Professional Information for Medicines for Human Use: AZITHROMYCIN 500 mg AUSTELL

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AZITHROMYCIN 500 mg AUSTELL film-coated tablets.

COMPOSITION

Each film coated tablet contains azithromycin dihydrate equivalent to 500 mg azithromycin.

Excipients

Calcium hydrogen phosphate, crospovidone, magnesium stearate, pregelatinised starch, sodium lauryl sulphate.

Film coating

Glyceryl triacetate, hydroxypropyl methyl cellulose, lactose monohydrate.

Contains sugar (lactose monohydrate 3 mg/tablet).

CATEGORY AND CLASS

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Azithromycin is a macrolide (azalide) 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 azithromycin includes: (*in vitro* sensitivity does not necessarily imply *in vivo* efficacy).

Staphylococcus aureus

Streptococcus spp., including *Streptococcus pyogenes* (Group A) and *Streptococcus pneumoniae*

Haemophilus influenzae, Haemophilus ducreyi

Moraxella catarrhalis

Legionella pneumophila

Bordatella Pertussis

Borrelia burgdorferi

Mycoplasma pneumoniae

Chlamydia trachomatis

Treponema pallidum

Pharmacokinetic properties

Azithromycin is absorbed rapidly from the gastrointestinal tract, with an oral bioavailability of approximately 37 %. No significant decrease in bioavailability occurs when azithromycin is administered with a meal. Peak concentration occurs approximately 2 to 3 hours after oral administration. Protein binding of azithromycin is low (51 %) and appears to be concentration dependent, decreasing with increasing concentrations. Azithromycin is widely distributed throughout the body and concentrates intracellularly. Azithromycin (35 % of the dose) is metabolised by the liver to inactive metabolites and excreted in the bile. More than 50 % of the dose is eliminated unchanged via the bile, while 6.5 % of the dose is eliminated in the urine, unchanged. The elimination half-life of azithromycin closely reflects the tissue depletion half-life of 2 to 4 days.

INDICATIONS

AZITHROMYCIN AUSTELL is indicated for the treatment of the following conditions in adults and children over 45 kg body weight.

AZITHROMYCIN AUSTELL is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms:

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis and Neisseria gonorrhoeae.*

Paediatric population:

AZITHROMYCIN AUSTELL is not suitable for children under 45 kg (see DOSAGE AND DIRECTIONS FOR USE).

CONTRAINDICATIONS

AZITHROMYCIN AUSTELL is contraindicated in patients:

- with a known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic or to any of the excipients of the formulation,
- hepatic function impairment, since biliary excretion is the major route of elimination.

Safety and efficacy in pregnancy and lactation has not been established (see HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS

Hypersensitivity

As with erythromycin and other macrolides, serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP) and

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported with the use of **AZITHROMYCIN AUSTELL**. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Hepatotoxicity

The use of **AZITHROMYCIN AUSTELL** should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. **AZITHROMYCIN AUSTELL** administration should be stopped if liver dysfunction has emerged.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There is no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, **AZITHROMYCIN AUSTELL** and ergot derivatives should not be co-administrated.

Prolongation of the QT interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with **AZITHROMYCIN AUSTELL** cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation; therefore caution is required when treating patients:

- with congenital or documented QT prolongation,
- currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of Classes Ia and III, cisapride and terfenadine,

- with electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesemia,
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection

Observation for signs of superinfection with non-susceptible organisms including fungi is recommended when taking **AZITHROMYCIN AUSTELL**.

***Clostridium difficile* associated diarrhoea**

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including **AZITHROMYCIN AUSTELL**, and may range in severity from mild diarrhoea to fatal colitis. Strains of *C. difficile* producing hypertoxin A and B contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Discontinuation of therapy with **AZITHROMYCIN AUSTELL** and the administration of specific treatment for *C. difficile* should be considered.

Streptococcal infections

Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. **AZITHROMYCIN AUSTELL** is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of **AZITHROMYCIN AUSTELL** in preventing acute rheumatic fever.

Renal impairment

In patients with severe renal impairment (GFR <10 ml/min) a 33 % increase in systemic exposure to **AZITHROMYCIN AUSTELL** was observed.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving **AZITHROMYCIN AUSTELL**.

Haematological malignancies

There is an increase in the rate of relapses in haematological malignancies if **AZITHROMYCIN AUSTELL** is used for indications other than that listed in this leaflet (see INDICATIONS) and if it is used outside the recommended dosage (see DOSAGE AND DIRECTIONS FOR USE).

Effects on ability to drive and use machines

There is no evidence to suggest that **AZITHROMYCIN AUSTELL** may have an effect on a patient's ability to drive or operate machinery

Contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take **AZITHROMYCIN AUSTELL**. Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

Concomitant use of **AZITHROMYCIN AUSTELL** with:

- **Antacids:** Decreases the peak serum concentration of **AZITHROMYCIN AUSTELL**. Take **AZITHROMYCIN AUSTELL** one hour before or two hours after taking an antacid.
- **Ergot alkaloids**: Has been associated with acute ergot toxicity characterised by severe peripheral vasospasm and dysesthesia. Coadministration of **AZITHROMYCIN AUSTELL** and ergot alkaloids is not recommended.
- **Anticoagulants such as warfarin**: Prothrombin time should be monitored.

- **Digoxin and colchicine:** Concomitant use with **AZITHROMYCIN AUSTELL** may increase serum digoxin and colchicine concentrations. Monitoring of digoxin serum concentrations is recommended.
- **AZITHROMYCIN AUSTELL** does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.
- **Terfenadine:** Concomitant use with **AZITHROMYCIN AUSTELL** may increase serum concentration of terfenadine.

  Serum levels of terfenadine should be monitored.
- **Theophylline:** The area under the plasma concentration-time curve may be increased. Monitoring of theophylline serum concentrations is recommended.
- **Ciclosporin:** Ciclosporin levels should be monitored with used with **AZITHROMYCIN AUSTELL** and the dose adjusted accordingly.

No clinically significant interactions have been reported with cimetidine, carbamazepine, methylprednisolone, cetirizine, didanosine, atorvastatin, efavirenz, fluconazole, indinavir, nelfinavir,midazolam, rifabutin, sildenafil, theophylline, triazolam,trimethoprim/sulfamethoxazole and zidovudine.

HUMAN REPRODUCTION

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

DOSAGE AND DIRECTIONS FOR USE

AZITHROMYCIN AUSTELL should be given as a single daily dose and should be swallowed whole with some water. **AZITHROMYCIN AUSTELL** should be taken at least 1 hour before or 2 hours after food.

Adults and children over 45 kg body weight, including elderly patients:

- The total dose of **AZITHROMYCIN AUSTELL** is 500 mg (one tablet) which should be given over three days.
- In uncomplicated genital infections due to *Chlamydia trachomatis*, the dose is 1000 mg (2 tablets) as a single oral dose.
- For susceptible *Neisseria gonorrhoeae* the recommended dose is 1000 mg (2 tablets) or 2000 mg (4 tablets) of **AZITHROMYCIN AUSTELL** in combination with 250 mg or 500 mg ceftriaxone according to clinical treatment guidelines.

Special populations

Paediatric population

AZITHROMYCIN AUSTELL is not suitable for children under 45 kg in weight.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min).

Hepatic impairment

Since azithromycin is metabolised in the liver and excreted in the bile, **AZITHROMYCIN AUSTELL** should not be given to patients suffering from severe liver disease.

SIDE-EFFECTS

The side-effects below are classified by system organ class and frequency according to the following convention:

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and unknown (cannot be estimated from the available data).

System organ class	**Side effect**	**Frequency**
Infections and infestations	Candidiasis, oral candidiasis, vaginal infection	Uncommon
	Pseudomembranous colitis	Unknown
Blood and lymphatic system disorders	Leukopenia, neutropenia	Uncommon
	Thrombocytopenia, haemolytic anaemia	Unknown
Immune system disorders	Angioedema, hypersensitivity	Uncommon
	Anaphylactic reaction	Not known
Metabolism and nutrition disorders	Anorexia	Common
Psychiatric disorders	Nervousness	Uncommon
	Agitation	Rare
	Aggression, anxiety	Not known
Nervous system disorders	Dizziness, headache, paraesthesia, dysgeusia	Common
	Hypoaesthesia, somnolence, insomnia	Uncommon
	Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis	Not known
Eye disorders	Visual impairment	Common
Ear and labyrinth disorders	Deafness	Common
	Impaired hearing, tinnitus	Uncommon
	Vertigo	Rare
Cardiac disorders	Palpitations	Uncommon
	Torsades de pointes, arrythmia including ventricular tachycardia	Unknown
Vascular disorders	Hypotension	Unknown

Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, flatulence	Very common
	Vomiting, dyspepsia	Common
	Gastritis, constipation	Uncommon
	Pancreatitis, tongue discolouration	Unknown
Hepato-biliary disorders	Hepatitis	Uncommon
	Hepatic function abnormality	Rare
	Hepatic failure, hepatitis fulminant, hepatic necrosis, cholestatic jaundice	Unknown
Skin and subcutaneous tissue disorders	Pruritus, rash	Common
	Stevens Johnsons syndrome, photosensitivity reaction, urticaria	Uncommon
	Acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)	Rare
	Toxic epidermal necrolysis, erythema multiforme	Unknown
Musculoskeletal and connective tissue disorders	Arthralgia	Common
Renal and urinary disorders	Acute renal failure, interstitial nephritis	Unknown
General disorders and administration site conditions	Fatigue	Common
	Chest pain, oedema, malaise, asthenia	Uncommon
Investigations	Decreased lymphocyte count, increased eosinophil count, decreased blood bicarbonate	Common
	Increased aspartate aminotransferase,	Uncommon

	increased alanine aminotransferase, increased blood bilirubin, increased blood urea, increased blood creatinine, abnormal blood potassium	
	Electrocardiogram QT prolonged	Unknown

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms of overdose:

There is no data on overdosage of **AZITHROMYCIN AUSTELL**. Typical symptoms are expected to be those associated with macrolide antibiotics and include severe gastrointestinal symptoms (nausea, vomiting and diarrhoea) and hearing loss.

Treatment of overdose:

Treatment is symptomatic and supportive. Gastric lavage may be indicated.

IDENTIFICATION

AZITHROMYCIN 500 mg AUSTELL tablets are capsule shaped, white scored film coated tablets.

PRESENTATION

White PVC, light resistant opaque, foil, heat sealed to aluminium foil, containing 2 or 3 tablets per pack, in an outer cardboard carton.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 25 ºC. Protect from light.

Keep blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A39/20.1.1/0020

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