APPROVED PACKAGE INSERT:

AUSTELL CLARITHROMYCIN 250/500 mg

SCHEDULING STATUS

S4

PROPRIETARY NAME (AND DOSAGE FORM)

AUSTELL CLARITHROMYCIN 250 mg TABLETS

AUSTELL CLARITHROMYCIN 500 mg TABLETS

COMPOSITION

AUSTELL CLARITHROMYCIN 250 mg:

Each tablet contains 257 mg clarithromycin (6-0 methyl erythromycin A) equivalent to 250 mg anhydrous clarithromycin.

Preservative: Sorbic acid 0,063 % m/m

AUSTELL CLARITHROMYCIN 500 mg:

Each tablet contains 515,5 mg clarithromycin (6-0 methyl erythromycin A) equivalent to 500 mg anhydrous clarithromycin.

Preservative: Sorbic acid 0,063 % m/m

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 – Medium and broad-spectrum antibiotics

PHARMACOLOGICAL ACTION

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-dependant 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

Legionelle pneumophilia

Mycoplasma pneumoniae

Chlamydia trachomatis

Moraxella (Branhamella) catarrhalis

Haemophilus influenzae

Staphylococcus aureas (methicillin sensitive)

Helicobacter pylori

Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare

Pharmacokinetics:

Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration, but its bioavailability is reduced to 50 to 55 % because of rapid first-pass 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 higher 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 – 70 % and is concentration-dependant. 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 are 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

AUSTELL CLARITHROMYCIN 250 mg Tablets and **AUSTELL CLARITHROMYCIN 500 mg** Tablets 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. influenza.*
- 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.

CONTRA-INDICATIONS

- Hypersensitivity to macrolide antibiotics or to any component of the formulation.
- Concomitant administration of **AUSTELL CLARITHROMYCIN** Tablets with astemizole, cisapride, pimozide and terfenadine. (See INTERACTIONS).
- Porphyria.

WARNINGS

AUSTELL CLARITHROMYCIN 250 mg Tablets and **AUSTELL CLARITHROMYCIN 500 mg** Tablets should be used with caution in:-

- Liver function impairment – The pharmacokinetics are altered. No dosage adjustment is required in patients wih hepatic function impairment, unless there is also concurrent severe renal function impairment.
- Renal function impairment (severe) – The elimination of **AUSTELL CLARITHROMYCIN 250 mg** Tablets and **AUSTELL CLARITHROMYCIN 500 mg** Tablets is reduced in patients with renal function impairment, especially those with a creatinine clearance of <30 ml/min.

The dose of **AUSTELL CLARITHROMYCIN 250 mg** Tablets and **AUSTELL CLARITHROMYCIN 500 mg** Tablets should be halved or the dosing interval doubled in patients with creatinine clearance of <30 ml/min.

- Rhabdomyolysis has been reported with concomitant use of **AUSTELL CLARITHROMYCIN** Tablets and the HMGCoA reductase inhibitors e.g. simvastatin (SEE INTERACTIONS).
- Rifabutin and rifampicin – May decrease serum concentration of **AUSTELL CLARITHROMYCIN** Tablets 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 the theophylline serum concentrations is recommended (SEE INTERACTIONS).
- Cross-resistance between **AUSTELL CLARITHROMYCIN** Tablets and other macrolides, lincomycin and clindamycin has been reported.

INTERACTIONS

Concomitant use of **AUSTELL CLARITHROMYCIN** Tablets with:

- Astemizole, cisapride, pimozide and terfenadine – Has resulted in cardiac arrhythmias, including QTc-interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation and torsade de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by

AUSTELL CLARITHROMYCIN Tablets. Concurrent use is contraindicated. See CONTRAINDICATIONS.

- Anticoagulants such as warfarin –**AUSTELL CLARITHROMYCIN** Tablets may result in the potentiation of the effects of warfarin. Prothrombin time should be monitored closely.
- Digoxin –**AUSTELL CLARITHROMYCIN** Tablets 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 for example, (alprazolam, cyclosporine, disopyramide, ergot alkaloids, methylprednisolone, midazolam, omeprazole, quinidine, sildenafil, simvastatin, tacrolimus, triazolam, vinblastine, phenytoin and valproate) – **AUSTELL CLARITHROMYCIN** Tablets 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 **AUSTELL CLARITHROMYCIN** Tablets and the HMGCoA reductase inhibitors e.g. simvastatin (SEE WARNINGS).
- Rifabutin and rifampicin – May decrease serum concentration of **AUSTELL CLARITHROMYCIN** Tablets by >50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (SEE WARNINGS).
- Theophylline – The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (SEE WARNINGS).

- Zidovudine – A decrease in the steady-state concentration of zidovudine may occur. Doses of zidovudine and **AUSTELL CLARITHROMYCIN** Tablets should be taken at least 4 hours apart.
- Ritonavir – The metabolism of **AUSTELL CLARITHROMYCIN** Tablets is inhibited. No dosage reduction of **AUSTELL CLARITHROMYCIN** Tablets is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dose of **AUSTELL CLARITHROMYCIN** Tablets 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 1g/day during concurrent administration of **AUSTELL CLARITHROMYCIN** Tablets with ritonavir.

  It has been suggested that other HIV-protease inhibitors and non-nucleoside revered transcriptase inhibitors may have a similar effect on **AUSTELL CLARITHROMYCIN** Tablets.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation have not been established.

AUSTELL CLARITHROMYCIN Tablets 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 mg 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 appropriate antibiotic and an acid lowering agent, for 7 to 10 days.

The safety and efficacy of **AUSTELL CLARITHROMYCIN** Tablets 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 **AUSTELL CLARITHROMYCIN** Tablets for more than 12 weeks. **AUSTELL CLARITHROMYCIN** Tablets should be used in conjunction with other antimycobacterial agents.

AUSTELL CLARITHROMYCIN Tablets may be taken with or without meals.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side Effects:

Haematological:

Less frequent: Leucopenia, thrombocytopenia.

Cardiovascular:

QT prolongation, ventricular tachycardia, torsades de pointes.

Nervous system:

Headache, anxiety, dizziness, insomnia, hallucinations, bad dreams, vertigo, tinnitus, disorientation, depersonalization, confusion, hearing loss, convulsions.

Endocrine/Metabolic:

Less frequent: Hypoglycaemia.

Gastrointestinal:

Frequent: Nausea, vomiting, abdominal pain, abnormal taste, diarrhoea.

Less frequent: Glossitis, stomatitis, oral candidiasis, tongue discolouration, tooth discolouration, pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever).

Liver:

Less frequent: Increased in liver enzymes, hepatocellular and/or cholestatic hepatitis (with or without jaundice), pancreatitis.

Skin:

Mild skin eruptions, urticaria, Steven's-Johnson syndrome, toxic epidermal necrolysis.

Other:

Allergic reactions, anaphylaxis.

Special Precautions:

Treatment with **AUSTELL CLARITHROMYCIN** Tablets 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. Isolated cases of increased serum creatinine have been reported but an association with **AUSTELL CLARITHROMYCIN** Tablets has not been established.

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 **AUSTELL CLARITHROMYCIN** Tablets over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, hearing disturbance, AST and ALT elevations, elevated BUN levels and abnormally low white blood cell and platelet counts. Additional low-frequency events included dyspnoea, insomnia and dry mouth.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See “SIDE EFFECTS AND SPECIAL PRECAUTIONS”)

Symptoms of overdose:

Ingestion of large amounts of **AUSTELL CLARITHROMYCIN** Tablets 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 overdosage:

Treatment is symptomatic and supportive. **AUSTELL CLARITHROMYCIN** Tablets is not expected to be appreciably affected by haemodialysis or dialysis.

IDENTIFICATION

AUSTELL CLARITHROMYCIN 250 mg:

Yellow, oval- shaped, convex tablets, scored on one side, film coated, 14 x 8 mm.

AUSTELL CLARITHROMYCIN 500 mg:

Yellow, oval- shaped, convex tablets, scored on one side, film coated, 19 x 10 mm.

PRESENTATION

AUSTELL CLARITHROMYCIN 250 mg is packed in clear PVC/PVDC-Aluminium blister packs of 10 or 14 tablets.

AUSTELL CLARITHROMYCIN 500 mg is packed in clear PVC/PVDC-Aluminium blister packs of 10 or 14 tablets.

STORAGE INSTRUCTIONS

Store in well closed container at or below 25 °C.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

AUSTELL CLARITHROMYCIN 250 mg: A38/20.1.1/0475

AUSTELL CLARITHROMYCIN 500 mg: A38/20.1.1/0476

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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