Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klaram 500mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of clarithromycin

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Yellow, oval, biconvex marked with `500` on one side and 'CL' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Clarithromycin is indicated in adults and children 12 years and older.

Clarithromycin is indicated for the treatment of infections due to susceptible organisms. Such infections include:-

1. Lower respiratory tract infections (e.g. bronchitis, pneumonia).
2. Upper respiratory tract infections (e.g. pharyngitis, sinusitis).
3. Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipalis).
4. Disseminated or localised mycobacterial infections due to Mycobacterium avium or Mycobacterium intracellulare. Localised infections due to Mycobacterium chelonae, Mycobacterium fortuitum or Mycobacterium kansasii.
5. Clarithromycin is indicated for the prevention of disseminated Mycobacterium avium complex infection in HIV - infected patients with CD4 lymphocyte counts less than or equal to 100/mm^3.
6. Clarithromycin in the presence of acid suppression is indicated for the eradication of H. pylori, resulting in decreased recurrence of duodenal ulcer. (See further information).

As with other antibiotics, it is recommended that guidelines on the prevalence of local resistance, and associated medical practice regarding the prescription of antibiotics, be consulted before prescribing clarithromycin.

Further Information: H. pylori is strongly associated with peptic ulcer disease. 90 to 100% of patients with duodenal ulcers are infected with this agent. Eradication of H. pylori has been shown to markedly reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy. In a well-controlled double-blind study, H. pylori infected patients with duodenal ulcer received clarithromycin 500 mg TID for 14 days with omeprazole 40 mg daily for 28 days. Clarithromycin has been used in other treatment regimens for the eradication of H. pylori. These regimens include: Clarithromycin plus tinidazole and omeprazole; and clarithromycin plus tetracycline, bismuth subsalicylate, and ranitidine.

4.2 Posology and method of administration

Adults and children older than 12 years
The usual recommended dosage of clarithromycin in adults is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 6 to 14 days.

Children younger than 12 years
Use of clarithromycin tablets is not recommended for children younger than 12 years. Use clarithromycin oral suspension.

In patients with renal impairment with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced by one-half, i.e.: 250 mg once daily, 250 mg twice daily in more severe infections. Treatments should not be continued beyond 14 days in these patients.

Dosage in patients with mycobacterial infections: The recommended starting dose is 500 mg twice daily. If no clinical or bacteriologic response is observed in 3 to 4 weeks, the dose may be increased to 1000 mg twice daily. Treatment of disseminated Mycobacterium Avium Complex (MAC) infections in AIDS patients should be continued, as long as clinical microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

Dosage for MAC prophylaxis: The recommended dosage of clarithromycin in adults is 500 mg twice daily.

Eradication of H. pylori:

Dual Therapy (14 days)
The recommended dose of clarithromycin is 500 mg three times daily for 14 days. (See further information).

Triple Therapy (7 days)
Clarithromycin 500 mg twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with amoxicillin 1000 mg twice daily for 7 days.

Triple Therapy (7 days)
Clarithromycin 500 mg twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with metronidazole 400 mg twice daily for 7 days.

Triple Therapy (7-10 days)
Clarithromycin 500 mg twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily for 7 to 10 days.

*see individual data sheets/ SPCs for the dose recommended for *H.pylori* eradication.

4.3 Contraindications

Use in patients with known hypersensitivity to macrolide antibiotic drugs or any of its excipients.

Use in patients with severe impairment of hepatic function, in combination with renal impairment.

Clarithromycin and ergotamine or dihydroergotamine derivatives should not be co-administered, as this may result in ergot toxicity.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: astemizole, cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular fibrillation and Torsade de Pointes (see section 4.5). Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including Torsades de Pointe (see section 4.4 and 4.5).

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment (see section 4.4).

Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

4.4 Special warnings and precautions for use

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2).

Clarithromycin is excreted principally by the liver and kidney, therefore caution must be exercised in its use in patients with impaired hepatic or renal function or in those concomitantly receiving potentially hepatotoxic drugs.

Cases of fatal hepatic failure (see section 4.8) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Prolonged or repeated use of clarithromycin may result in overgrowth of non-susceptible bacteria. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). If concomitant administration of colchicine and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening.

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

CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of anti bacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam and midazolam (see section 4.5).

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesemia, bradycardia (<50 bpm), or when co-administered with other medicinal products associated with QT prolongation (see section 4.5). Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Pneumonia: In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

HMG-CoA reductase inhibitors: Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (see section 4.5). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered.

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 hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral anticoagulants: There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Use of any antimicrobial therapy, such as clarithromycin, to treat H. pylori infection may select for drug-resistant organisms.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

4.5 Interaction with other medicinal products and other forms of interaction

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

Cisapride, pimozide, astemizole and terfenadine
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and Torsades de Pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 2 to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

Effects of Other Medicinal Products on Clarithromycin

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

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

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

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

Ritonavir
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered:
- For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.
- For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%.
- Doses of clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional drug interactions).

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics
There have been postmarketing reports of Torsade de Pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide.
Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

CY3A4-based interactions
Co-administration of clarithromycin, 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. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

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 (Cmax, AUC0-24, and t1/2 increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

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

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

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population

subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

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

Other drug interactions

Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4).

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

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

Phenytoin and Valproate
There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional drug interactions

Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with

creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

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

Saquinavir
Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatine capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are coadministered for a limited time at the doses/formulations studied.

Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with the combination therapy of saquinavir and ritonavir, therefore when this combination therapy is co-administered with clarithromycin consideration should be given to the potential effects of ritonavir on clarithromycin.

Verapamil
Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

4.6 Fertility, pregnancy and lactation

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

Clarithromycin is excreted into human breast milk.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics. (see section b of section 4.8)

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

b. Tabulated summary of adverse reactions

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

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

System Organ Class	Very common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known (cannot be estimated from the available data)
Infections and infestations			Candidiasis, vaginal infection	Pseudomembranous colitis, erysipelas, erythrasma
Blood and lymphatic system			Leukopenia, neutropenia, eosinophilia	Agranulocytosis, thrombocytopenia
Immune system disorders[1]			Hypersensitivity	Anaphylactic reaction
Metabolism and nutrition disorders			Anorexia, decreased appetite	Hypoglycaemia[2]
Psychiatric disorders		Insomnia	Anxiety	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams
Nervous system disorders		Dysgeusia, headache, taste perversion	Dizziness, somnolence[2], tremor	Convulsion, ageusia, parosmia, anosmia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Electrocardiogram QT prolonged[1], palpitations	Torsade de pointes[1], ventricular tachycardia[1]
Vascular disorders				Hemorrhage[2]
Gastrointestinal disorders		Diarrhea[1], vomiting, dyspepsia, nausea, abdominal pain	Gastritis, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis, hepatitis, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic failure[1], jaundice hepatocellular
Skin and		Rash,	Pruritus, urticaria	Stevens-Johnson

subcutaneous tissue disorders		hyperhidrosis		syndrome[1], toxic epidermal necrolysis[1], drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders				Rhabdomyolysis[1], myopathy
Renal and urinary disorders				Renal failure, nephritis interstitial
General disorders and administration site conditions			Malaise, asthenia, chest pain, chills, fatigue	
Investigations			Blood alkaline phosphatase increased, blood lactate dehydrogenase increased	International normalised ratio increased[2], prothrombin time prolonged[2], urine color abnormal

[1] See section a)

[2] See section c)

c. Description of selected adverse reactions

In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications (see section 4.4).

A special attention to diarrhoea should be paid as *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. (see section 4.4)

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated (see section 4.4).

As with other macrolides, QT prolongation, ventricular tachycardia, and *torsade de pointes* have rarely been reported with clarithromycin (see section 4.4 and 4.5).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents (see section 4.4).

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome. (see sections 4.4 and 4.5).

There have been rare reports of hypoglycemia, some of which have occurred in patients on concomitant oral hypoglycemic agents or insulin (see section 4.4 and 4.5).

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently (see section 4.4 and 4.5).

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of 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 antibiotic.

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

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

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

e. ***Other special populations***

Immunocompromised patients

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

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

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

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and general supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

One patient who has a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactonic ring. Specifically, clarithromycin is 6-0-Methyl Erythromycin A.

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppressing protein synthesis.

Microbiology: Clarithromycin has demonstrated excellent *in-vitro* activity against standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms.

The minimum inhibitory concentrations (MICs) of clarithromycin are generally one $\log^2$ dilution more potent than the MICs of erythromycin.

In-vitro data also indicate clarithromycin has excellent activity against *Legionella pneumophila*, and *Mycoplasma pneumoniae*. It is bactericidal to *Helicobacter pylori*; this activity of clarithromycin is greater at neutral pH than at acid pH.
In-vitro and *in-vivo* data show that this antibiotic has activity against clinically significant mycobacterial species.

The *in-vitro* antibacterial spectrum of clarithromycin is as follows. Please see below for table of MIC breakpoints.

USUALLY SENSITIVE BACTERIA	NON-SENSITIVE BACTERIA
Streptococcus agalactiae	*Enterobacteriacae*
Streptococcus pyogenes	Pseudomonas species
Streptococcus viridans	
Streptococcus pneumoniae	
Haemophilus influenzae	
Haemophilus parainfluenzae	
Neisseria gonorrhoea	
Listeria monocytogenes	
Legionella pneumophila	
Pasteurella multocida	
Mycoplasma pneumoniae	
Helicobacter (Campylobacter) pylori	
Campylobacter jejuni	
Chlamydia pneumoniae (TWAR)	
Chlamydia trachomatis	
Moraxella (Branhamella) catarrhalis	
Bordetella pertussis	
Borrelia burgdorferi	
Staphylococcus aureus	
Clostridium perfringens	
Peptococcus niger	
Propionibacterium acnes	
Bacterioides melaninogenicus	

Mycobacterium avium
Mycobacterium leprae
Mycobacterium kansaii
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium intracellulare

The principal metabolite of clarithromycin in man and other primates is a microbiologically-active metabolite, 14-OHclarithromycin.
This metabolite is as active or 1 to 2 fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH-metabolite exert either an additive or synergistic effect on *H. influenzae*. In guinea pigs with Legionella infection, an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility Tests: Quantitative methods that require measurement of zone diameters give the most precise estimate of susceptibility of bacteria to antimicrobial agents.

One recommended procedure uses disc impregnated with 15 mcg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC value for clarithromycin. The MICs are determined by the broth or agar dilution method. The recommended test medium for susceptibility testing of Haemophilus influenzae according to the National Committee of Clinical Laboratory Standards (NCCLS) is the Haemophilus Test Medium (H.T.M.).

The correlation of disc inhibition zone diameters with MICs is given in the following Table:

Clarithromycin Interpretative Standards

	Inhibition Zone Diameter (mm)			MIC (mcg/ml)		
Organisms	S	I	R	S	I	R
All organisms (except Haemophilus and Staphlococci	≥ 18	14-17	≤ 13	≤ 1	2-4	≥ 8
Staphlococci	≥ 20	---	≤ 19	≤ 0.5	-	≥ 1
Haemophilus influenzae when tested on HTM*	≥ 13	11-12	≤ 10	≤ 8	16	≥ 32
*HTM = Haemophilus Test Medium	S = Susceptible I = Intermediate			R= Resistant		

With these procedures, a report from the laboratory of “susceptible” indicates that the infecting organism is likely to respond to therapy. A report of “resistant” indicates that the infective organism is not likely to respond to therapy.

A report of “Intermediate Susceptability” suggests that the therapeutic effect of the drug may be equivocal or that the organism would be susceptible if higher doses were used (latter also referred to as moderately susceptible).

Breakpoints
The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptability Testing (EUCAST).

Breakpoints (MIC, µ/ml)		
Microorganism	Susceptible (≤)	Resistant (>)
Streptococcus spp.	0.25 µg/ml	0.5 µg/ml
Staphlococcus spp.	1 µg/ml	2 µg/ml
Haemophilus spp.	1 µg/ml	32 µg/ml
Moraxella catarrhalis	0.25 µg/ml	0.5 µg/ml

Clarithromycin is used for the eradication of H. pylori; minimum inhibitory concentration (MIC) ≤ 0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

5.2 Pharmacokinetic properties

The non-linear kinetics of orally administered clarithromycin have been studied extensively in a number of animal species and adult humans. These studies have shown that clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. No accumulation was found and the metabolic disposition did not change in any species following multiple dosing.

Results of these animal studies showed that clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels.
The highest concentrations were usually found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

In-vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 - 4.5 mcg/ml. A decrease in binding to 41% at 45.0 mcg/ml suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic drug levels.

Clarithromycin and its 14-OH-metabolite distribute readily into the body tissues and fluids.
Limited data from a small number of patients suggest that clarithromycin does not achieve significant levels in cerebrospinal fluid (CSF) after oral doses (i.e. only 1 to 2 percent of serum levels in CSF in patients with normal blood-CSF barriers). Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented below:

Tissue Type	Tissue (mcg/g)	Serum (mcg/ml)
Tonsil	1.6	0.8
Lung	8.8	1.7

With BID dosing at 250 mg, the peak steady state plasma concentration was attained in 2 to 3 days and averaged about 1 mcg/ml for clarithromycin and 0.6 mcg/ml for 14-OH-clarithromycin, while the elimination half-lives of the parent drug and metabolite were 3 - 4 hours and 5 - 6 hours, respectively. With BID dosing at 500 mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite averaged 2.7 - 2.9 mcg/ml and 0.88 - 0.83 mcg/ml, respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 - 4.8 hours, while that of the 14-OHclarithromcyin was 6.9 - 8.7 hours. At steady state, the 14-OH-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation product at the higher doses, indicate that metabolism of clarithromycin approaches saturation at high doses.

A pharmacokinetic study was conducted with clarithromycin 500 mg t.i.d. and omeprazole 40 mg q.i.d. When clarithromycin was given alone at 500 mg q8h, the mean steady-state C_{max} value was approximately 31% higher and C_{min} value was approximately 119% higher than when clarithromycin is compared with a previous study at 500mg q12h. The mean AUC for clarithromycin was 65% greater when 500 mg clarithromycin was given q8h rather than q12h. Neither T_{max} nor half-life values appeared substantially different between the q8h and q12h regimens.

When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean omeprazole AUC_{0-24} was 89% greater and the harmonic mean for omeprazole $T_{1/2}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max} C_{min} and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively over values achieved when clarithromycin was administered with placebo.

In human adults given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Faecal elimination accounted for 40.2% and 29.1% of these respective doses.

At steady state, clarithromycin gastric mucus concentrations six hours after dosing were approximately 25-fold higher in the clarithromycin/omeprazole group compared with the clarithromycin alone group. Six hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately 2-fold higher when clarithromycin was given with omeprazole than when clarithromycin was given with placebo.

In a study comparing one group of healthy human subjects with a group of subjects with liver impairment who were given 250 mg of clarithromycin BID for two days and a single 250 mg dose the third day, steady state plasma levels and systemic clearing of clarithromycin were not significantly different between the two groups. In contrast, steady state concentrations of the 14-OH metabolite were markedly lower in the group of hepatic-impaired subjects. This decreased metabolic clearance of the parent compound by 14-hydroxylation was partially offset by an increase in the renal clearance of parent drug, resulting in comparable steady state levels of parent drug in the hepatic impaired and healthy subjects.

These results indicate that no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

A study was conducted to evaluate and compare the pharmacokinetic profile of multiple 500 mg oral doses of clarithromycin in subjects with normal and decreased renal function. This plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. K_{elim} and urinary excretion were lower.

The extent to which these parameters differed was correlated with the degree of renal impairment: the more severe the renal impairment, the more significant the difference.

Pharmacokinetics in elderly subjects: A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent drug and the 14-OH metabolite.
However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age *per se*.

Pharmacokinetics in patients with mycobacterial infections: Steady-state concentrations of clarithromycin and 14-OHclarithromycin observed following administration of usual doses to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at the usual doses.

In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady-state clarithromycin C_{max} values ranged from 5-10 mcg/ml. C_{max} values as high as 27 mcg/ml have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses. Elimination half-lives appeared to be lengthened at these higher doses as compared to those seen with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

5.3 Preclinical safety data

Acute, Subchronic and Chronic Toxicity: Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.

In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5g/kg body weight. The median lethal dose, therefore, was greater than 5g/kg, the highest feasible dose for administration.

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or 35 mg/kg/day for 1 month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for 1 month, to 35 kg/day for 3 months, or 8 mg/kg/day for 6 months.

Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days. 10 mg/kg/day for 1 and 3 months, and 4 mg/kg/day for 6 months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration, and hyperactivity. Two of ten monkeys receiving 400 mg/kg/day died on treatment day 8; yellow discoloured faeces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxocity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase.

Discontinuation of the drug generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility, Reproduction, and Teratogenicity: Fertility and reproduction studies have shown daily dosages of 150-160 mg/kg/day to male and female rats caused no adverse effects on the oestrous cycle, fertility, parturition and a number of viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, 1 study in New Zealand White Rabbits and one study in cynomologous monkeys failed to demonstrate any teratogenicity from clarithromycin.

Only in one additional study in Sprague- Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony.

Two studies in mice also revealed a variable incidence of cleft palate (3-30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg BID), but not at the 35 times the maximal daily human clinical dose, suggesting maternal and foetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 10 times the upper range of the usual daily human dose (500 mg BID), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Mutagenicity: Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagagenic potential at drug concentrations of 25 mcg/petri plate or less. At a concentration of 50 mcg, the drug was toxic for all strains tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Starch, pregelatinised
Croscarmellose sodium
Povidone (k-value 81.0 – 96.3)
Talc
Magnesium stearate
Silica, colloidal anhydrous
Opadry II, 40L22444 Yellow containing:
Titanium dioxide (E171)
Polydextrose (E1200)
Hypromellose ((E464)
Triacetin (E1518)
Macrogol
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC/PVdC Strip or HDPE Tablet Container with LDPE Cap
Pack sizes: 7, 14, 21, 28, 30, 50, 100, 250, 500 or 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

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