SCHEDULING STATUS:
S4

PROPRIETARY NAME AND DOSAGE FORM:
KLARIZON 250 TABLETS
KLARIZON 500 TABLETS

COMPOSITION:
KLARIZON 250: Each film coated tablet contains clarithromycin 250 mg.
KLARIZON 500: Each film coated tablet contains clarithromycin 500 mg.
Preservative: Sorbic acid 0,06% m/m.
The following inactive ingredients are included in the uncoated tablets: colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, povidone K25, stearic acid, talc, magnesium stearate.
The film coating contains the following inactive ingredients: hydroxypropylmethyl cellulose, propylene glycol, sorbitan mono-oleate, vanilla dry flavour, quinoline yellow lake, titanium dioxide, hydroxypropyl cellulose, sorbic acid.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION:
A 20.1.1: Medium and broad spectrum antibiotics

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties
Clarithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting bacterial RNA-dependent protein synthesis. The *in vitro* antibacterial spectrum of pathogens sensitive to clarithromycin includes:
(*in vitro* sensitivity does not necessarily imply *in vivo* efficacy)
Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae
Legionella pneumophilia
Mycoplasma pneumoniae
Chlamydia trachomatis
Moraxella (Branhamella) catarrhalis
Haemophilus influenzae
Staphylococcus aureus (methicillin sensitive)
Helicobacter (Campylobacter) pylori
*Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellula*re
Clarithromycin is bactericidal to Helicobacter pylori, this activity is greater at neutral pH than at acidic pH.
The incidence of bacterial resistance to clarithromycin is higher in penicillin-resistant strains than among penicillin-sensitive strains. Therefore methicillin-resistant and oxacillin-resistant Staphylococcus and Streptococcus are also resistant to clarithromycin and cross-resistant to other macrolide antibiotics. Isolated cases of *Helicobacter pylori* and *Mycobacterium avium* with clarithromycin resistance caused by genetic mutations have been reported.
Pharmacokinetic properties
Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration, but its bioavailability is reduced to 50 – 55 % because of rapid first-past metabolism. Peak plasma concentration occurs approximately 2 hours after administration. Clarithromycin may be given with or without food. Clarithromycin is metabolised by the liver to the active metabolite, 14-hydroxyclarithromycin, as well as to several other metabolites. Both clarithromycin and 14-hydroxyclarithromycin distribute widely throughout the body and achieve high intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of clarithromycin ranges from 40 to 70 % and is concentration dependent. The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 and 5 to 9 hours respectively. Longer half-lives are observed after larger doses. Clarithromycin is eliminated by renal and nonrenal routes. The amount of clarithromycin excreted unchanged in the urine ranges from 20 to 40 %, depending on the dose administered and the formulation. Between 10 and 15 % of the dose is excreted in the urine as the 14-hydroxy metabolite. Although the pharmacokinetics of clarithromycin is altered in patients with hepatic or renal dysfunction, dosage adjustment is not necessary unless a patient has severe renal dysfunction (creatinine clearance of < 30 ml/minute). At higher doses in HIV-infected patients clarithromycin and 14-hydroxyclarithromycin concentrations are much higher when compared with usual doses in non-infected patients. The elimination half-lives also appear to be lengthened.

INDICATIONS:
KLARIZON is indicated for the treatment of the following mild to moderate severe infections caused by susceptible organisms:
- Lower respiratory tract infections such as bronchitis and pneumonia.
- Upper respiratory tract infections such as pharyngitis and sinusitis.
- Mild to moderately severe acute otitis media due to *S. pneumoniae, M. catarrhalis* and *H. influenzae*.
- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas.
- Eradication of *Helicobacter pylori* when used in combination with a proton pump inhibitor and another antibiotic to decrease recurrence of duodenal ulcer.

CONTRAINDICATIONS:
- Hypersensitivity to macrolide antibiotics or to any of the components of KLARIZON.
- Concomitant administration of KLARIZON with astemizole, cisapride, pimozide, and ergotamine or dihydroergotamine (see INTERACTIONS).
- Patients receiving astemizole, cisapride or pimozide therapy, who have pre-existing cardiac abnormalities (dysrhythmia, bradycardia, QT-interval prolongation, ischaemic heart disease, congestive heart failure, etc.) or electrolyte disturbance (See INTERACTIONS AND WARNINGS AND SPECIAL PRECAUTIONS).
- Safety and efficacy in infants less than 6 months of age have not been established.

WARNINGS AND SPECIAL PRECAUTIONS:
KLARIZON should be used with caution in:
- Liver function impairment - The pharmacokinetics are altered. No dosage adjustment is required in patients with hepatic function impairment, unless there is also concurrent severe renal function impairment. Treatment with KLARIZON should be discontinued if any signs of hepatic dysfunction develop. Hepatic dysfunction is usually reversible but may be severe. In rare instances, hepatic failure with fatal outcome has been reported, usually associated with other serious underlying diseases and/or concomitant medicines. Cases of increased serum creatinine have been reported but an association with KLARIZON has not been established.
- Renal function impairment (severe) - The elimination of KLARIZON is reduced in patients with renal function impairment, especially those with a creatinine clearance of < 30 ml/min. The dose of KLARIZON should be halved or the dosing interval doubled in patients with a creatinine clearance of < 30 ml/min.
- Rhabdomyolysis has been reported with concomitant use of KLARIZON and the HMGCoA reductase inhibitors e.g. simvastatin and lovastatin (See INTERACTIONS).
- Rifabutin and rifampicin - May decrease serum concentration of KLARIZON by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (See INTERACTIONS).
- Theophylline - The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (See INTERACTIONS).
- Cross-resistance between KLARIZON and other macrolides, lincomycin and clindamycin have been reported.
- Porphyria.
- Pseudomembranous colitis has been reported with KLARIZON and it may range in severity from mild to life-threatening. Therefore it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of KLARIZON.
- Colchicine toxicity with concomitant use of KLARIZON and colchicine have been reported during post-marketing experience, especially in the elderly, some of which occurred in patients with renal insufficiency. Fatalities have been reported in such patients (see INTERACTIONS).
- There have been less frequent reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics or insulin.
- Adverse effects in immunocompromised patients treated with higher doses of KLARIZON over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, hearing disturbance, AST and ALT elevations, elevated blood urea levels and abnormally low white blood cell and platelet counts. Additional events included dyspnoea, insomnia and dry mouth.
- Long-term use may result in colonisation with increased numbers of non-susceptible bacteria and fungi. If super-infections occur, appropriate therapy should be instituted.

Effects on ability to drive and use machines
KLARIZON could have a minor influence on the patient's ability to drive and use machines and the effect on the individual should be established before driving or using machinery.

INTERACTIONS:
Concomitant use of KLARIZON with:
- Astemizole, cisapride and pimozide – Have resulted in cardiac dysrhythmias, including QTc-interval prolongation, ventricular dysrhythmia, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by KLARIZON. Concurrent use is contraindicated. See CONTRAINDICATIONS.
- Anticoagulants such as warfarin - KLARIZON may result in the potentiation of the effects of warfarin. Prothrombin time/INR should be monitored closely.
- Digoxin - KLARIZON has been shown to increase serum digoxin concentrations. Monitoring of digoxin serum concentrations is recommended.
- Carbamazepine or other medicines metabolised by the cytochrome P450 enzyme system CYP3A isoenzyme for example (alprazolam, astemizole, cyclosporine, disopyramide, cizapride, ergot alkaloids, methylprednisolone, midazolam, omeprazole, warfarin, pimozide, rifabutin, quinidine, sildenafil, tadalafil, vardenafil, simvastatin, tacrolimus, triazolam, vinblastine, phenytoin, theophylline and valproate) - KLARIZON may be associated with increased levels of these medicines. Serum concentrations of these medicines may require monitoring. Rhabdomyolysis has been reported with concomitant use of KLARIZON and the HMGCoA reductase inhibitors e.g. simvastatin and lovastatin (See WARNINGS AND SPECIAL PRECAUTIONS).
- Rifabutin and rifampicin – May decrease serum concentration of KLARIZON by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (See WARNINGS AND SPECIAL PRECAUTIONS).
- Theophylline – The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (See WARNINGS AND SPECIAL PRECAUTIONS).
- Zidovudine – A decrease in the steady-state concentration of zidovudine may occur. Doses of zidovudine and KLARIZON should be taken at least 4 hours apart.
- Ritonavir – The metabolism of KLARIZON is inhibited. No dosage reduction of KLARIZON is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dose of KLARIZON as follows:
  Creatinine clearance 30 to 60 ml/min – Reduce dose by 50 %
  Creatinine clearance of < 30 ml/min – Reduce dose by 75 %
  Do not exceed a dose of 1 g/day during concurrent administration of KLARIZON with ritonavir.
  It has been suggested that other HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors may have a similar effect on KLARIZON.
- Colchicine – is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). KLARIZON and other macrolides are known to inhibit CYP3A and Pgp. When colchicine and KLARIZON are co-administered, inhibition of Pgp and/or CYP3A by KLARIZON may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see WARNINGS AND SPECIAL PRECAUTIONS). Fatalities have been reported in elderly patients with renal insufficiency that have been receiving concomitant colchicine.
- Ergotamine/dihydroergotamine – Post-marketing reports indicate that concomitant use of KLARIZON with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Permanent tissue damage may result.

PREGNANCY AND LACTATION:
Safety and efficacy in pregnancy and lactation have not been established.
KLARIZON is excreted in the breast milk.

DOSAGE AND DIRECTIONS FOR USE:
Adults: 250 mg twice daily.
In more severe infections, the dosage may be increased to 500 mg twice daily.
Renal impairment:
Creatinine clearance (< 30 ml/min): Reduce dose by half i.e. 250 mg once daily or 250 twice daily for severe infections. Limit the duration of treatment to 14 days.
Eradication of H.pylori:
Adults: 500 mg twice daily, in combination with an appropriate antibiotic and an acid lowering agent, for 7 to 10 days.
The safety and efficacy of KLARIZON in combination with proton-pump inhibitors other than omeprazole has not been established.
Atypical mycobacterial infections (MAC) in HIV patients:
Adults: 500 mg twice daily
Treatment of disseminated MAC infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients taking KLARIZON for more than 12 weeks. KLARIZON should be used in conjunction with other antimycobacterial agents.
KLARIZON may be taken with or without meals.

SIDE EFFECTS:
Blood and lymphatic system disorders
Less frequent: Thrombocytopenia.
The following were reported but the frequency is unknown: Leucopenia, neutropenia.
Infections and infestations
Less frequent: Infection (fever and chills, cough or hoarseness, lower back or side pain, painful or difficult urination).
Cardiac disorders
The following were reported but the frequency is unknown: QT prolongation, torsades de pointes, ventricular tachycardia and dysrhythmias.
Nervous system disorders
Less frequent: Headache.
The following were reported but the frequency is unknown: Anxiety, dizziness, insomnia, hallucinations, nightmares, vertigo, tinnitus, disorientation, depersonalisation, confusion, hearing loss, convulsions.
Endocrine disorders
The following was reported but the frequency is unknown: Hypoglycaemia.
Gastrointestinal disorders
Less frequent: Abnormal taste sensation, dyspepsia, flatulence, gastrointestinal disturbances.
The following were reported but the frequency is unknown: Anorexia, nausea, vomiting, diarrhoea, glossitis, stomatitis, oral candidiasis, pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever).
Hepato-biliary disorders
Less frequent: Hepatotoxicity.
The following were reported but the frequency is unknown: Increase in liver enzymes, hepatocellular and/or cholestatic hepatitis (with or without jaundice), pancreatitis, hepatic dysfunction.
Skin disorders
The following were reported but the frequency is unknown: Mild skin eruptions, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Immune system disorders
Less frequent: Hypersensitivity reactions, anaphylaxis.
General disorders
The following were reported but the frequency is unknown: Tongue and tooth discolouration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
(See WARNINGS AND SPECIAL PRECAUTIONS)
Symptoms of overdose:
Ingestion of large amounts of KLARIZON can be expected to produce gastrointestinal symptoms. Allergic reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures.
Treatment of overdose:
Treatment is symptomatic and supportive. KLARIZON serum levels are not expected to be appreciably affected by haemodialysis or dialysis.

IDENTIFICATION:
KLARIZON 250: Yellow, film coated, oval-shaped, biconvex tablets, scored on one side (14,5 mm).
KLARIZON 500: Yellow, film coated, oval-shaped, biconvex tablets, scored on one side (19,0 mm).

PRESENTATION:
KLARIZON 250: PVC/PVDC blister packs containing 10 tablets, packed into an outer carton together with a package insert.
KLARIZON 500: PVC/PVDC blister packs containing 10 or 14 tablets, packed into an outer carton together with a package insert.

STORAGE INSTRUCTIONS:
Store at or below 25 °C and protect from light.
Keep the blisters in the carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:
KLARIZON 250: A38/20.1.1/0724
KLARIZON 500: A38/20.1.1/0725

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Biotech Laboratories (Pty) Ltd.
Ground Floor, Block K West, Central Park
400 16th Road, Randjespark, Midrand, 1685
South Africa

DATE OF PUBLICATION OF PACKAGE INSERT:
Date of registration: 11 August 2006
Date of notification with regard to amended Reg. 9 and 10: 13 February 2015

SKEDULERINGSTATUS:
S4

EIENDOMSNAAM EN DOSEERVORM:
KLARIZON 250 TABLETTE
KLARIZON 500 TABLETTE

SAMESTELLING:
KLARIZON 250: Elke filmbedekte tablet bevat 250 mg klaritromisien.
KLARIZON 500: Elke filmbedekte tablet bevat 500 mg klaritromisien.
Preserveermiddel: Sorbiensuur 0,06% m/m.
Tabletkern: croscarmellose natrium, kolloïdale anhidriese silika, magnesiumstearaat, mikrokristallyn sellulose, povidoon K25, steariensuur, talk.
Tabletlaag: hidroksipropielmetielsellulose, hidroksipropielsellulose, propileenglikool, quinoline yellow lake, sorbitaan mono-oleaat, povidoon K25, sorbiensuur, titaniumdioksied, vanielje droë geursel. Suikervry.

FARMAKOLOGIESE KLASSIFIKASIE:
A 20.1.1: Medium- en breëspektrumantibiotika

FARMAKOLOGIESE WERKING:
Farmakodinamiese eienskappe
Klaritromisien is 'n makroliedantibiotikum. Dit oefen sy antibakteriële werking uit deur omkeerbaar aan die 50S-ribosomale subeenheid van die 70S-ribosoom van sensitiewe mikro-organismes te bind en rem sodoende RNA-afhanklike proteïensintese deur die bakterie. Die in vitro antibakteriële spektrum van patogene wat sensitief vir klaritromisien is, is onder meer (*in vitro*-sensitiwiteit impliseer nie noodwendig *in vivo*-effektiwiteit nie):
Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae
Legionella pneumophilia
Mycoplasma pneumoniae
Chlamydia trachomatis
Moraxella (Branhamella) catarrhalis
Haemophilus influenzae
Staphylococcus aureus (metisilliensensitief)
Helicobacter pylori
Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare
Klaritromisien is bakteriedodend vir *Helicobacter pylori*, hierdie aktiwiteit is groter by neutrale pH as by suur pH.
Die voorkoms van bakteriese weerstand teen klaritromisien is hoër in penisillienresistente stamme as onder penisillien-sensitiewe stamme. Daarom is metisillienresistente en oksasillien-resistente Staphylococcus en Streptococcus ook bestand teen klaritromisien en kruisbestand teen ander makroliedantibiotika.
Geïsoleerde gevalle van *Helicobacter pylori* en *Mycobacterium avium* met klaritromisienweerstandigheid as gevolg van genetiese mutasies is aangemeld.
Farmakokinetiese eienskappe
Klaritromisien word na orale toediening vinnig uit die gastro-intestinale kanaal geabsorbeer, maar die biobeskikbaarheid daarvan is net 50 tot 55 % vanweë vinnige eerstedeurgangmetabolisme. Piek konsentrasies in die plasma word ongeveer 2 uur na toediening bereik. Klaritromisien kan met of sonder voedsel gegee word. Klaritromisien word deur die lewer na die aktiewe metaboliet, 14 hidroksiklaritromisien, asook verskeie ander metaboliete gemetaboliseer. Sowel klaritromisien as 14-hidroksiklaritromisien versprei wyd deur die liggaam en bereik hoë intraselluläre konsentrasies. Konsentrasies in die weefsel oorskry gewoonlik dié in die serum. Klaritromisien bereik nie beduidende vlakke in die serebrospinale vloeistof nie. Die binding van klaritromisien aan proteïene wissel van 40 tot 70 % en is van die konsentrasie afhanklik. Die eliminasiehalfleeftyd van klaritromisien en 14-hidroksiklaritromisien is ongeveer 3 tot 7 en 5 tot 9 uur, onderskeidelik. Langer halfleeftye word na groter dosisse waargeneem. Klaritromisien word deur renale en nie-renale roetes uitgeskei. Die hoeveelheid klaritromisien wat onveranderd in die urien uitgeskei word wissel van 20 tot 40 %, afhangende van die dosis toegedien en die formulering. Tussen 10 en 15 % van die dosis word as die 14-hidroksimetaboliet in die urien uitgeskei. Hoewel die farmakokinetika van klaritromisien in pasiënte met ingekorte lewer- of nierfunksie verskillend is, is aanpassings in die dosis nie nodig nie, tensy die pasiënt ernstige ingekorte nierfunksie het (kreatinienopruiming < 30 ml/min). Teen hoër dosisse in pasiënte met MIV is die konsentrasies van klaritromisien en 14-hidroksiklaritromisien baie hoër vergeleke met die gewone dosisse in nie-besmette pasiënte. Dit lyk ook asof die eliminasiehalfleeftye langer is.

INDIKASIES:
KLARIZON is aangedui vir die behandeling van die volgende ligte tot matige infeksies veroorsaak deur vatbare organismes:
- Infeksies van die onderste lugweg soos brongitis en longontsteking
- Infeksies van die boonste lugweg soos faringitis en sinusitis
- Ligte tot matige akute otitis media vanweë *S. pneumoniae*, *M. catarrhalis* en *H. influenza*
- Infeksies van die vel en sagte weefsel soos follikulitis, sellulitis of erisipelas
- Uitwissing van *Helicobacter pylori* as dit in kombinasie met 'n protonpompremmer en 'n ander antibiotikum gebruik word om die terugkeer van duodenale ulkusse te verminder.

KONTRA-INDIKASIES:
- Hipersensitiwiteit teenoor makroliedantibiotika of teenoor enige bestanddeel van KLARIZON.
- Toediening van KLARIZON saam met astemisool, sisapried, pimosied, ergotamien of dihidroergotamien (kyk INTERAKSIES).
- Pasiënte wat behandel word met astemisool, sisapried, pimosied en voorafbestaande kardiovaskulêre siekte het (hartdisritmie, verlenging in die QTc-interval, isgemiese hartsiekte of kongestiewe hartversaking) of elektrolietverteuring (kyk INTERAKSIES EN WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).
- Babas jonger as 6 maande.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:
KLARIZON moet versigtig gebruik word by:
- Pasiënte met swak lewerfunksie - Die farmakokinetika is aangetas. Geen aanpassing in die dosis is nodig vir pasiënte met swak lewerfunksie nie, tensy daar terselfdertyd ook ernstige swak nierfunksie is. Behandeling met KLARIZON moet gestaak word as enige tekens van ingekorte lewerfunksie ontwikkel. Ingekorte lewerfunksie is gewoonlik omkeerbaar, maar kan ernstig wees. In enkele gevalle is lewerversaking met noodlottige gevolge aangemeld en gewoonlik saam met ander ernstige onderliggende siektes en/of gelyktydige gebruik van medisyne. Geïsoleerde gevalle van hoër vlakke kreatinien in die serum is aangemeld, maar 'n verband met KLARIZON is nie bepaal nie.
- Pasiënte met swak nierfunksie (ernstig) - Die eliminasie van KLARIZON is stadiger in pasiënte met swak nierfunksie en veral in dié met 'n kreatinienopruiming van < 30 ml/min. Die dosis van KLARIZON moet halveer word of die dosisinterval verdubbel word vir pasiënte met 'n kreatinienopruiming van < 30 ml/min.
- Rabdomiolise is aangemeld tydens gebruik van KLARIZON saam met die HMGKoA-reduktaseremmers, bv. simvastatien en lovastatien (kyk INTERAKSIES).
- Rifabutien en rifampisien - kan die serumkonsentrasie van KLARIZON met > 50 % verminder. Dit is aangemeld dat gesamentlike toediening 'n hoër insidensie van uveïtis veroorsaak vergeleke met rifabutien alleen (kyk INTERAKSIES).
- Teofillien - die oppervlak onder die plasmakonsentrasie-tydkurwe (AOK) is groter. Monitering van die konsentrasies van teofillien in die serum word aanbeveel (kyk INTERAKSIES).
- Kruisweerstandigheid tussen KLARIZON en ander makroliede, linkomisien en klindamisien is aangemeld.
- Porfirie.
- Pseudomembraneuse kolitis is aangemeld met KLARIZON behandeling en die graad mag wissel van matig tot lewensbedreigend. Dit is daarom belangrik om hierdie diagnose in gedagte te hou by pasiënte wat presenteer met diarree nadat hul KLARIZON behandeling ontvang het.
- Kolgisien toksisiteit met gelyktydige gebruik van KLARIZON en kolgisien is aangemeld tydens na-bemarkingsondervinding, veral by bejaardes, waarvan sommige voorgekom het by pasiënte met nierinkorting. Sterftes is aangemeld onder sulke pasiënte (kyk INTERAKSIES).
- Daar was enkele verslae van hipoglisemie waarvan sommige voorgekom het in pasiënte wat terselfdertyd orale hipoglisemiese middels of insulien gebruik het.
- Nadelige effekte in pasiënte wie se immuunstelsel verswak is en wat met hoër dosisse KLARIZON oor lang periodes behandel is, was onder meer: naarheid, braking, smaakversteuring, buikpyn, diarree, veluitslag, winderigheid, hoofpyn, gehoorversteurings, toename in AST en ALT, toename in vlakke van BUS en abnormale lae tellings witbloedselle en plaatjies. Effekte wat teen lae frekwensie voorgekom het, was onder meer dispnee, slaaploosheid en 'n droë mond.
- Langtermyn gebruik van KLARIZON kan lei tot kolonisasie met verhoogde aantal nie-vatbare bakterieë en swamme. As superinfeksies voorkom, moet toepaslike behandeling gegee word.

Uitwerking op vermoë om 'n voertuig te bestuur en masjinerie te gebruik:
KLARIZON kan 'n geringe invloed op die pasiënt se vermoë hê om 'n voertuig te bestuur en masjinerie te gebruik en die effek op die individu moet vasgestel word voordat 'n voertuig bestuur of masjinerie gebruik word.

INTERAKSIES:
Gebruik van KLARIZON saam met
- Astemisool, sisapried, pimosied en terfenadien - het gelei tot hartdisritmieë waaronder verlenging in die QTc-interval, ventrikulêre disritmie, ventrikulêre tagikardie, ventrikulêre fibrillasie en torsade de pointes. Sterftes het voorgekom. Die mees waarskynlike oorsaak is inhibisie van die metabolisme van hierdie middels deur KLARIZON. Gelyktydige gebruik is teenaangedui. (kyk KONTRA-INDIKASIES).
- Antikoagulante soos warfarien - KLARIZON kan die effekte van warfarien versterk. Die protrombientyd moet noukeurig gemonitor word.
- Digoksien – dit is aangetoon dat KLARIZON die vlakke van digoksien in die serum verhoog. Monitering van die konsentrasies van digoksien in die serum word aanbeveel.
- Karbamasepien en ander medisyne wat deur die sitochroom P450-ensiemstelsel gemetaboliseer word, bv alprasolam, astemisool, siklosporien, disopiramied, sisapried, ergotalkaloïede, metielprednisoloon, midasolam, omeprasool, pimosied, kinidien, sildenafiel, tadalafiel, vardenafiel, simvastatien, takroli mus, triasolam, vinblastien, fenitoïen en valproaat) - KLARIZON kan geassosieer word met verhoogde vlakke van hierdie medisyne. Die konsentrasies van hierdie medisyne in die serum moet gemonitor word. Rabdomiolise is aangemeld tydens gebruik van KLARIZON saam met die HMGKoA-reduktaseremmers, bv. simvastatien (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).
- Rifabutien en rifampisien - kan die serumkonsentrasie van KLARIZON met > 50 % verminder. Dit is gemeld dat gesamentlike toediening 'n hoër insidensie van uveïtis veroorsaak vergeleke met rifabutien alleen (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).
- Teofillien - die oppervlak onder die plasmakonsentrasie-tydkurwe is groter. Monitering van die konsentrasies van teofillien in die serum word aanbeveel (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).
- Sidovudien - 'n afname in die konsentrasie van sidovudien by gelykvlakke kan voorkom. Die dosisse van sidovudien en KLARIZON moet ten minste 4 uur uitmekaar geneem word.
- Ritonavir - die metabolisme van KLARIZON word gerem. Geen verlaging in die dosis van KLARIZON is nodig vir pasiënte met normale nierfunksie nie. Vir pasiënte met swak nierfunksie moet die dosis van KLARIZON as volg verlaag word:
  Kreatinienopruiming 30 tot 60 ml/min - verlaag die dosis met 50 %
  Kreatinienopruiming < 30 ml/min - verlaag die dosis met 75 %
  'n Dosis van 1 g/dag moet nie oorskry word tydens toediening van KLARIZON saam met ritonavir nie. Dit is voorgestel dat ander MIV-proteaseremmers en nie-nukleosied omgekeerde transkriptaseremmers dieselfde effek op KLARIZON kan hê.
- Kolgisien - is 'n substraat vir beide CYP3A en P-glikoproteïen (Pgp) ensieme. KLARIZON en ander makroliede is bekend om CYP3A en Pgp ensiemwerking te inhibeer. Wanneer kolgisien en KLARIZON saam toegedien word, kan KLARIZON Pgp en / of CYP3A ensiemwerking inhibeer wat tot verhoogde blootstelling aan kolgisien kan lei. Pasiënte moet gemonitor word vir kliniese simptome van kolgisien toksisiteit (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS). Sterftes is gerapporteer by bejaarde pasiënte met ingekorte nierfunksie wat gelyktydig kolgisien ontvang het.
- Ergotamien / Dihidroergotamien - na-bemarkingsverslae dui aan dat gelyktydige gebruik van KLARIZON met ergotamien of dihidroergotamien geassosieer word met akute ergot-toksisiteit wat gekenmerk word deur vasospasma en isgemie van die ledemate en ander weefsels, insluitende die sentrale senuweestelsel. Dit kan permanente weefselskade tot gevolg hê.

SWANGERSKAP EN LAKTASIE:
Die veiligheid en effektiwiteit tydens swangerskap en borsvoeding is nie bepaal nie.
KLARIZON word in borsmelk uitgeskei.

DOSIS EN GEBRUIKSAANWYSINGS:
Volwassenes: 250 mg twee keer per dag.
Vir meer ernstige infeksies kan die dosis tot 500 mg twee keer per dag verhoog word.
Swak nierfunksie:
Kreatinienopruiming (< 30 ml/min): Verminder die dosis met die helfte, d.i. 250 mg een keer per dag of 250 mg twee keer per dag vir ernstige infeksies. Beperk die duur van behandeling tot 14 dae.
Uitwissing van H. pylori:
Volwassenes: 500 mg twee keer per dag in kombinasie met 'n geskikte antibiotikum en 'n middel wat maagsuur verlaag, vir 7 tot 10 dae.
Die veiligheid en effektiwiteit van KLARIZON in kombinasie met 'n protonpompremmer anders as omeprasool is nie bepaal nie.
Atipiese infeksies deur mikobakterieë (MAK) in MIV-positiewe pasiënte:
Volwassenes: 500 mg twee keer per dag.
Behandeling van gedissemineerde infeksies deur mikobakterieë in VIGS-pasiënte moet voorgesit word vir so lank as wat kliniese en mikrobiologiese voordeel aangetoon word. 'n Afname in effektiwiteit is waargeneem in pasiënte wat KLARIZON vir meer as 12 weke gebruik het. KLARIZON moet saam met ander middels teen mikobakterieë gebruik word.
KLARIZON kan met of sonder voedsel gedrink word.

NEWE-EFFEKTE:
Versteurings van die bloed en limfstelsel
Minder dikwels: trombositopenie
Die volgende is aangemeld, maar die frekwensie is onbekend: leukopenie, neutropenie
Infeksies en infestasies
Minder dikwels: infeksie (koors en kouekoors, hoes of heesheid, pyn in die lae rug of sy, pynlike of moeilike urinering)
Hartversteurings
Die volgende is aangemeld, maar die frekwensie is onbekend: verlenging in QT-tyd, torsades de pointes, ventrikulêre tagikardie en disritmie
Versteurings van die senuweestelsel
Minder dikwels: hoofpyn
Die volgende is aangemeld, maar die frekwensie is onbekend: angs, duiseligheid, slaaploosheid, hallusinasies, nagmerries, vertigo, tinnitus, disoriëntasie, depersonifikasie, verwardheid, gehoorverlies, konvulsies
Versteurings van endokrienstelsel
Die volgende is aangemeld, maar die frekwensie is onbekend: hipoglisemie
Gastro-intestinale versteurings
Minder dikwels: abnormale smaaksensasie, slegte spysvertering, winderigheid, gastro-intestinale versteurings
Die volgende is aangemeld, maar die frekwensie is onbekend: anoreksie, naarheid, braking, diarree, glossitis, stomatitis, orale kandidiase, pseudomembraneuse kolitis (buikkrampe of -pyn, teerheid, erge waterige diarree wat bloederig kan wees, koors)
Hepatobiliêre versteurings
Minder dikwels: hepatotoksisiteit
Die volgende is aangemeld, maar die frekwensie is onbekend: toename in lewerensieme, hepatosellulêre en/of cholestatiese hepatitis (met of sonder geelsug), pankreatitis, lewerdisfunksie
Vel en subkutane weefselversteurings
Die volgende is aangemeld, maar die frekwensie is onbekend: ligte uitbarstings op die vel, urtikarie, Stevens-Johnsonsindroom, toksiese epidermale nekrolise
Versteurings van immuunstelsel
Minder dikwels: hipersensitiwiteitsreaksies, anafilakse
Algemene versteurings en toestande van die plek waar toegedien
Die volgende is aangemeld, maar die frekwensie is onbekend: verkleuring van die tong en tande

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
(Kyk NEWE-EFFEKTE EN WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS)
Simptome van oordosering:
Dit kan verwag word dat inname van groot hoeveelhede KLARIZON gastro-intestinale simptome kan veroorsaak. Allergiese reaksies vanweë oordosering moet behandel word deur vroegtydige eliminasie van ongeabsorbeerde medisyne en ondersteunende maatreëls.
Behandeling van oordosering:
Behandeling is simptomaties en ondersteunend. Dit word nie verwag dat KLARIZON deur hemodialise of dialise uitgeskei sal word nie.

IDENTIFIKASIE:
KLARIZON 250: Geel, filmbedekte, ovaalvormige, bikonvekse tablette met 'n breeklyn op die een kant (14,5 mm).
KLARIZON 500: Geel, filmbedekte, ovaalvormige, bikonvekse tablette met 'n breeklyn op die een kant (19.0 mm).

AANBIEDING:
KLARIZON 250: PVC/PVCD-stulppakke met 10 tablette, saam met 'n voubiljet in 'n karton verpak.
KLARIZON 500: PVC/PVCD-stulppakke met 10 of 14 tablette, saam met 'n voubiljet in 'n karton verpak.

BERGINGSINSTRUKSIES:
Bewaar teen of benede 25 °C en beskerm teen lig.
Hou die stulpstroke in die karton tot benodig vir gebruik.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS:
KLARIZON 250: A38/20.1.1/0724
KLARIZON 500: A38/20.1.1/0725

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:
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