1.3
PRODUCT INFORMATION

1.3.1
Summary Of Product Characteristics (SPC)

renal insufficiency. Deaths have been reported in some such patients . Concomitant administration of clarithromycin and colchicine is contraindicated .
Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam

Cardiovascular Events:
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including clarithromycin
Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes), clarithromycin should be used with caution in the following patients;
• Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
• Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia.
• Patients concomitantly taking other medicinal products associated with QT prolongation

• Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfendine is contraindicated
• Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.
Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infraction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.
Pneumonia: In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where *beta*–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum* (erythrasma), acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme.

HMG-CoA reductase inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated . Caution should be exercised when prescribing clarithromycin with other statins.

Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended .

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin . INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted. Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes.

In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids:

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated.

Oral Midazolam

When midazolam was coadministered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated.

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g.fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Effects of Other Medicinal Products on Clarithromycin

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir. Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional drug interactions)

Effect of Clarithromycin on Other Medicinal Products

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with

caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine but this list is not exhaustive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

There have been post-marketed reports of torsade de points occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.

There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant

administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil and vardenafil

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine.

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised by CYP3A (e.g. phenytoin and valproate).

Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional drug interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers

resulted in steady-state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5: Ritonavir). Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding

The safety of clarithromycin for using during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

1.3.1.6.8 UNDESIRABLE EFFECTS

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and peadiatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion.

These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed. reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	Very common≥1/10	Common ≥1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known* (cannot be estimated from the available data)
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric		Insomnia	Anxiety, nervousness[3]	Psychotic disorder,

disorders				confusional state[5], depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor	Convulsion, ageusia, parosmia, anosmia paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders		Vasodilation[1]		Haemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesphagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry	Pancreatitis acute, tongue discolouration, tooth discolouration

			mouth, eructation, flatulence,	
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Severe cutaneous adverse reactioms (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne.
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,6], myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	

Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased[9], prothrombin time prolonged[9], urine color abnormal

[1] ADRs reported only for the Powder for Solution for Injection formulation

[2]ADRs reported only for the Extended-Release Tablets formulation

[3] ADRs reported only for the Granules for Oral Suspension formulation

[4] ADRs reported only for the Immediate-Release Tablets formulation

[5,6] See section c)

* Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (see section e).

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age.

Therefore, children under 12 years of age should use clarithromycin paediatric suspension.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. *Other special populations*

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 mg and 2000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000mg or 2000mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000mg daily for all parameters except White Blood Cell.

1.3.1.6.9 OVERDOSE

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, Clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic Properties

5.1 Pharmacodynamic properties

ATC Classification:

Pharmacotherapeutic Group: Antibacterial for systemic use, macrolide

ATC Code: J01FA09

Mechanism of action:

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal subunit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is Haemophilus influenza where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro:-

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus)pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.*

Gram-negative Bacteria: *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Helicobacter pylori; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae;*

Anaerobes: Macrolide-susceptible *Bacteroides fragilis; Clostridium perfringens;* Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes.*

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H. pylori* and *Campylobacter spp.*

Breakpoints

The following breakpoints have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, mg/L)		
Microorganism	Susceptible (≤)	Resistant (>)
Staphylococcus spp.	1 mg/L	2 mg/L
Streptococcus A, B, C and G	0.25 mg/L	0.5 mg/L
Streptococcus pneumonia	0.25 mg/L	0.5 mg/L
Viridans group streptococcus	IE	IE
Haemophilus spp.	1 mg/L	32 mg/L
Moraxella catarrhalis	0.25 mg/L[1]	0.5 mg/L[1]
Helicobacter pylori	0.25 mg/L[1]	0.5 mg/L

[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduces susceptibility.
"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.

1.3.1.7.2 Pharmacokinetic Properties

5.2 Pharmacokinetic properties

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with the agent. *H. pylori* is also implicated as a major contribution factor in the development of gastric and ulcer recurrence in such patients.
Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include:
Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.
Clinical studies using various different *H. pylori* eradication regimens have shown that eradication of *H. pylori* prevents ulcer recurrence.
Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of Clarithromycin and formation of the 14-hydroxymetabolite.
The pharmacokinetics of Clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.
When Clarithromycin 500 mg is given three times daily, the Clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.
Clarithromycin also penetrates the gastric mucus. Levels of Clarithromycin in gastric mucus and gastric tissue are higher when Clarithromycin is co-administered with omeprazole than when Clarithromycin is administered alone.

1.3.1.7.3 Preclinical safety data

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg).
In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.
Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Spraque-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from Clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities, which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels, which were clearly toxic to the mothers.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Excipients	**Specifications**
Maize Starch	BP
Maize Starch (For Paste)	BP
Sodium Starch Glycolate	BP
Microcrystalline Cellulose	BP
Povidone K-30	BP
Sodium Starch Glycolate	BP
Purified Talc	BP
Magnesium Stearate	BP
Brilliant Blue	IHS
Isopropyl Alcohol	BP
Methylene Chloride	BP

1.3.1.8.2 Incompatibilities:

Not Applicable

1.3.1.8.3 Shelf life:

36 months.

1.3.1.8.4 Special precautions for storage:

Do not store above 25°C. Keep in a dry place in the original package.

1.3.1.8.5 Nature and contents of container:

Each kit contains 2 tablets of Tinidazole, 2 tablets of Clarithromycin and 2 capsule of Omeprazole.

1.3.1.8.6 Special precautions for disposal and other Special handling:

None

Adolescents and children over 4 years of age

• In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Adults

Treatment of duodenal ulcers

The recommended dose in patients with an active duodenal ulcer is Omeprazole 20 mg once daily. In most patients healing occurs within two weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further two weeks treatment period. In patients with poorly responsive duodenal ulcer Omeprazole 40 mg once daily is recommended and healing is usually achieved within four weeks.

Prevention of relapse of duodenal ulcers

For the prevention of relapse of duodenal ulcer in *H. pylori* negative patients or when *H. pylori* eradication is not possible the recommended dose is Omeprazole 20 mg once daily. In some patients a daily dose of 10 mg may be sufficient. In case of therapy failure, the dose can be increased to 40 mg.

Treatment of gastric ulcers

The recommended dose is Omeprazole 20 mg once daily. In most patients healing occurs within four weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further four weeks treatment period. In patients with poorly responsive gastric ulcer Omeprazole 40 mg once daily is recommended and healing is usually achieved within eight weeks.

Prevention of relapse of gastric ulcers

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

H. pylori eradication in peptic ulcer disease

For the eradication of *H. pylori* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.

1.3.1.6.4 WARNING AND PRECAUTIONS

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.
Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.
Omeprazole, as all acid-blocking medicinal products, 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.
Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
Severe hypomagnesaemia has been reported in patients treated with PPIs like omeprazole 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.
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 recognised risk factors. Observational studies suggest that 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.

Subacute cutaneous 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 Omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, [nationally completed name] treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). 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.

Paediatric population

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

Omeprazole contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicinal product.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile* (see section 5.1).

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of omeprazole on the pharmacokinetics of other active substances

Active substances with pH dependent absorption

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

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3).

Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4).

Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. 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 to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both

observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged (see section 4.4).

Other active substances

The absorption of posaconazole, 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 is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such medicinal products are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol

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

Phenytoin

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism

Saquinavir

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus

Concomitant administration of omeprazole 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 dose of tacrolimus adjusted if needed.

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.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors of CYP2C19 and/or CYP3A4

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse events of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Breast-feeding

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

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Omeprazole is not likely to affect the ability to drive or use machines. Adverse reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machinery.

1.3.1.6.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The most common adverse reactions (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

Tabulated list of adverse reactions

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. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: 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).

SOC/frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Rare:	Leukopenia, thrombocytopenia
Very rare:	Agranulocytosis, pancytopenia
Immune system disorders	
Rare:	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	
Rare:	Hyponatraemia
Not known:	Hypomagnesaemia. Severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
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	
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, fundic gland polyps (benign)
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis
Not known:	Microscopic colitis
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(TEN)
Not known:	Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders	
Uncommon:	Fracture of the hip, wrist or spine (see section 4.4)
Rare:	Arthralgia, myalgia
Very rare:	Muscular weakness
Renal and urinary disorders	
Rare:	Interstitial nephritis
Reproductive system and breast disorders	
Very rare:	Gynaecomastia
General disorders and administration site conditions	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating

Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive esophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long term data regarding the effects of omeprazole treatment on puberty and growth.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

1.3.1.6.9 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.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic Properties

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), 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 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 *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 medicinal products may lead to slightly increased risk of gastrointestinal infections such as *Salmonella and Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile.*

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.
An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.
Paediatric population
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 gastro-oesophageal 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 (Héliot 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.

1.3.1.7.2 Pharmacokinetic Properties

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.

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 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. 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 sulphone).

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).

Paediatric population

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.

1.3.1.7.3 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 active substance.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Excipients	Specifications
Non Parel Micro pellet (Sugar Spheres)	BP
Orange/ Black size "2" empty hard gelatin capsules	IHS

1.3.1.8.2 Incompatibilities:

Not Applicable

1.3.1.8.3 Shelf life:

36 months.

1.3.1.8.4 Special precautions for storage:

Do not store above 25°C.

For blister: Store in the original package in order to protect from light and moisture.

For HDPE bottle: Keep the bottle tightly closed in order to protect from light and moisture.

1.3.1.8.5 Nature and contents of container:

Each kit contains 2 tablets of Tinidazole, 2 tablets of Clarithromycin and 2 capsule of Omeprazole.

1.3.1.8.6 Special precautions for disposal and other Special handling:

None

3) Tinidazole BP

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains:

Tinidazole BP ……..500 mg

Colour: Brilliant Blue FCF

1.3.1.5 PHARMACEUTICAL FORM

Solid Dosage Form

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1Therapeutic indications

Treatment of the following infections:

1. Eradication of *Helicobacter pylori* associated with duodenal ulcers, in the presence of antibiotic and acid suppressant therapy (see section 4.2).

2. Anaerobic infections such as:

Intraperitoneal infections: peritonitis, abscess.

Gynaecological infections: endometritis, endomyometritis, tube-ovarian abscess.

Bacterial septicaemia.

Post-operative wound infections.

Skin and soft tissue infections.

Upper and lower respiratory tract infections: pneumonia, empyema, lung abscess.

3. Non-specific vaginitis.

4. Acute ulcerative gingivitis.

5. Urogenital trichomoniasis in both male and female patients.

6. Giardiasis.

7. Intestinal amoebiasis.

8. Amoebic involvement of the liver.

9. Prophylaxis: The prevention of post-operative infections caused by anaerobic bacteria, especially those associated with colonic, gastro-intestinal and gynaecological surgery.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Route: Oral administration during or after a meal.

Posology

Eradication of H. pylori associated with duodenal ulcers:

Adults: the usual dose of twice daily coadministered with omeprazole 20mg twice daily and clarithromycin 250mg twice daily for 7 days.

Clinical studies using this 7 day regimen have shown similar *H. pylori* eradication rates when omeprazole 20mg once daily was used. For further information on the dosage for omeprazole see Astra data sheet.

Anaerobic infections*:*

Adults: an initial dose of 2g the first day followed by 1g daily given as a single dose or as 500mg twice daily. Treatment for 5 to 6 days will generally be adequate but clinical judgement must be used in determining the duration of therapy, particularly when eradication of infection from certain sites may be difficult. Routine clinical and laboratory observation is recommended if it is considered necessary to continue therapy for more than 7 days.

Children: < 12 years – there is no data available.

Non-specific vaginitis:

Adults: non-specific vaginitis has been successfully treated with a single oral dose of 2g. Higher cure rates have been achieved with 2g single doses on 2 consecutive days (total dose 4g).

Acute Ulcerative Gingivitis:

Adults: a single oral dose of 2g.

Urogenital trichomoniasis:

(when infection with *Trichomonas vaginalis* is confirmed, simultaneous treatment of the consort is recommended).

Adults: a single dose of 2g.

Children: a single dose of 50 to 75mg/kg of body weight. It may be necessary to repeat this dose.

Giardiasis:

Adults: a single dose of 2g.

Children: a single dose of 50 to 75mg/kg of body weight. It may be necessary to repeat this dose.

Intestinal Amoebiasis:

Adults: a single daily dose of 2g for 2 to 3 days.

Children: a single daily dose of 50 to 60mg/kg of body weight on each of 3 successive days.

Amoebic involvement in the liver:

Adults: total dosage varies from 4.5 to 12g, depending on the virulence of the *Entamoeba histolytica*.

For amoebic involvement of the liver, the aspiration of pus may be required in addition to therapy with.

Initiate treatment with 1.5 to 2g as a single oral daily dose for three days. Occasionally when a three day course is ineffective, treatment may be continued for up to six days.

Children: a single dose of 50 to 60 mg/kg of body weight per day for five successive days.

Use in Renal impairment

Dosage adjustments in patients with impaired renal function are generally not necessary. However, because tinidazole is easily removed by haemodialysis, patients may require additional doses of tinidazole to compensate.

Prevention of post-operative infection:

Adults: a single dose of 2g approximately 12 hours before surgery.

Children: < 12 years – there is no data available.

It is recommended that tinidazole be taken during or after a meal.

Use in the elderly**:** there are no special recommendations for this age group.

Method of administration

Oral administration. Swallow tablets whole with a glass of water during or after a meal.

1.3.1.6.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

As with other drugs of similar structure, tinidazole is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal studies.

Tinidazole should be avoided in patients with organic neurological disorders.

Tinidazole, other 5-nitroimidazole derivatives or any of the components of this product should not be administered to patients with known hypersensitivity to the drug.
Use of tinidazole is contraindicated during the first trimester of pregnancy and in nursing mothers (see section 4.6).

1.3.1.6.4 WARNING AND PRECAUTIONS

As with related compounds, alcoholic beverages should be avoided during therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing
Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with abnormal neurological signs develop, therapy should be discontinued.
Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although carcinogenicity data is not available for tinidazole, the two drugs are structurally related and therefore there is a potential for similar biologic effects. Mutagenicity results with tinidazole were mixed (positive and negative) (see section 5.3). The use of tinidazole for longer treatment than usually required should be carefully considered.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Alcohol: Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided, (see section 4.4).
Anticoagulants: Drugs of similar chemical structure have been shown to potentiate the effects of oral anticoagulants. Prothrombin time should be closely monitored and adjustments to the dose of the anticoagulants should be made as necessary.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

Animal studies have shown reproductive toxicity (see section 5.3). Tinidazole crosses the placental barrier. Since the effects of compounds of this class on foetal development are unknown, tinidazole is contraindicated in the first trimester of pregnancy.

There is no evidence that tinidazole is harmful during the latter stages of pregnancy, but it should be used in the second and third trimesters only in cases where it is absolutely necessary, when the benefits of therapy outweigh possible risks to both mother and foetus (see section 5.3).

Breast-feeding

Tinidazole is excreted in breast milk. Tinidazole may continue to appear in breast milk for more than 72 hours after administration. Women should not nurse until at least 3 days after having discontinued taking.

Fertility

There are no human data on the effect of tinidazole on fertility. Male and female fertility may be impacted based on animal studies that have shown adverse effects on male and female fertility (see section 5.3).

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No special precautions should be necessary. However, drugs of similar chemical structure, including have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If any abnormal neurological signs develop during therapy, the drug should be discontinued.

1.3.1.6.8 UNDESIRABLE EFFECTS

Reported side effects have generally been infrequent, mild and self-limiting.

The reported undesirable effects are listed below according to MedDRA system organ class classification and frequency. Within each frequency category, the ADRs are presented in the order of clinical importance. Frequency categories are expressed as: 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 (the frequency cannot be estimated from the available data).

System Organ Class	*Common*	*Not known*

Blood and the lymphatic system disorders		Leukopenia
Immune system disorders		Drug hypersensitivity
Metabolism and nutrition disorders	Decreased appetite	
Nervous system disorders	Headache	Convulsions Neuropathy peripheral Paraesthesia Hypoaesthesia Sensory disturbances Ataxia Dizziness Dysgeusia
Ear and labyrinth disorders	Vertigo	
Vascular disorders		Flushing
Gastrointestinal disorders	Vomiting Diarrhoea Nausea Abdominal pain	Glossitis Stomatitus Tongue discolouration
Skin and subcutaneous tissue disorders	Dermatitis allergic Pruritis	Angioedema Urticaria
Renal and urinary disorders		Chromaturia
General disorders and administration site conditions		Pyrexia Fatigue

1.3.1.6.9 OVERDOSE

Signs and symptoms of overdosage: There are no reported overdoses in humans with.
Treatment for overdosage: There is no specific antidote for treatment of overdosage with tinidazole. Treatment is symptomatic and supportive. Gastric lavage may be useful. Tinidazole is easily dialysable.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic Properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for systemic use
ATC code: J 01XD02 is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves *Trichomonas vaginalis, Entamoeba histolytica* and *Giardia lamblia.*
The mode of action of against anaerobic bacteria and protozoa involves penetration of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.
is active against *Helicobacter pylori, Gardnerella vaginalis* and most anaerobic bacteria including *Bacteroides fragilis, Bacteroides melaninogenicus*, Bacteroides spp., Clostridium spp., Eubacterium spp., Fusobacterium spp., Peptococcus spp., Peptostreptococcus spp. and Veillonella spp.
Helicobacter pylori (H.pylori) 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 agent. *H.pylori* is also implicated as a major contributing factor in the development of gastritis and ulcer recurrence in such patients. Evidence suggests a causative link between *H.pylori* and gastric carcinoma.
Clinical evidence has shown that the combination of with omeprazole and clarithromycin eradicates 91-96% of *H.pylori* isolates.
Various different *H.pylori* eradication regimens have shown that eradication of *H.pylori* heals duodenal ulcers and reduces the risk of ulcer recurrence.

1.3.1.7.2 Pharmacokinetic Properties

Pharmacokinetic properties

Tinidazole is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2g tinidazole orally, peak serum levels of 40-51 micrograms/ml were achieved within two hours and decreased to between 11-19 micrograms/ml at 24 hours. Healthy volunteers who received 800mg and 1.6g tinidazole IV over 10-15 minutes achieved peak plasma concentrations that ranged from 14 to 21mcg/ml for the 800mg dose and averaged 32mcg/ml for the 1.6g dose. At 24 hours postinfusion, plasma levels of tinidazole decreased to 4-5mcg/ml and 8.6mcg/ml respectively, justifying once daily dosing. Plasma levels decline slowly and tinidazole can be detected in plasma at concentrations of up to 1 microgram/ml at 72 hours after oral administration. The plasma elimination half-life for tinidazole is between 12-14 hours.
Tinidazole is widely distributed in all body tissues and also crosses the blood brain barrier, obtaining clinically effective concentrations in all tissues. The apparent volume of distribution is about 50 litres. About 12% of plasma tinidazole is bound to plasma protein.
Tinidazole is excreted by the liver and kidneys. Studies in healthy patients have shown that over 5 days, 60-65% of an administered dose is excreted by the kidneys with 20-25% of the administered dose excreted as unchanged tinidazole. Up to 5% of the administered dose is excreted in the faeces. Studies in patients with renal failure (creatinine clearance <22ml/min) indicate that there is no statistically significant change in tinidazole pharmacokinetic parameters in these patients, (see section 4.2).

1.3.1.7.3 Preclinical safety data

Repeat-dose toxicity

In a repeat-dose toxicity study in beagle dogs, oral administration of tinidazole increased atrophy of the thymus in both sexes at 300 and 600 mg/kg/day, and atrophy of the prostate in males at all doses of 100, 300 and 600 mg/kg/day. The initial highest dose of 1000 mg/kg/day was lowered to 600 mg/kg/day due to severe clinical signs. The no-observed-adverse-effect level for females was 100 mg/kg/day (approximately 0.9 times the highest human dose based upon plasma AUC).

Genotoxicity/carcinogenicity

Tinidazole showed some evidence of mutagenic potential. In an in vitro mutagenicity assay, tinidazole was mutagenic in the TA 100, S. typhimurium tester strain both with and without

metabolic activation. Tinidazole was negative for mutagenicity in a mammalian cell culture system utilising Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

Tinidazole carcinogenicity studies in rats, mice or hamsters have not been reported. However, metronidazole, a chemically-related nitroimidazole, has been reported to be carcinogenic in mice and rats but not hamsters. In several studies metronidazole showed evidence of pulmonary, hepatic, and lymphatic tumorigenesis in mice and mammary and hepatic tumours in female rats.

Reproductive and developmental toxicity

Tinidazole did not cause malformations in mice or rats. In rats, oral administration of tinidazole reduced embryo-foetal viability and growth retardation (reduced foetal weight and increased skeletal variations) from 500 mg/kg/day (approximately 2 times the highest human therapeutic dose based upon body surface area). In a rat developmental toxicity study, a higher incidence of foetal mortality was noted following oral administration of 600 mg/kg (approximately 3 times the highest human therapeutic dose based upon body surface area). Embryo-foetal toxicity was not observed in mice at the highest dose level of 2,500 mg/kg (approximately 6 times the highest human therapeutic dose based upon body surface area).

In a male rat fertility study, oral administration of tinidazole reduced fertility at 600 mg/kg/day. Degeneration of the seminiferous tubules in the testes with corresponding effects on spermatogenic measures were noted at 300 and 600 mg/kg/day. The NOAEL for testicular and spermatogenic effects was 100 mg/kg/day (approximately 0.5 times the highest human therapeutic dose based upon body surface area). In another study, oral administration of tinidazole reduced fertility in male rats at 300 mg/kg/day and in female rats at 150 and 300 mg/kg/day.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Excipients	Specifications
Maize Starch	BP

Sodium Methyl Hydroxybenzoate	BP
Sodium Propyl Hydroxybenzoate	BP
Gelatin	BP
Maize Starch (For Paste)	BP
Cross Caramellulose Sodium	BP
Sodium Starch Glycolate	BP
Sodium Lauryl Sulphate	BP
Purified Talc	BP
Magnesium Stearate	BP
Colloidal Anhydrous Silica	BP
Sodium Starch Glycolate	BP
Sodium Lauryl Sulphate	BP
Brilliant Blue	IHS
Isopropyl Alcohol	BP
Methylene Chloride	BP

1.3.1.8.2 Incompatibilities:

Not Applicable

1.3.1.8.3 Shelf life:

36 months.

1.3.1.8.4 Special precautions for storage:

Store below 25°C in the original pack to protect from light and moisture.

1.3.1.8.5 Nature and contents of container:

Each kit contains 2 tablets of Tinidazole, 2 tablets of Clarithromycin and 2 capsule of Omeprazole.

1.3.1.8.6 Special precautions for disposal and other Special handling:

None

1.3.1.9 Marketed by:

AQUATIX PHARMACEUTICALS LIMITED.
NO. 14, PRINCE BODE OLUWO STREET,
MENDE, MARYLAND,
LAGOS NIGERIA.

1.3.1.10 Manufactured by:

M/s. McW Healthcare Pvt. Ltd.
286, 287A, 287B,
Sector-E, Industrial Area,
Sanwer Road,
Indore (M.P.) India