ABGRESS-HP™

Tablets

Combikit of Clarithromycin IP 500 mg + Esomerprzole IP 40 mg + Amoxicillin IP 1000 mg Tablets USP

Therapeutic Indications

Abgress HP Combo is indicated for the eradication of *H. pylori* in patients with active chronic gastritis, gastric ulcer and duodenal ulcer.

Posology and Method of Administration

Dosage

One **Abgress HP Combo** pack contains two tablets of esomeprazole (40 mg), two tablets of amoxicillin (750 mg) and two tablets of clarithromycin (500 mg). One pack is for 1 day of treatment. From this specially designed pack, one tablet each of esomeprazole, amoxicillin, and clarithromycin is to be taken in the morning and similarly one each in the evening. The duration of therapy recommended is for 14 days.

Method of Administration

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

Special Populations

Esomeprazole

Renal impairment

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section **Pharmacokinetic Properties**).

Hepatic impairment

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg esomeprazole should not be exceeded (see section **Pharmacokinetic Properties**).

Geriatric population

Dose adjustment is not required in the elderly.

Pediatric Population

Safety and effectiveness of esomeprazole in pediatric patients have not been established

Amoxicillin

Elderly

No dose adjustment is considered necessary.

Renal impairment

Table 1. Dosage Adjustments in Patients with Renal Impairment

GFR (ml/min)	**Adults**
greater than 30	no adjustment necessary
10 to 30	maximum 500 mg twice daily
less than 10	maximum 500 mg/day.

In patients receiving haemodialysis

Amoxicillin may be removed from the circulation by haemodialysis.

	Haemodialysis
Adults	500 mg every 24 h Prior to haemodialysis one additional dose of 500 mg should be adminis restore circulating drug levels, another dose of 500 mg should be admini haemodialysis.

In patients receiving peritoneal dialysis

Amoxicillin maximum 500 mg/day.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections **Special Warnings and Precautions for Use** and **Undesirable Effects**).

Clarithromycin

Renal Impairment

See Table 2 for dosage adjustment in patients with moderate or severe renal impairment with or without concomitant atazanavir or ritonavir-containing regimens (see section **Drug Interactions**).

Table 2. Dosage Adjustments in Patients with Renal Impairment

Recommended Clarithromycin Dosage Reduction	
Patients with severe renal impairment (CL_{cr} of <30 mL/min)	Reduce the dosage by 50%
Patients with moderate renal impairment (CL_{cr} of 30 to 60 mL/min) taking concomitant atazanavir or ritonavir-containing regimens	Reduce the dosage by 50%
Patients with severe renal impairment (CL_{cr} of <30 mL/min) taking concomitant atazanavir or ritonavir-containing regimens	Reduce the dosage by 75%

Dosage Adjustment Due to Drug Interactions

Decrease the dose by 50 % when co-administered with atazanavir (see section **Drug Interactions**). Dosage adjustments for other drugs when co-administered with clarithromycin may be recommended due to drug interactions.

Contraindications

Esomeprazole

Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria (see section **Undesirable Effects**).

Esomeprazole should not be used concomitantly with nelfinavir.

Amoxicillin

Hypersensitivity to the active substance, to any of the penicillins

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

Clarithromycin

Hypersensitivity

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibacterial drugs (see section **Special Warnings and Precautions for Use).**

Cisapride and Pimozide

Concomitant administration of clarithromycin with cisapride and pimozide is contraindicated (see section **Drug Interactions**).

There have been post-marketing reports of drug interactions when clarithromycin is co-administered with cisapride or pimozide, resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and *torsades de pointes*) most likely due to inhibition of metabolism of these drugs by clarithromycin. Fatalities have been reported.

Cholestatic Jaundice/Hepatic Dysfunction

Clarithromycin is contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction associated with prior use of clarithromycin.

Colchicine

Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Lomitapide, Lovastatin, and Simvastatin

Concomitant administration of clarithromycin with lomitapide is contraindicated due to potential for markedly increased transaminases (see sections **Special Warnings and Precautions for Use** and **Drug Interactions**).

Concomitant administration of clarithromycin with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin) is contraindicated, due to the increased risk of myopathy, including rhabdomyolysis (see sections **Special Warnings and Precautions for Use** and **Drug Interactions**).

Ergot Alkaloids

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated (see section **Drug Interactions**).

Contraindications for Co-administered Drugs

For information about contraindications of other drugs indicated in combination with clarithromycin, refer to their full prescribing information.

Special Warnings and Precautions for Use

Esomeprazole

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, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Long Term Use

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

On Demand Treatment

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.

Helicobacter pylori Eradication

When prescribing esomeprazole for eradication of *Helicobacter pylori*, possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

Gastrointestinal Infections

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section **Pharmacodynamic Properties**).

Absorption of Vitamin B12

Esomeprazole, like all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy (e.g. longer than 3 years).

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole 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.

Risk of Fracture

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

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving esomeprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Presence of Gastric Malignancy

In adults, symptomatic response to therapy with esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including esomeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops (see section **Contraindications**)

Clostridium difficile-Associated Diarrhea

Published observational studies suggest that PPI therapy like esomeprazole may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve (see section **Undesirable Effects**).

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole, refer to **Special Warnings and Precautions for Use** section of the corresponding prescribing information.

Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Combination with other medicines

Co-administration of esomeprazole with atazanavir is not recommended (see section **Drug Interactions**). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section **Drug Interactions**). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

When prescribing esomeprazole for on demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered (see section **Drug Interactions**).

Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole with St. John's Wort or rifampin.

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section **Pharmacodynamic Properties**).

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.

Amoxicillin

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued, and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders.

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment.

Skin reactions

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires amoxicillin discontinuation and contra-indicates any subsequent administration.

Amoxicillin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during, or subsequent to, the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Crystalluria

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.

The presence of amoxicillin may distort assay results for oestriol in pregnant women.

Clarithromycin

Severe Acute Hypersensitivity Reactions

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, and acute generalized exanthematous pustulosis, discontinue clarithromycin therapy immediately and institute appropriate treatment.

QT Prolongation

Clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of *torsades de pointes* have been spontaneously reported during postmarketing surveillance in patients receiving clarithromycin. Fatalities have been reported.

Avoid clarithromycin in the following patients:

- patients with known prolongation of the QT interval, ventricular cardiac arrhythmia, including *torsades de pointes*
- patients receiving drugs known to prolong the QT interval (see section **Contraindications**)

- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia and in patients receiving Class IA (e.g., quinidine, procainamide, disopyramide) or Class III (e.g., dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval (see **Use in Special Population**).

Hepatotoxicity

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Symptoms of hepatitis can include anorexia, jaundice, dark urine, pruritus, or tender abdomen. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur.

Serious Adverse Reactions Due to Concomitant Use with Other Drugs

Drugs metabolized by CYP3A4: Serious adverse reactions have been reported in patients taking clarithromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; markedly increased transaminases with lomitapide; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; hypoglycemia and cardiac arrhythmias (e.g., *torsades de pointes*) with disopyramide; and hypotension and acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine). Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 involved elderly patients 65 years of age or older. Use clarithromycin with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme. The use of clarithromycin with lomitapide, simvastatin, lovastatin, ergotamine, or dihydroergotamine is contraindicated (see sections **Contraindications** and **Drug Interactions**).

Colchicine: Life-threatening and fatal drug interactions have been reported in patients treated with clarithromycin and colchicine. Clarithromycin is a strong CYP3A4 inhibitor and this interaction may occur while using both drugs at their recommended doses. If co-administration of clarithromycin and colchicine is necessary in patients with normal renal and hepatic function, reduce the dose of colchicine. Monitor patients for clinical symptoms of colchicine toxicity. Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment (see sections **Contraindications** and **Drug Interactions**).

Lomitapide: Concomitant use of clarithromycin with lomitapide is contraindicated (see section **Contraindications**). Lomitapide is metabolized by CYP3A4, and concomitant

treatment with clarithromycin increases the plasma concentration of lomitapide, which increases the risk of elevation in transaminases (see section **Drug Interactions**). If treatment with clarithromycin cannot be avoided, therapy with lomitapide must be suspended during the course of treatment.

HMG-CoA Reductase Inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section **Contraindications**) 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. Cases of rhabdomyolysis have been reported in 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.

Exercise caution when prescribing clarithromycin with atorvastatin or pravastatin. In situations where the concomitant use of clarithromycin with atorvastatin or pravastatin cannot be avoided, atorvastatin dose should not exceed 20 mg daily and pravastatin dose should not exceed 40 mg daily. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. It is recommended to prescribe the lowest registered dose if concomitant use cannot be avoided.

Oral Hypoglycemic Agents/Insulin: The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended (see section **Drug Interactions**).

Quetiapine: Use quetiapine and clarithromycin concomitantly with caution. Co-administration could result in increased quetiapine exposure and quetiapine related toxicities such as somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, and QT prolongation. Refer to quetiapine prescribing information for recommendations on dose reduction if co-administered with CYP3A4 inhibitors such as clarithromycin (see section **Drug Interactions**).

Oral Anticoagulants: There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. Monitor INR and prothrombin times frequently while patients are receiving clarithromycin and oral anticoagulants concurrently (see section **Drug Interactions**).

Benzodiazepines: Increased sedation and prolongation of sedation have been reported with concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam and midazolam (see section **Drug Interactions**).

All-Cause Mortality in Patients with Coronary Artery Disease 1 to 10 Years After Clarithromycin Exposure

In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality one year or more after the end of treatment was observed in patients randomized to receive clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. The cause of the increased risk has not been established. Other epidemiologic studies evaluating this risk have shown variable results (see section **Undesirable Effects**). Consider balancing this potential risk with the treatment benefits when prescribing clarithromycin in patients who have suspected or confirmed coronary artery disease.

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

1. *difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Embryo-Fetal Toxicity

Based on findings from animal studies, clarithromycin is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If clarithromycin is used during pregnancy, or if pregnancy occurs while the patient is taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin demonstrated adverse effects on pregnancy outcome and/or embryo fetal development, including fetal malformations, in pregnant animals administered oral clarithromycin (see section **Use in Special Population**).

Exacerbation of Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving clarithromycin therapy.

Development of Drug Resistant Bacteria

Prescribing clarithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions

Esomeprazole

Effects of esomeprazole on the pharmacokinetics of other medicinal products

Protease inhibitors

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). 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 with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once daily without omeprazole 20 mg once daily. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir AUC, C_{max}, and C_{min} by 36–39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section **Special Warnings and Precautions for Use**) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section **Contraindications**).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once daily). Treatment with omeprazole 20 mg once daily had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once daily had no effect on the exposure of amprenavir (with and

without concomitant ritonavir). Treatment with omeprazole 40 mg once daily had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate

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

Tacrolimus

Concomitant administration of esomeprazole 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 dosage of tacrolimus adjusted if needed.

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, atazanavir, iron salts, mycophenolate mofetil (MMF), itraconazole, and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. 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). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic medicinal product monitoring of digoxin should then be reinforced.

Co-administration of omeprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving esomeprazole and MMF. Use esomeprazole with caution in transplant patients receiving MMF.

Medicinal products metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased, and a dose reduction could be needed.

This should be considered especially when prescribing esomeprazole for on-demand therapy.

Diazepam

Concomitant oral administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin

Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUCτ by 15% and 41%, respectively.

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. 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.

Cisapride

In healthy volunteers, concomitant oral administration of 40 mg esomeprazole and cisapride resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Warfarin

Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing of oral esomeprazole, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

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 esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

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.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

Investigated medicinal products with no clinically relevant interaction

Amoxicillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Naproxen or rofecoxib

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCτ by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

Medicinal products known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism. Avoid concomitant use of St. John's Wort or rifampin with esomeprazole.

Pediatric population

Interaction studies have only been performed in adults.

Amoxicillin

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections **Special Warnings and Precautions for Use** and **Undesirable Effects**).

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Clarithromycin

Co-administration of clarithromycin is known to inhibit CYP3A, and a drug primarily metabolized 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 metabolized by this enzyme. Adjust dosage when appropriate and monitor serum concentrations of drugs primarily metabolized by CYP3A closely in patients concurrently receiving clarithromycin.

Table 3: Clinically Significant Drug Interactions with Clarithromycin

Drug(s) with Pharmacokinetics Affected by Clarithromycin	**Recommendation**	**Comments**
Antiarrhythmics: Disopyramide Quinidine Dofetilide Amiodarone Sotalol Procainamide	Not Recommended	Disopyramide, Quinidine: There have been p reports of torsades de pointes occurring wit of clarithromycin and quinidine or disopyran Electrocardiograms should be monitored fo prolongation during coadministration of cla these drugs (see section **Special Warnings for Use**). Serum concentrations of these me also be monitored. There have been sponta published reports of CYP3A based interactio clarithromycin with disopyramide and quini been postmarketing reports of hypoglycemi concomitant administration of clarithromyc disopyramide. Therefore, blood glucose leve monitored during concomitant administrati clarithromycin and disopyramide.
Digoxin	Use With Caution	Digoxin: Digoxin is a substrate for P-glycopro clarithromycin is known to inhibit Pgp. Wher and digoxin are co-administered, inhibition clarithromycin may lead to increased expos Elevated digoxin serum concentrations in pa clarithromycin and digoxin concomitantly ha reported in postmarketing surveillance. Son shown clinical signs consistent with digoxin including potentially fatal arrhythmias. Mon digoxin concentrations should be considere

		patients with digoxin concentrations in the u range.
Oral Anticoagulants: Warfarin	Use With Caution	Oral anticoagulants: Spontaneous reports i postmarketing period suggest that concomi administration of clarithromycin and oral an potentiate the effects of the oral anticoagul Prothrombin times should be carefully mon patients are receiving clarithromycin and ora simultaneously (see section **Special Warni Precautions for Use**).
Antiepileptics: Carbamazepine	Use With Caution	Carbamazepine: Concomitant administratio of clarithromycin and carbamazepine has b result in increased plasma concentrations c carbamazepine. Blood level monitoring of ca may be considered. Increased serum conce carbamazepine were observed in clinical tri clarithromycin. There have been spontaneo reports of CYP3A based interactions of clari carbamazepine.
Antifungals: Itraconazole	Use With Caution	Itraconazole: Both clarithromycin and itracc substrates and inhibitors of CYP3A, potentia bi-directional drug interaction when adminis concomitantly (see also Itraconazole under **Affect the Pharmacokinetics of Clarithron** table below). Clarithromycin may increase t concentrations of itraconazole. Patients tak and clarithromycin concomitantly should be closely for signs or symptoms of increased c adverse reactions.
Fluconazole	No Dose Adjustment	Fluconazole: (see section **Pharmacokinetic**

Anti-Gout Agents: Colchicine (in patients with renal or hepatic impairment) Colchicine (in patients with normal renal and hepatic function)	Contraindicated Use With Caution	Colchicine: Colchicine is a substrate for bot efflux transporter, P-glycoprotein (Pgp). Clar other macrolides are known to inhibit CYP3A dose of colchicine should be reduced when with clarithromycin in patients with normal function (see sections **Contraindications** a **Warnings and Precautions for Use**).
Antipsychotics: Pimozide Quetiapine	Contraindicated	Pimozide: (see section **Contraindications**) Quetiapine: Quetiapine is a substrate for CY inhibited by clarithromycin. Co-administrati clarithromycin could result in increased que and possible quetiapine related toxicities. T postmarketing reports of somnolence, ortho hypotension, altered state of consciousness malignant syndrome, and QT prolongation d concomitant administration. Refer to quetia information for recommendations on dose r administered with CYP3A4 inhibitors such a
Antispasmodics: Tolterodine (patients deficient in CYP2D6 activity)	Use With Caution	Tolterodine: The primary route of metabolism is via CYP2D6. However, in a subset of the p of CYP2D6, the identified pathway of metab CYP3A. In this population subset, inhibition in significantly higher serum concentrations Tolterodine 1 mg twice daily is recommende deficient in CYP2D6 activity (poor metaboliz administered with clarithromycin.
Antivirals: Atazanavir	Use With Caution	Atazanavir: Both clarithromycin and atazana substrates and inhibitors of CYP3A, and the

Saquinavir (in patients with decreased renal function) Ritonavir Etravirine Maraviroc		a bi-directional drug interaction (see Atazan “ **Drug(s) that Affect the Pharmacokinetic** **Clarithromycin**” in the table below) (see section **Pharmacokinetic Properties**). Saquinavir: Both clarithromycin and saquina are substrates and inhibitors of CYP3A and t of a bi-directional drug interaction (see Saquinavir under “**Drug(s) that Affect t** **Pharmacokinetics of Clarithromycin**” in th (see section **Pharmacokinetic Properties**) Ritonavir, Etravirine: (see Ritonavir and Etravirine Etravirine under “**Drug(s) that Affe** **Pharmacokinetics of Clarithromycin**” in the table below) (see section **Pharmacokin** Maraviroc: Clarithromycin may result in increases in maraviroc exposures by inhibiti metabolism. Boceprevir: Both clarithromycin and bocepr substrates and inhibitors of CYP3A, potentia bi-directional drug interaction when co-adm dose adjustments are necessary for patient renal function. Zidovudine: Simultaneous oral administrati clarithromycin immediate-release tablets a HIV-infected adult patients may result in de state zidovudine concentrations. Administra clarithromycin and zidovudine should be se least two hours (see section **Pharmacokine**

Boceprevir (in patients with normal renal function) Didanosine Zidovudine	No Dose Adjustment	The impact of co-administration of clarithromycin extended-release tablets or g zidovudine has not been evaluated.
Calcium Channel Blockers: Verapamil Amlodipine Diltiazem Nifedipine	Use With Caution	Verapamil: Hypotension, bradyarrhythmias, lactic acidosis have been observed in patie receiving concurrent verapamil, (see section **Special Warnings and Precautions Use**) Amlodipine, Diltiazem: (see section **Special Precautions for Use**) Nifedipine: Nifedipine is a substrate for CYP Clarithromycin and other macrolides are kn CYP3A. There is potential of CYP3Amediate

		between nifedipine and clarithromycin. Hyp peripheral edema were observed when clari taken concomitantly with nifedipine (see se **Warnings and Precautions for Use**).
Ergot Alkaloids: Ergotamine Dihydroergotamine	Contraindicated	Ergotamine, Dihydroergotamine: Postmarke indicate that coadministration of clarithrom ergotamine or dihydroergotamine has been acute ergot toxicity characterized by vasosp ischemia of the extremities and other tissue central nervous system (See section **Contra**
Gastroprokinetic Agents: Cisapride	Contraindicated	Cisapride: (See section **Contraindications**)
Lipid-lowering agents: Lomitapide Lovastatin Simvastatin	Contraindicated	Lomitapide, Lovastatin, Simvastatin: Clarith increase the exposure of these drugs by inhi metabolism, thereby increasing the risk of t these drugs (see sections **Contraindication** **Warnings and Precautions for Use**)
Atorvastatin Pravastatin Fluvastatin	Use With Caution No Dose Adjustment	Atorvastatin, Pravastatin, Fluvastatin: (see s **Warnings and Precautions for Use**)
Hypoglycemic Agents: Nateglinide Pioglitazone	Use With Caution	Nateglinide, Pioglitazone, Repaglinide, Rosi sections **Special Warnings and Precaution** **Use** and **Undesirable Effects**)

Repaglinide Rosiglitazone Insulin		Insulin: (see sections **Special Warnings an** **for Use** and **Undesirable Effects**)
Immunosuppressants: Cyclosporine Tacrolimus	Use With Caution	Cyclosporine: There have been spontaneou reports of CYP3A based interactions of clari cyclosporine. Tacrolimus: There have been spontaneous c reports of CYP3A based interactions of clari tacrolimus.
Phosphodiesterase inhibitors: Sildenafil Tadalafil Vardenafil	Use With Caution	Sildenafil, Tadalafil, Vardenafil: Each of thes phosphodiesterase inhibitors is primarily m CYP3A, and CYP3A will be inhibited by conc administration of clarithromycin. Co-admin clarithromycin with sildenafil, tadalafil, or va result in increased exposure of these phosp inhibitors. Co-administration of these phosp inhibitors with clarithromycin is not recomm Increased systemic exposure of these drugs clarithromycin; reduction of dosage for phos inhibitors should be considered (see their re prescribing information).
Proton Pump Inhibitors: Omeprazole	No Dose Adjustment	Omeprazole: The mean 24-hour gastric pH v when omeprazole was administered alone a coadministered with clarithromycin as a res omeprazole exposures (see section **Pharma** **Properties**) (see also Omeprazole under **"D** **the Pharmacokinetics of Clarithromycin"** below).

Xanthine Derivatives: Theophylline	Use With Caution	Theophylline: Clarithromycin use in patients receiving theophylline may be associated w serum theophylline concentrations (see section **Pharmacokinetic Properties**). Mon theophylline concentrations should be cons patients receiving high doses of theophyllin concentrations in the upper therapeutic ran
Triazolobenzodiazepines and Other Related Benzodiazepines: Midazolam Alprazolam Triazolam	Use With Caution	Midazolam: When oral midazolam is co-adr clarithromycin, dose adjustments may be n possible prolongation and intensity of effect anticipated (see sections **Special Warnings Precautions for Use** and **Pharmacokinetic** Triazolam, Alprazolam: Caution and approp adjustments should be considered when triazolam or alprazolam is co-administered clarithromycin. There have been postmarke drug interactions and central nervous syste (e.g., somnolence and confusion) with the c of clarithromycin and triazolam. Monitoring increased CNS pharmacological effects is s In postmarketing experience, erythromycin reported to decrease the clearance of triazo midazolam, and thus, may increase the pha effect of these benzodiazepines. Temazepam, Nitrazepam, Lorazepam: For b which are not metabolized by CYP3A (e.g., t nitrazepam, lorazepam), a clinically importa with clarithromycin is unlikely.

Temazepam Nitrazepam Lorazepam	No Dose Adjustment	
Cytochrome P450 Inducers: Rifabutin	Use With Caution	Rifabutin: Concomitant administration of rifabutin and resulted in an increase in rifabutin, and decr clarithromycin serum levels together with ar of uveitis (see Rifabutin under "**Drug(s) that Pharmacokinetics of Clarithromycin**" in th
Other Drugs Metabolized by CYP3A: Alfentanil Bromocriptine Cilostazol Methylprednisole Vinblastine Phenobarbital St. John's Wort	Use With Caution	There have been spontaneous or published based interactions of clarithromycin with alt methylprednisolone, cilostazol, bromocripti phenobarbital, and St. John's Wort.

Other Drugs Metabolized by CYP450 Isoforms Other than CYP3A: Hexobarbital Phenytoin Valproate	Use With Caution	There have been postmarketing reports of in clarithromycin with drugs not thought to be CYP3A, including hexobarbital, phenytoin, a

Drug(s) that Affect the Pharmacokinetics of Clarithromycin	**Recommendation**	**Comments**
Antifungals: Itraconazole	Use With Caution	Itraconazole: Itraconazole may increa concentrations of clarithromycin. Pati itraconazole and clarithromycin conc be monitored closely for signs or symp increased or prolonged adverse reacti Itraconazole under "**Drug(s) with Pha Affected by Clarithromycin"** in the ta
Antivirals: Atazanavir	Use With Caution	Atazanavir: When clarithromycin is co with atazanavir, the dose of clarithrom decreased by 50%. Since concentrations of 14-OH clarith significantly reduced when clarithrom administered with atazanavir, alternat therapy should be considered for indi than infections due to *Mycobacterium* Doses of clarithromycin greater than 1

Ritonavir (in patients with decreased renal function) Saquinavir (in patients with decreased renal function)		should not be co-administered with p inhibitors. Ritonavir: Since concentrations of 14- clarithromycin are significantly reduce clarithromycin is co-administered wit alternative antibacterial therapy shou for indications other than infections d to *Mycobacterium avium* (see section **Pharmacokinetic Properties** clarithromycin greater than 1000 mg p not be co-administered with protease Saquinavir: When saquinavir is co-adr ritonavir, consideration should be give effects of ritonavir on clarithromycin (above) (see section **Pharmacokinetic** Etravirine: Clarithromycin exposure w decreased by etravirine; however, con the active metabolite, 14-OH-clarithro increased. Because 14-OH-clarithrom reduced activity against *Mycobacteriu avium* complex (MAC), overall activity pathogen may be altered; therefore, a clarithromycin should be considered of MAC.

Etravirine Saquinavir (in patients with normal renal function) Ritonavir (in patients with normal renal function)	No Dose Adjustment	
Proton Pump Inhibitors: Omeprazole	Use With Caution	Omeprazole: Clarithromycin concentr gastric tissue and mucus were also in concomitant administration of omepr section **Pharmacokinetic Properties**
Miscellaneous Cytochrome P450 Inducers: Efavirenz Nevirapine Rifampicin Rifabutin	Use With Caution	Inducers of CYP3A enzymes, such as nevirapine, rifampicin, rifabutin, and r increase the metabolism of clarithron decreasing plasma concentrations of while increasing those of 14-OHclarit the microbiological activities of clarith OHclarithromycin are different for diff

Rifapentine		the intended therapeutic effect could during concomitant administration of and enzyme inducers. Alternative anti treatment should be considered when receiving inducers of CYP3A. There ha spontaneous or published reports of C interactions of clarithromycin with rifa Rifabutin under "**Drug(s) with Pharma** **Affected by Clarithromycin"** in the ta

Use in Special Population

Esomeprazole

Pregnant Women

Clinical data on exposed pregnancies with esomeprazole are insufficient. With the racemic mixture, omeprazole data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect.

Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing esomeprazole to pregnant women.

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section **Animal Toxicology or Pharmacology**).

Lactating Women

It is not known whether esomeprazole is excreted in human breast milk, there is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

Fertility

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

Pediatric Use

Safety and effectiveness of esomeprazole in the pediatric population have not been established.

Geriatric Use

Of the total number of patients who received esomeprazole in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age. No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amoxicillin

Pregnant Women

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Lactating Women

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

Clarithromycin

Pregnant Women

Based on findings from animal studies, clarithromycin is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus (see section **Special Warnings and Precautions for Use**).

Limited data from a small number of published human studies with clarithromycin use during pregnancy are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies,

administration of oral clarithromycin to pregnant mice, rats, rabbits, and monkeys during the period of organogenesis produced malformations in rats (cardiovascular anomalies) and mice (cleft palate) at clinically relevant doses based on body surface area comparison. Fetal effects in mice, rats, and monkeys (e.g., reduced fetal survival, body weight, body weight gain) and implantation losses in rabbits were generally considered to be secondary to maternal toxicity.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactating Women

Based on limited human data, clarithromycin and its active metabolite 14-OH clarithromycin are present in human milk at less than 2% of the maternal weight-adjusted dose. In a separate observational study, reported adverse effects on breast-fed children (rash, diarrhea, loss of appetite, somnolence) were comparable to amoxicillin. No data are available to assess the effects of clarithromycin or 14-OH clarithromycin on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for clarithromycin and any potential adverse effects on the breast-fed child from clarithromycin or from the underlying maternal condition.

Data

Human

Serum and milk samples were obtained after 3 days of treatment, at steady state, from one published study of 12 lactating women who were taking clarithromycin 250 mg orally twice daily. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively human milk fed infant would receive an estimated average of 136 mcg/kg/day of clarithromycin and its active metabolite, with this maternal dosage regimen. This is less than 2% of the maternal weight-adjusted dose (7.8 mg/kg/day, based on the average maternal weight of 64 kg), and less than 1% of the pediatric dose (15 mg/kg/day) for children greater than 6 months of age.

A prospective observational study of 55 breastfed infants of mothers taking a macrolide antibacterial (6 were exposed to clarithromycin) were compared to 36 breastfed infants of mothers taking amoxicillin. Adverse reactions were comparable in both groups. Adverse reactions occurred in 12.7% of infants exposed to macrolides and included rash, diarrhea, loss of appetite, and somnolence.

Effects on Ability to Drive and Use Machines

Esomeprazole

Esomeprazole has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) have been reported (see section **Undesirable Effects**). If affected patients should not drive or use machines.

Amoxicillin

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

Clarithromycin

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

Undesirable Effects

Esomeprazole

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse medicinal product reactions have been identified or suspected in the clinical trials programme for esomeprazole administered orally or intravenously and post-marketing when administered orally. The reactions are classified according to frequency: 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).

Table 4. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia

	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever, angioe anaphylactic reaction/shock
	Not known	Systemic lupus erythematosus
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia (see section **Special W Precautions for Use**); severe hypomagnes correlate with hypocalcaemia. Hypomagne 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	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, fl nausea/vomiting, fundic gland polyps (ben
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis, pancreatitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients liver disease

Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson sy epidermal necrolysis (TEN)
	Not known	Subacute cutaneous lupus erythematosus section **Special Warnings and Precaution** hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist, or spine (see sec **Warnings and Precautions for Use**)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis: in some patients, rena reported concomitantly
	Not known	Acute kidney injury
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

Pediatrics

Safety and effectiveness of esomeprazole in pediatric patients have not been established.

<u>Amoxicillin</u>

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash. The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

- 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)

Table 5. Tabulated list of adverse reactions

Infections and infestations	
Very rare	Mucocutaneous candidiasis
Blood and lymphatic system disorders	
Very rare	Reversible leucopenia (including severe neutropenia or agr reversible thrombocytopenia and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (see s **Warnings and Precautions for Use**).
Immune system disorders	
Very rare	Severe allergic reactions, including angioneurotic oedema, serum sickness and hypersensitivity vasculitis (see section **Warnings and Precautions for Use**).
Not known	Jarisch-Herxheimer reaction (see section **Special Warning** **Precautions for Use**).
Nervous system disorders	
Very rare	Hyperkinesia, dizziness and convulsions (see section **Spec** **and Precautions for Use**).
Gastrointestinal disorders	
Clinical Trial Data	
*Common	Diarrhoea and nausea
*Uncommon	Vomiting
Post-marketing Data	
Very rare	Antibiotic associated colitis (including pseudomembraneo haemorrhagic colitis; see section **Special Warnings and P** **Use**). Black hairy tongue
Hepatobiliary disorders	

Very rare	Hepatitis and cholestatic jaundice. A moderate rise in AST
Skin and subcutaneous tissue disorders	
Clinical Trial Data	
*Common	Skin rash
*Uncommon	Urticaria and pruritus
Post-marketing Data	
Very rare	Skin reactions such as erythema multiforme, Stevens-Johr toxic epidermal necrolysis, bullous and exfoliative dermati generalised exanthematous pustulosis (AGEP) (see sectior **Warnings and Precautions for Use**), and drug reaction wit and systemic symptoms (DRESS).
Renal and urinary tract disorders	
Very rare:	Interstitial nephritis Crystalluria (see sections **Special Warnings and Precauti Use** and **Overdose**)
* The incidence of these AEs was derived from clinical studies involving a total of approximately 6,000 paediatric patients taking amoxicillin.	

Clarithromycin

The following serious adverse reactions are described below and elsewhere in the labelling (see section **Special Warnings and Precautions for Use**):

- Acute Hypersensitivity Reactions
- QT Prolongation
- Hepatotoxicity
- Serious Adverse Reactions Due to Concomitant Use with Other Drugs
- *Clostridium difficile* Associated Diarrhea
- Exacerbation of Myasthenia Gravis

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Based on pooled data across all indications, the most frequent adverse reactions for both adult and pediatric populations observed in clinical trials are abdominal pain, diarrhea, nausea, vomiting and dysgeusia. Also reported were dyspepsia, liver function test abnormal, anaphylactic reaction, candidiasis, headache, insomnia, and rash.

The subsequent subsections list the most common adverse reactions for prophylaxis and treatment of mycobacterial infections and duodenal ulcer associated with *H. pylori* infection. In general, these profiles are consistent with the pooled data described above.

Prophylaxis of Mycobacterial Infections

In AIDS patients treated with clarithromycin over long periods of time for prophylaxis against *M. avium*, it was often difficult to distinguish adverse reactions possibly associated with clarithromycin administration from underlying HIV disease or intercurrent illness. Median duration of treatment was 10.6 months for the clarithromycin group and 8.2 months for the placebo group.

Table 6. Incidence Rates (%) of Selected Adverse Reactions[a] in Immunocompromised Adult Patients Receiving Prophylaxis Against *M. avium Complex*

Body System[b] Adverse Reaction	**Clarithromycin (n=339) %**	**Placebo %**
Body as a Whole		
Abdominal pain	5%	4%
Headache	3%	1%
Digestive		
Diarrhea	8%	4%
Dyspepsia	4%	3%
Flatulence	2%	1%
Nausea	11%	7%
Vomiting	6%	3%
Skin & Appendages		
Rash	3%	4%

Special Senses		
Taste Perversion	8%[c]	0.3%

[a] Includes those events possibly or probably related to study drug and excludes concurrent conditions

[b] 2% or greater Adverse Reaction Incidence Rates for either treatment group

[c] Significant higher incidence compared to the placebo-treated group

Discontinuation due to adverse reactions occurred in 18% of patients receiving clarithromycin compared to 17% of patients receiving placebo in this trial. Primary reasons for discontinuation in clarithromycin treated patients include headache, nausea, vomiting, depression, and taste perversion.

Changes in Laboratory Values

Selected laboratory adverse experiences that were reported during therapy in greater than 2 % of adult patients treated with clarithromycin in a randomized double-blind clinical trial involving 682 patients are presented in Table 7.

In immunocompromised patients receiving prophylaxis against *M. avium*, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal value (i.e., the extreme high or low limit) for the specified test.

Table 7. Percentage of Patients[a] Exceeding Extreme Laboratory Values in Patients Receiving Prophylaxis Against *M. avium* Complex

		Clarithromycin 500 mg twice a day	**Placebo**
WBC Count	<1 x 10^9/L	2/103 (4%)	0/95
SGOT	>5 x ULN[b]	7/196 (4%)	5/208 (2%)
SGPT	>5 x ULN[b]	6/217 (3%)	4/232 (2%)

[a] Includes only patients with baseline values within the normal range or borderline high (hematology va within normal range or borderline low (chemistry variables)

[b] ULN= Upper Limit of Normal

Treatment of Mycobacterial Infections

The adverse reaction profiles for both the 500 mg and 1000 mg twice a day-dose regimens were similar.

In AIDS patients 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 reactions possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

The following analysis summarizes experience during the first 12 weeks of therapy with clarithromycin. Data are reported separately for trial 1 (randomized, double-blind) and trial 2 (open-labeled, compassionate use) and also combined. Adverse reactions were reported less frequently in trial 2, which may be due in part to differences in monitoring between the two studies.

In adult patients receiving clarithromycin 500 mg twice a day, the most frequently reported adverse reactions, considered possibly or possibly related to study drug, with an incidence of 5% or greater, are listed below (Table 8). Approximately 8% of the patients who received 500 mg twice a day and 12% of the patients who received 1000 mg twice a day discontinued therapy due to drug related adverse reactions during the first 12 weeks of therapy; adverse reactions leading to discontinuation in at least 2 patients included nausea, vomiting, abdominal pain, diarrhea, rash, and asthenia.

Table 8. Selected Treatment-Related[a] Adverse Reaction Incidence Rates (%) in Immunocompromised Adult Patients During the First 12 Weeks of Therapy with 500 mg Twice a Day Clarithromycin Dose

Adverse Reaction	Trial 1 (n=53)	Trial 2 (n=255)	Combined (
Abdominal Pain	8	2	3
Diarrhea	9	2	3
Flatulence	8	0	1
Headache	8	0	2
Nausea	28	9	12
Rash	9	2	3
Taste Perversion	19	0	4
Vomiting	25	4	8

[a] Includes those events possibly or probably related to study drug and excludes concurrent conditions

Changes in Laboratory Values

In the first 12 weeks of starting on clarithromycin 500 mg twice a day, 3% of patients has SGOT increases and 2% of patients has SGPT increases > 5 times the upper limit of normal in trial 2 (469 enrolled adult patients) while trial 1 (154 enrolled patients) had no elevation of transaminases. This includes only patients with baseline values within the normal range or borderline low.

Duodenal ulcer associated with H. pylori Infection

In clinical trials using combination therapy with clarithromycin plus omeprazole and amoxicillin, no adverse reactions specific to the combination of these drugs have been observed. Adverse reactions that have occurred have been limited to those that have been previously reported with clarithromycin, omeprazole or amoxicillin.

The adverse reaction profiles are shown below (Table 9) for four randomized double-blind clinical trials in which patients received the combination of clarithromycin 500 mg three times a day, and omeprazole 40 mg daily for 14 days, followed by omeprazole 20 mg once a day, (three studies) or 40 mg once a day (one study) for an additional 14 days. Of the 346 patients who received the combination, 3.5% of patients discontinued drug due to adverse reactions.

Table 9. Adverse Reactions with an Incidence of 3% or Greater

Adverse Reaction	**Clarithromycin + Omeprazole (n=346) % of Patients**	**Omeprazole (n=355) % of Patients**	**Clarith % of Pa**
Taste Perversion	15	1	16
Nausea	5	1	3
Headache	5	6	9
Diarrhea	4	3	7
Vomiting	4	<1	1
Abdominal Pain	3	2	1
Infection	3	4	2
a Only two of four studies			

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance in patients taking clarithromycin and omeprazole in four randomized double-blind trials in 945 patients are as follows: Hepatic: elevated direct bilirubin <1%; GGT <1%; SGOT (AST) <1%; SGPT (ALT) <1%, Renal: elevated serum creatinine <1%.

Less Frequent Adverse Reactions Observed During Clinical Trials of Clarithromycin

Based on pooled data across all indications, the following adverse reactions were observed in clinical trials with clarithromycin at a rate less than 1%:

Blood and Lymphatic System Disorders: Leukopenia, neutropenia, thrombocythemia, eosinophilia

Cardiac Disorders: Electrocardiogram QT prolonged, cardiac arrest, atrial fibrillation, extrasystoles, palpitations

Ear and Labyrinth Disorders: Vertigo, tinnitus, hearing impaired

Gastrointestinal Disorders: Stomatitis, glossitis, esophagitis, gastrooesophageal reflux disease, gastritis, proctalgia, abdominal distension, constipation, dry mouth, eructation, flatulence

General Disorders and Administration Site Conditions: Malaise, pyrexia, asthenia, chest pain, chills, fatigue

Hepatobiliary Disorders: Cholestasis, hepatitis

Immune System Disorders: Hypersensitivity

Infections and Infestations: Cellulitis, gastroenteritis, infection, vaginal infection

Investigations: Blood bilirubin increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, albumin globulin ratio abnormal

Metabolism and Nutrition Disorders: Anorexia, decreased appetite

Musculoskeletal and Connective Tissue Disorders: Myalgia, muscle spasms, nuchal rigidity

Nervous System Disorders: Dizziness, tremor, loss of consciousness, dyskinesia, somnolence

Psychiatric Disorders: Anxiety, nervousness

Renal and Urinary Disorders: Blood creatinine increased, blood urea increased

Respiratory, Thoracic and Mediastinal Disorders: Asthma, epistaxis, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: Urticaria, dermatitis bullous, pruritus, hyperhidrosis, rash maculo-papular

Gastrointestinal Adverse Reactions

In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse reactions were reported by a proportion of patients taking clarithromycin.

All-Cause Mortality in Patients with Coronary Artery Disease 1 to 10 Years Following Clarithromycin Exposure

In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality was observed in

patients randomized to clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. Patients were treated with clarithromycin or placebo for 14 days and observed for primary outcome events (e.g., all-cause mortality or non-fatal cardiac events) for several years. A numerically higher number of primary outcome events in patients randomized to receive clarithromycin was observed with a hazard ratio of 1.06 (95% confidence interval 0.98 to 1.14). However, at follow-up 10 years post-treatment, there were 866 (40%) deaths in the clarithromycin group and 815 (37%) deaths in the placebo group that represented a hazard ratio for all-cause mortality of 1.10 (95% confidence interval 1.00 to 1.21). The difference in the number of deaths emerged after one year or more after the end of treatment. The cause of the difference in all-cause mortality has not been established. Other epidemiologic studies evaluating this risk have shown variable results (see section **Special Warnings and Precautions for Use**).

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of clarithromycin. 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.

Blood and Lymphatic System: Thrombocytopenia, agranulocytosis

Cardiac: Ventricular arrhythmia, ventricular tachycardia, *torsades de pointes*

Ear and Labyrinth: Deafness was reported chiefly in elderly women and was usually reversible

Gastrointestinal: Pancreatitis acute, tongue discoloration, tooth discoloration was reported and was usually reversible with professional cleaning upon discontinuation of the drug

There have been reports of clarithromycin 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 diarrhea. 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 antibacterial drug.

Hepatobiliary: Hepatic failure, jaundice hepatocellular. Adverse reactions related to hepatic dysfunction have been reported with clarithromycin (see section **Special Warnings and Precautions for Use**).

Infections and Infestations: Pseudomembranous colitis (see section **Special Warnings and Precautions for Use**)

Immune System: Anaphylactic reactions, angioedema

Investigations: Prothrombin time prolonged, white blood cell count decreased, international normalized ratio increased. Abnormal urine color has been reported, associated with hepatic failure.

Metabolism and Nutrition: Hypoglycemia has been reported in patients taking oral hypoglycemic agents or insulin.

Musculoskeletal and Connective Tissue: Myopathy rhabdomyolysis was reported and in some of the reports, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see sections **Contraindications** and **Special Warnings and Precautions for Use**).

Nervous System: Parosmia, anosmia, ageusia, paresthesia and convulsions

Psychiatric: Abnormal behavior, confusional state, depersonalization, disorientation, hallucination, depression, manic behavior, abnormal dream, psychotic disorder. These disorders usually resolve upon discontinuation of the drug.

Renal and Urinary: Nephritis interstitial, renal failure

Skin and Subcutaneous Tissue: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), Henoch-Schonlein purpura, acne, acute generalized exanthematous pustulosis

Vascular: Hemorrhage

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. If your patient experiences any side-effects, write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

Esomeprazole

There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280 mg were gastrointestinal symptoms and weakness. Single oral doses of 80 mg esomeprazole. No specific antidote is known.

Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience.

Amoxicillin

Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses (see sections **Special Warnings and Precautions for Use** and **Undesirable Effects**).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin can be removed from the circulation by haemodialysis.

Clarithromycin

Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

Treat adverse reactions accompanying overdosage by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

PHARMACOLOGICAL PROPERTIES

Esomeprazole

Mechanism of Action

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacodynamic Properties

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6–7 hours after dosing on day five.

After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours respectively, over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

One week's treatment with esomeprazole 20 mg twice daily and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.

After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomised, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10% respectively) were randomised to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72-hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group was 7.7% vs 13.6%.

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 both children and adults during long-term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term oral treatment with antisecretory medicinal products, gastric glandular cysts have been reported to occur at 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 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*.

Clinical efficacy

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 an d/or with previous ulcer), including COX-2 selective NSAIDs.

Pediatric population

No relevant data is available for esomeprazole in pediatric population.

Pharmacokinetic Properties

Absorption

Esomeprazole is acid labile and is administered orally as enteric-coated granules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose.

The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once daily administration. For 20 mg esomeprazole, the corresponding values are 50% and 68%, respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Biotransformation

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

Elimination

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

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent medicinal product is found in urine.

Linearity/non-linearity

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg twice daily. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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 esomeprazole and/or its sulphone metabolite.

Special patient populations

Poor metabolisers

Approximately 2.9 ±1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals, the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once daily administration of 40 mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of esomeprazole.

Gender

Following a single oral dose of 40 mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once daily administration. These findings have no implications for the posology of esomeprazole.

Hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Pediatric population

No relevant data is available for esomeprazole in pediatric population.

Amoxicillin

Mechanism of Action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the

bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Pharmacodynamic Properties

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The main mechanisms of resistance to amoxicillin are:

- Inactivation by bacterial beta-lactamases.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 5.0.

Table 10. MIC breakpoints for amoxicillin

Organism	**MIC breakpoint (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacteriaceae	8[1]	8
Staphylococcus spp.	Note[2]	Note[2]
Enterococcus spp.[3]	4	8
Streptococcus groups A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	Note[5]	Note[5]
Viridans group steprococci	0.5	2
Haemophilus influenzae	2[6]	2[6]
Moraxella catarrhalis	Note[7]	Note[7]

Neisseria meningitidis	0.125	1
Gram positive anaerobes except *Clostridium difficile*[8]	4	8
Gram negative anaerobes[8]	0.5	2
Helicobacter pylori	0.125[9]	0.125[9]
Pasteurella multocida	1	1
Non- species related breakpoints[10]	2	8

[1]Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries pre
wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpo

[2]Most staphylococci are penicillinase producers, which are resistant to amoxicillin. Methicillin resistar
with few exceptions, resistant to all beta-lactam agents.

[3]Susceptibility to amoxicillin can be inferred from ampicillin

[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenic
susceptibility.

[5]Breakpoints relate only to non-meningitis isolates. For isolates categorised as intermediate to ampicil
treatment with amoxicillin. Susceptibility inferred from the MIC of ampicillin.

[6]Breakpoints are based on intravenous administration. Beta-lactamase positive isolates should be rep

[7]Beta lactamase producers should be reported resistant

[8]Susceptibility to amoxicillin can be inferred from benzylpenicillin.

[9]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type is
with reduced susceptibility.

[10]The non-species related breakpoints are based on doses of at least 0.5 g x 3 or 4 doses daily (1.5 to 2

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table 11. *In vitro* susceptibility of micro-organisms to Amoxicillin
Commonly Susceptible Species
Gram-positive aerobes:
Enterococcus faecalis

Beta-hemolytic streptococci (Groups A, B, C and G)
Listeria monocytogenes
Species for which acquired resistance may be a problem
Gram-negative aerobes:
Escherichia coli
Haemophilus influenzae
Helicobacter pylori
Proteus mirabilis
Salmonella typhi
Salmonella paratyphi
Pasteurella multocida
Gram-positive aerobes:
Coagulase negative staphylococcus
Staphylococcus aureus£
Streptococcus pneumoniae
Viridans group streptococcus
Gram-positive anaerobes:
Clostridium spp.
Gram-negative anaerobes:
Fusobacterium spp.
Other:
Borrelia burgdorferi
Inherently resistant organisms†
Gram-positive aerobes:
Enterococcus faecium†
Gram-negative aerobes:
Acinetobacter spp.

Enterobacter spp. *Klebsiella* spp. *Pseudomonas* spp.
Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.
† Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ Almost all *S. aureus* are resistant to amoxicillin due to production of penicillinase. In addition, all met strains are resistant to amoxicillin.

Pharmacokinetic properties

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (T_{max}) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

C_{max}	**T_{max} ***	**AUC $_{(0-24h)}$**	**T ½**
(µg/ml)	(h)	((µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as C_{max} and AUC). The absorption is not influenced by simultaneous food intake. Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material. Amoxicillin, like most penicillins, can be detected in breast milk (see section **Use in Special Population**).

Amoxicillin has been shown to cross the placental barrier (see section **Use in Special Population**).

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose.

Elimination

The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24-hour period.

Concomitant use of probenecid delays amoxicillin excretion (see section **Drug Interactions**).

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function (see sections **Posology and Method of Administration** and **Special Warnings and Precautions for Use**).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

Clarithromycin

Mechanism of Action

Clarithromycin is a macrolide antimicrobial drug.

Pharmacodynamic Properties

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria resulting in inhibition of protein synthesis.

Resistance

The major routes of resistance are modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity or drug efflux pumps. Beta-lactamase production should have no effect on clarithromycin activity.

Most isolates of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

If *H. pylori* is not eradicated after treatment with clarithromycin-containing combination regimens, patients may develop clarithromycin resistance in *H. pylori* isolates. Therefore, for patients who fail therapy, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin-resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy; omeprazole/clarithromycin/amoxicillin triple therapy; lansoprazole/clarithromycin/amoxicillin triple therapy; or other regimens which include clarithromycin as the sole antibacterial agent.

Antimicrobial Activity

Clarithromycin has been shown to be active against most of the isolates of the following microorganisms both *in vitro* and in clinical infections.

Gram-Positive Bacteria

- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Gram-Negative Bacteria

- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*

Other Microorganisms

- *Chlamydophila pneumoniae*
- *Helicobacter pylori*
- *Mycobacterium avium* complex (MAC) consisting of *avium* and *M. intracellulare*
- *Mycoplasma pneumoniae*

At least 90 percent of the microorganisms listed below exhibit in vitro minimum inhibitory concentrations (MICs) less than or equal to the clarithromycin susceptible MIC breakpoint for organisms of similar type to those shown in Table 10. However, the efficacy of clarithromycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

- *Streptococcus agalactiae*
- Streptococci (Groups C, F, G)
- Viridans group streptococci

Gram-Negative Bacteria

- *Legionella pneumophila*
- *Pasteurella multocida*

Anaerobic Bacteria

- *Clostridium perfringens*
- *Peptococcus niger*
- *Prevotella melaninogenica*
- *Propionibacterium acnes*

Pharmacokinetic Properties

Absorption

The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24% but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, Clarithromycin may be given without regard to food. In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing.

Distribution

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented below.

Table 12. Tissue and Serum Concentrations of Clarithromycin

CONCENTRATION (after 250 mg every 12 hours)		
Tissue Type	**Tissue**	**Serum**
(mcg/g)	**(mcg/mL)**	
Tonsil	1.6	0.8
Lung	8.8	1.7

Metabolism and Elimination

Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 mcg/mL to 2 mcg/mL with a 250 mg dose administered every 12 hours and 3 mcg/mL to 4 mcg/mL with a 500 mg dose administered every 8 hours to 12 hours. The elimination half-life of clarithromycin was about 3 hours to 4 hours with 250 mg administered every 12 hours but increased to 5 hours to 7 hours with 500 mg administered every 8 hours to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 hours to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 mcg/mL and has an elimination half-life of 5 hours to 6 hours. With a 500-

mg every 8 hours to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 mcg/mL), and its elimination half-life is about 7 hours to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 days to 4 days.

After a 250-mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250 mg or a 500 mg tablet administered every 12 hours.

Specific Populations

HIV Infection

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500-mg or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2 mcg/mL to 4 mcg/mL and 5 mcg/mL to 10 mcg/mL, respectively.

Hepatic Impairment

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

Renal Impairment

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function (see sections **Use in Special Population** and **Posology and Method of Administration**).

Drug Interactions

Fluconazole

Following administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers, the steady-state clarithromycin C_{min} and AUC increased

33% and 18%, respectively. Clarithromycin exposures were increased and steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

Colchicine

When a single dose of colchicine 0.6 mg was administered with clarithromycin 250 mg twice daily for 7 days, the colchicine C_{max} increased 197% and the AUC0-∞ increased 239% compared to administration of colchicine alone.

Atazanavir

Following administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily), the clarithromycin AUC increased 94%, the 14-OH clarithromycin AUC decreased 70% and the atazanavir AUC increased 28%.

Ritonavir

Concomitant administration of clarithromycin and ritonavir (n = 22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin.

Saquinavir

Following administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers, the steady-state saquinavir AUC and C_{max} increased 177% and 187% respectively compared to administration of saquinavir alone. Clarithromycin AUC and C_{max} increased 45% and 39% respectively, whereas the 14±OH clarithromycin AUC and C_{max} decreased 24% and 34% respectively, compared to administration with clarithromycin alone.

Didanosine

Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Zidovudine

Following administration of clarithromycin 500 mg tablets twice daily with zidovudine 100 mg every 4 hours, the steady-state zidovudine AUC decreased 12% compared to administration of zidovudine alone (n=4). Individual values ranged from a decrease of 34% to an increase of 14%. When clarithromycin tablets were administered two to four hours prior to zidovudine, the steady-state zidovudine C_{max} increased 100% whereas the AUC was unaffected (n=24).

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 t½ increases of 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin.

The plasma levels of clarithromycin and 14±OH clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC0-8 was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14±OH clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC0-8 was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Table 13. Clarithromycin Tissue Concentrations 2 hours after Dose (mcg/mL)/(mcg/g)

Treatment	**N**	**antrum**	**fundus**	**N**	**Mucu**
Clarithromycin	5	10.48 ± 2.01	20.81 ± 7.64	4	4.15 ±
Clarithromycin + Omeprazole	5	19.96 ± 4.71	24.25 ± 6.37	4	39.29

Theophylline

In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Midazolam

When a single dose of midazolam was co-administered with clarithromycin tablets (500 mg twice daily for 7 days), midazolam AUC increased 174% after intravenous administration of midazolam and 600% after oral administration.

NONCLINICAL PROPERTIES

Animal Toxicology or Pharmacology

Esomeprazole

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

Amoxicillin

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

Clarithromycin

Corneal opacity occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose (on a body surface area basis). Lymphoid depletion occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose (on a body surface area basis).

DESCRIPTION

Helicobacter pylori (H. pylori) is probably the most common bacterial infection, with a worldwide prevalence of approximately 50%. *H. pylori* is implicated in the etiology of gastritis and peptic ulcers in humans.

Newer triple therapies, including proton-pump inhibitors (PPIs) such as esomeprazole, amoxicillin, and clarithromycin, serve as a shorter, simpler and effective drug regimen for the eradication of *H. pylori*.

The active ingredient in esomeprazole tablets is bis(5-methoxy-2[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S-and R-isomers. (Initial U.S. approval of esomeprazole magnesium: 2001). Its molecular formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis.

The structural formula is:

The chemical name of amoxicillin is (2S,5R,6R)-6-[(R)-2-amino-2-(4-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid.

Amoxicillin trihydrate is a white or almost white, crystalline powder, which is slightly soluble in water and in ethanol (96%) and is practically insoluble in chloroform, in

ether, and in fixed oils.

The chemical structure for amoxicillin trihydrate is:

Clarithromycin is a semi-synthetic macrolide antimicrobial for oral use. Chemically, it is 6-0methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

PHARMACEUTICAL PROPERTIES

Incompatibilities

Not applicable.

Shelf-life

As on the pack.

Packaging Information

Each Kit contains

2 Clarithromycin Tablets IP

2 Esomeprazole Tablets IP

2 Amoxicillin Tablets USP

Storage and Handling Instructions

Store below 25°C. Protect from light and moisture.

PATIENT COUNSELLING INFORMATION

What is Abgress HP Combo used for

Abgress HP Combo is a combination pack, which contains three different medicines. When taken together in the right doses, they will kill the bacteria in your stomach called *Helicobacter pylori* and let your peptic ulcer heal.

Depending on the position of the ulcer it is called a gastric or duodenal ulcer. A gastric ulcer occurs in the stomach. A duodenal ulcer occurs in the duodenum which is the tube leading out from the stomach.

Most people who have a peptic ulcer also have a bacterium called Helicobacter pylori in their stomach. If the bacteria are killed it is unlikely that your ulcer will come back.

Abgress HP Combo contains esomeprazole, amoxicillin, and clarithromycin. Amoxicillin and clarithromycin are both types of antibiotic.

How Abgress HP Combo works

Esomeprazole is a type of medicine called a proton-pump inhibitor. Esomeprazole works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allow healing to take place.

This does not stop food being digested in the normal way.

Amoxicillin and clarithromycin are both antibiotics that help kill *H. pylori*. Esomeprazole also helps kill the bacteria. When all three are taken together they are more effective than taken one or two at a time. It is possible that the antibiotics may not always kill *Helicobacter pylori*.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

Your doctor may prescribe this medicine for another use.

There is no evidence that **Abgress HP Combo** is addictive.

This medicine is available only with a doctor's prescription.

Before you take Abgress HP Combo

When you must not take it

Do not take* Abgress HP Combo *if you have an allergy to:

- any medicines containing esomeprazole, amoxicillin or clarithromycin
- any ingredients listed at the end of the leaflet
- any other similar medicines such as proton pump inhibitors, penicillins, cephalosporins or macrolide antibiotics

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take* Abgress HP Combo *if you are taking any of the following medicines*:*

- ergotamine
- cisapride

- pimozide
- dihydroergotamine
- astemizole
- terfenadine
- cilostazol
- atazanavir
- colchicine
- simvastatin
- lovastatin
- ticagrelor
- ranolazine
- colchicine
- oral midazolam
- domperidone

Please check with your doctor or pharmacist if you are taking any of these medicines. These medicines will be affected by the medicines in **Abgress HP Combo** and it is more likely you will get side effects.

Do not take Abgress HP Combo if you have a history of heart conditions such as QT prolongation or ventricular cardiac arrhythmia.

Do not take Abgress HP Combo if you have low potassium levels.

Do not take Abgress HP Combo if you have both liver and kidney problems.

Abgress HP Combo is not recommended for use in children.

There is no information about the use of **Abgress HP Combo** in children.

Do not take this medicine after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking this medicine, talk to your doctor.

Before you start to use it

Tell your doctor if you have allergies to any other medicines, foods, preservatives or dyes.

You must tell your doctor if you have:

- problems with your blood
- problems with your liver or kidneys
- any heart conditions, such as QT prolongation or ventricular cardiac arrhythmia
- you have glandular fever
- myasthenia gravis, a condition in which the muscles become weak and tire easily
- been diagnosed with osteoporosis
- low potassium, low magnesium or any other electrolyte imbalances
- if you have ever had a skin reaction after treatment with a medicine similar to esomeprazole that reduces stomach acid

Tell your doctor if you are pregnant or plan to be pregnant, are breast-feeding or plan to breast-feed.

It is not known if it is safe for you to take **Abgress HP Combo** if you are pregnant. The medicines in **Abgress HP Combo** may affect the developing baby.

Your baby can take in all the medicines in **Abgress HP Combo** from breast milk if you are breast-feeding. **Abgress HP Combo** is not recommended when breast-feeding.

Your doctor can discuss with you the risks and benefits of using **Abgress HP Combo** if you are pregnant or breast-feeding.

If you have not told your doctor about any of the above, tell them before you start taking Abgress HP Combo.

Taking other medicines

Do not take Abgress HP Combo if you are taking the following medicines:

- ergotamine or dihydroergotamine - medicines used to treat migraine headaches
- astemizole or terfenadine – medicines used to treat hayfever and allergies
- atazanavir - a medicine used to treat Human Immunodeficiency Virus (HIV)
- cilostazol - a medicine used to treat intermittent claudication

- colchicine - a medicine used to treat gout
- lovastatin or simvastatin – medicines used to treat high cholesterol
- ticagrelor - a medicine used to treat blood clots
- oral midazolam - a medicine used for surgical sedation
- domperidone - a medicine used for nausea

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from a pharmacy, supermarket or health food shop.

Some medicines and **Abgress HP Combo** may interfere with each other. These include:

- diazepam, triazolam or alprazolam - medicines used as sedatives or to treat anxiety
- ketoconazole, itraconazole, voriconazole or fluconazole - medicines used to treat fungal infections
- warfarin and clopidogrel – medicines used to prevent blood clots
- allopurinol or probenecid – medicines used to treat gout
- phenytoin, sodium valproate or carbamazepine - medicines used to treat seizures
- atorvastatin or rosuvastatin – medicines used to treat high cholesterol
- theophylline - a medicine used to treat asthma
- zidovudine, saquinavir, efavirenz, etravirine, nevirapine, nelfinavir or ritonavir - medicines used to treat HIV
- insulin, repaglinide, nateglinide, pioglitazone or rosiglitazone – medicines used to treat diabetes
- digoxin, quinidine or disopyramide - medicines used to treat heart conditions
- citalopram, fluoxetine, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- rifabutin, rifapentine, rifampicin or erythromycin - medicines used to treat bacterial infections
- sildenafil, tadalafil or vardenafil - medicines used to treat impotence
- tolterodine - a medicine used to treat incontinence

- verapamil, amlodipine or diltiazem - medicines used to treat high blood pressure and some heart conditions
- methylprednisolone - a corticosteroid
- vinblastine - a medicine used to treat cancer
- oral contraceptives or birth control pills.

Talk to your doctor about the need for an additional method of contraception while on **Abgress HP Combo**

- tacrolimus or ciclosporin – medicines used to prevent organ transplant rejection or to treat certain problems with the immune system
- methotrexate - a medicine used to treat arthritis and some types of cancer
- erlotinib or related medicines used to treat cancer
- phenobarbitone - a medicine used to treat epilepsy
- tetracycline and aminoglycoside antibiotics - medicines used to treat certain infections
- atypical antipsychotics - medicines used to treat psychiatric conditions, such as schizophrenia and bipolar disorder (e.g. quetiapine)
- ibrutinib - a medicine used to treat cancer

These medicines may affect **Abgress HP Combo** or may affect how well it works. You may need different amounts of your medicines or you may need to take different medicines.

Your doctor and pharmacist have more information on medicines to be careful with or avoid while taking this medicine.

If you have not told your doctor about any of these things, tell them before you take any Abgress HP Combo.

How to take Abgress HP Combo

Follow all directions given to you by your doctor or pharmacist carefully. They may differ from the information contained in this leaflet.

If you do not understand the instructions on the box, ask your doctor or pharmacist for help.

How much to take

There are three different medicines in **Abgress HP Combo**. It is very important that you take **Abgress HP Combo** exactly as follows:

Esomeprazole = E

Take one 40 mg tablet in the morning and at night.

Amoxicillin = A

Take one 750 mg tablet in the morning and at night.

Clarithromycin = C

Take one 500 mg tablet in the morning and at night.

Morning

1 E, 1 A, 1 C

Night

1 E, 1 A, 1 C

How to take it

Swallow the **Abgress HP Combo** tablets whole with a glass of water.

Do not crush or chew the tablets as they will not work properly.

Take medicines in **Abgress HP Combo** during or after meals.

How long to take it

Continue taking the tablets until you finish the course or until your doctor tells you to stop.

If you do not complete the full course prescribed by your doctor, the *Helicobacter pylori* may not clear completely and your symptoms may return.

Tell your doctor if your symptoms return.

It is possible that the antibiotics may not kill *Helicobacter pylori*. You may need treatment with more antibiotics.

If you forget to take it

If you forget to take any of the medicines in **Abgress HP Combo** take it as soon as you remember, as long as it is more than four hours before the next dose of that medicine is due.

Do not take a double dose to make up for any dose that you miss.

If you are unsure what to do ask your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or go to the emergency room at your nearest hospital if you think that you or anyone else may have taken too much **Abgress HP Combo** even if there are no signs of discomfort or poisoning.

If you take too much **Abgress HP Combo**, you may vomit and have severe stomach problems.

While you are using Abgress HP Combo

Things you must do

Take **Abgress HP Combo** exactly as your doctor has prescribed.

If you are about to be started on any new medicine, tell your doctor and pharmacist that you are taking **Abgress HP Combo**.

If you become pregnant while you are taking **Abgress HP Combo**, tell your doctor.

If you get severe diarrhoea, tell your doctor, pharmacist or nurse immediately.

Do this even if it occurs several weeks after **Abgress HP Combo** has been stopped.

Diarrhoea may mean that you have a serious condition affecting your bowel. You may need urgent medical care. Do not take medicine to stop the diarrhoea without first checking with your doctor.

If you get a sore, white mouth or tongue while taking, or soon after stopping **Abgress HP Combo**, tell your doctor. Also tell your doctor if you get vaginal itching or discharge.

This may mean you have a fungal infection called thrush. Sometimes the use of **Abgress HP Combo** allows fungi to grow and the above symptoms to occur. **Abgress HP Combo** does not work against fungal infections.

Tell any other doctors, dentists and pharmacists who are treating you that you are taking **Abgress HP Combo**.

If you need to have any medical tests while you are taking **Abgress HP Combo**, tell your doctor. It may affect the results of some tests.

Drink plenty of water or fluids while taking **Abgress HP Combo**.

Things you must not do

Do not take **Abgress HP Combo** to treat any other complaints unless your doctor tells you to.

Do not stop taking **Abgress HP Combo**, or change any of the doses, unless you have discussed it with your doctor.

You need to take all the tablets in the pack for it to work properly. If you stop taking it, your ulcer may come back and be harder to treat next time.

Do not give **Abgress HP Combo** to anyone else, even if they have the same condition as you.

Things to be careful of

Be careful driving or operating machinery until you know how **Abgress HP Combo** affects you.

Abgress HP Combo may cause dizziness in some people. Make sure you know how you react to **Abgress HP Combo** before you do anything that may be dangerous if you are dizzy.

Please talk to your doctor or pharmacist about these possibilities if you think they may bother you.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Abgress HP Combo.

Abgress HP Combo helps most people with peptic ulcer and *Helicobacter pylori* infection, but it may have unwanted side effects in a few people.

All medicines can have side effects.

Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- diarrhoea, nausea or vomiting
- headache
- dizziness
- constipation
- loss of appetite
- stomach pain (e.g. cramps)
- wind
- dryness of the mouth or other body cavities
- soreness of mouth or tongue

- "pins and needles"
- metallic taste or other change in taste or smell
- chills
- fatigue
- excessive burping

These side effects are usually mild.

Tell your doctor immediately or go to emergency room at your nearest hospital if you notice the following:

- muscle pain or weakness
- increase in breast size (males)
- fever
- changes in sleep patterns
- mood changes, hallucinations, confusion or depression
- change in sexual function
- blurred vision, hearing disturbances
- hair loss
- bleeding or bruising more easily than normal
- signs of frequent infections such as fever, severe chills, sore throat or mouth ulcers
- skin rash
- blood in urine
- tremor
- convulsions or fits
- overgrowth of yeast infections (thrush)
- fainting, irregular heart heat
- yellowing of the eyes or skin

These may be serious side effects. You may need urgent medical attention.

If any of the following happen, stop taking Abgress HP Combo and tell your doctor immediately or go to emergency room at your nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- chest pain
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- severe upper stomach pain, with nausea and vomiting
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite
- skin reaction, especially in sun-exposed areas, with joint pain
- severe stomach or abdominal cramps, watery and severe diarrhoea, which may also be bloody (this may occur several weeks after you stop taking **Abgress HP Combo**).

Do not take any medicine to stop the diarrhoea unless advised by your doctor.

These are very serious side effects. If you have them, you may have had a serious reaction to one of the medicines in **Abgress HP Combo**. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Abgress HP Combo**.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

After using Abgress HP Combo

Storage

Keep the three medicines in **Abgress HP Combo** in their separate blisters until it is time to take them.

Keep it in a cool dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car on hot days.

Heat and dampness can destroy some medicines.

Protect from light and moisture.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.