shorter time period. For patients expected to be on prolonged treatment or who take PPIs with other medicines such as digoxin or medicines that may cause hypomagnesaemia, consideration should be given to monitoring magnesium levels prior to initiation and periodically thereafter.

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8 Undesirable effects). Acute tubulointerstitial nephritis can progress to renal failure. Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

4.5 Interaction with other medicines and other forms of interaction

Effects Of Omeprazole On The Pharmacokinetics Of Other Medicines

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir

Omeprazole has been reported to interact with some antiretroviral medicines. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicine. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Concomitant administration with omeprazole and medicines such as atazanavir and nelfinavir is therefore not recommended.

Citalopram/Escitalopram

Co administration of omeprazole (20 mg) with citalopram (20 mg single dose) doubles the AUC of the S-isomer of citalopram, but the R-isomer of citalopram is not affected. A reduction in the dose of citalopram may be necessary based on clinical judgement. For patients taking omeprazole, the citalopram dose should not exceed the maximum dose of 20 mg/day.

Co-administration of omeprazole (30 mg) with escitalopram (20 mg single dose) increased the plasma levels (approximately 50%) and terminal half-life (31%) of escitalopram. A reduction in the dose of escitalopram may be necessary based on clinical judgement.

Digoxin

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily, i.e. four times the recommended dose) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 46%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

It is, however, uncertain to what extent this interaction is clinically important. One prospective, randomised (but incomplete) study (in over 3760 patients comparing placebo with omeprazole 20 mg in patients treated with clopidogrel and ASA) and non-randomised, post-hoc analyses of data from large, prospective, randomised clinical outcome studies (in over 47000 patients) did not show any evidence of an increased risk for adverse cardiovascular outcome when clopidogrel and PPIs, including omeprazole, were given concomitantly.

Results from a number of observational studies are inconsistent with regard to increased risk or no increased risk for CV thromboembolic events when clopidogrel is given together with a PPI.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects 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 subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA.

Other active substances

The absorption of **erlotinib**, **ketoconazole** and **itraconazole** is significantly reduced and thus clinical efficacy may be impaired. For Posaconazole and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19

Omeprazole inhibits CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant medicines also metabolised by CYP2C19, such as **diazepam**, **phenytoin**, **warfarin (R-warfarin)** or other **vitamin K antagonists** and **cilostazo**l, may be delayed.

Phenytoin

Monitoring of patients receiving phenytoin is recommended and a reduction of the phenytoin dose may be necessary. However, concomitant treatment with omeprazole 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with this medicine.

Warfarin or other Vitamin K antagonists

In patients receiving warfarin or other vitamin K antagonists, monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary. Concomitant treatment with omeprazole 20 mg daily did, however, not change coagulation time in patients on continuous treatment with warfarin.

Cilostazol

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Other

Omeprazole is partly metabolised also by CYP3A4, but omeprazole does not inhibit this enzyme. Thus, omeprazole does not affect the metabolism of medicines metabolised by CYP3A4, such as **cyclosporin, lignocaine, quinidine, oestradiol, erythromycin** and **budesonide**.

Results from a range of interaction studies with omeprazole versus other medicines demonstrate that omeprazole, 20-40 mg daily, has no significant influence on any other CYP enzymes relevant for medicine metabolism, as shown by the lack of metabolic interaction with substrates for CYP1A2 (such as **caffeine**, **theophylline**), CYP2C9 (such as **S-warfarin**, **piroxicam, diclofenac, naproxen**), CYP2D6 (such as **metoprolol, propranolol**), CYP2E1 (such as **ethanol**). **Unknown mechanism:**

Tacrolimus

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

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

Saquinavir

For other antiretroviral medicines, such as saquinavir, elevated serum levels have been reported. There are also some antiretroviral medicines of which unchanged serum levels have been reported when given with omeprazole.

Effects Of Other Medicines On The Pharmacokinetics Of Omeprazole:

Inhibitors of CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, medicines known to inhibit CYP 2C19 or CYP 3A4 or both (such as **clarithromycin** and **voriconazole**) may lead to increased omeprazole serum levels by decreasing the rate of omeprazole's metabolism. Concomitant **voriconazole** treatment resulted in more than doubling of the omeprazole exposure. Since high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not required during temporary concomitant use.

Inducers of CYP2C19 and/or CYP3A4

Medicines known to induce CYP 2C19 or CYP 3A4 or both (such as **rifampicin** and **St John's wort**) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Fertility, pregnancy and lactation

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the fetus/newborn child. OMEPRAZOLE ACTAVIS can be used during pregnancy.

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

4.7 Effects on ability to drive and use machines

OMEPRAZOLE ACTAVIS is not likely to affect the ability to drive or use machines.

4.8 Undesirable effects

The following adverse reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related.

The reactions are classified according to frequency (common >1/100, <1/10; uncommon >1/1000, <1/100; rare >1/10000, <1/1000; very rare <1/10000).

Blood and lymphatic system disorders

Rare: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Rare: Hyponatraemia

Very Rare: Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, aggression, confusion, depression, hallucinations

Nervous system disorders

Common: Headache

Uncommon: Dizziness, paraesthesia, somnolence

Rare: Taste disturbance

Eye disorders

Rare: 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

Rare: Dry mouth, stomatitis, gastrointestinal candidiasis, microscopic colitis

Hepatobiliary disorders

Uncommon: Increased liver enzymes

Rare: Hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, pruritus, rash, urticaria

Rare: Alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Rare: Tubulointerstitial nephritis (with possible progression to renal failure)

Reproductive system and breast disorders

Rare: Gynaecomastia

General disorders and administration site conditions

Uncommon: Malaise

Rare: Increased sweating, peripheral oedema

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (https://nzphvc.otago.ac.nz/reporting/).

4.9 Overdose

Rare reports have been received of overdosage with omeprazole. 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 from overdosage with omeprazole. Also apathy, depression and confusion have been described in single cases.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitor, ATC code: A02B C01

Omeprazole, a racemic mixture of two active 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 rapid acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Site and mechanism of action

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 the stimulus.

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% twenty-four 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/normalises acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

No tachyphylaxis has been observed during treatment with omeprazole.

Effect on *Helicobacter pylori*

Helicobacter pylori is associated with acid peptic 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* has been found to play a causal role in the development of gastric carcinoma.

Omeprazole has a bactericidal effect on *H.pylori in vitro.*

Eradication of *H.pylori* 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.

Other effects related to acid inhibition

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also chromogranin A (cgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped 5 to 14 days before CgA measurements. Measurements should be repeated if levels have not normalised by this time.

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 omeprazole. The findings are considered to be of no clinical significance.

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 medicines may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*

5.2 Pharmacokinetic properties

Absorption and distribution

Omeprazole and omeprazole magnesium are acid labile and is therefore administered orally as enteric-coated pellets in capsules.

Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. The systemic bioavailability of omeprazole from a single oral dose of omeprazole is approximately 40%. After repeated once daily administration, the bioavailability increases to about 60%. The apparent volume of distribution in healthy subjects is approximately 0.3 L/kg and a similar value is also seen in patients with renal insufficiency. In elderly patients, and in patients with hepatic insufficiency, the volume of distribution is slightly decreased. Concomitant intake of food has no influence on the bioavailability. The plasma protein binding of omeprazole is about 95%.

Metabolism and excretion

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed, specific isoform CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. 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.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 30-40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once daily dosing. 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 (eg, the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration.

No metabolite has been found to have any effect on gastric acid secretion. Almost 80% of an orally given dose is excreted as metabolites in the urine, and the remainder is found in the faeces, primarily originating from bile secretion.

Poor metabolisers: 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.

Special patient populations

Impaired hepatic function: 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.

Impaired renal function: 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).

Children: Available data from children (1 year and older) suggests that the pharmacokinetics, within the recommended dosages (see Dose and method of administration), is similar to those reported in adults.

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 H_2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

10 mg: Sucrose, Maize Starch, Sodium Laurilsulfate, Anhydrous Disodium Phosphate, Mannitol, Hypromellose, Macrogol 6000, Talc, Polysorbate 80, Titanium Dioxide, Methacrylic Acid-Ethyl Acrylate Copolymer dispersion, Quinoline Yellow and Gelatin.

20 mg: Sucrose, Maize Starch, Sodium Laurilsulfate, Anhydrous Disodium Phosphate, Mannitol, Hypromellose, Macrogol 6000, Talc, Polysorbate 80, Titanium Dioxide, Methacrylic Acid-Ethyl Acrylate Copolymer dispersion, and Gelatin.

40 mg: Sucrose, Maize Starch, Sodium Laurilsulfate, Anhydrous Disodium Phosphate, Mannitol, Hypromellose, Macrogol 6000, Talc, Polysorbate 80, Titanium Dioxide, Methacrylic Acid-Ethyl Acrylate Copolymer dispersion, Indigo Carmine, Gelatin.

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
HDPE bottles containing 90 capsules and 100 capsules.

Blister pack containing 90 capsules and 100 capsules.

Not all pack types or pack sizes may be marketed.

6.6 Special precautions for disposal
No special precautions for disposal.

7. MEDICINE SCHEDULE
Prescription Medicine.

8. SPONSOR
Teva Pharma (New Zealand) Limited
P.O Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL
21 August 2014

10. DATE OF REVISION OF THE TEXT
22 June 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Inclusion of renal impairment section, withdrawal of long-term proton pump inhibitor therapy
4.5	Include subheadings and minor editorial
4.8	Inclusion of rare side effect – renal and urinary disorders