MACTHRAL 500

[Azithromycin Tablets USP 500 mg]

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

MACTHRAL 500 [Azithromycin Tablets USP 500 mg)

2. Qualitative & Quantitative Composition

Each film coated tablet contains:
Azithromycin Dihydrate USP
Equivalent to anhydrous Azithromycin 500 mg
Excipients ….q.s
Approved colour(s) used

Quantitative Declaration

S.No.	Name of the Material	STD.	Rationale	Qty/ Tablet (mg)	Qty/Batch (kg)
Core					
1.	Azithromycin Dihydrate	USP 42	Active	524.0	52.400
2.	Microcrystalline cellulose	BP 2020	Diluent	20.00	2.00
3.	Maize Starch	BP 2020	Diluent	216.0	21.60
4.	Sodium starch Glycolate	BP 2020	Disintegrant	80.00	8.00
5.	PVP K 30 (P)	BP 2020	Binder	20.00	2.00
6.	Purified water	BP 2020	Vehicle	300.0 ml	30.0 L
7.	Colloidal Anhydrous Silica	BP 2020	Glidant	6.500	0.65
8.	Purified Talc	BP 2020	Glidant	17.50	1.75
9.	Magnesium Stearate	BP 2020	Lubricant	16.00	1.60
Coating					
10.	Film Coat Universal	IHS	Polymer	20.00	2.00
11.	Macrogol-6000	BP 2020	Plasticizer	2.000	0.20
12.	Dichloromethane	BP 2020	Solvent	q. s.	35.0 L

13.	Isopropyl Alcohol	BP 2020	Solvent	q. s.	35.0 L
	Average Weight			922.00mg	92.20 kg

3. Pharmaceutical Form:

A white to off white coloured oblong shaped, slightly biconvex film coated tablet scored on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Azithromycin 500 mg tablets are indicated for the treatment in adults of the following:

- Acute bacterial sinusitis.
- Acute bacterial otitis media.
- Pharyngitis, tonsillitis.
- Acute exacerbation of chronic bronchitis (adequately diagnosed).
- Skin and soft tissue infections.

Uncomplicated Chlamydia trachomatis urethritis and cervicitis

4.2 Posology and method of administration

Posology

Children and adolescents with a body weight above 45 kg, adults and the elderly: The total dose is 1500 mg, administered as 500 mg once daily for 3 days.

Method of administration:

Azithromycin 500mg tablets taken orally.

4.3 Contraindications

Hypersensitivity to Azithromycin, to other macrolide antibiotics, or to any of the excipients

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin 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 administration should be stopped if liver dysfunction has emerged.

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

4.5 Interaction with other medicinal products and other forms of interaction

Theophylline: Pharmacokinetic research has shown no interaction between azithromycin and theophylline on co-administration to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.
Oral coumarin-type anticoagulants
Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was seen on the pharmacokinetics of carbamazepine or the active metabolite of carbamazepine.
Ciclosporin: On the basis of limited pharmacokinetic data on interaction between Azithromycin and ciclosporin in healthy volunteers, caution should be exercised in concurrent administration of these medicinal products. If concurrent administration is necessary, the ciclosporin levels must be checked and if necessary the ciclosporin dosage adjusted.
Digoxin: It is known that some macrolide antibiotics limit the metabolism of digoxin in the bowel. In patients who are treated concurrently with Azithromycin and digoxin, account should be taken of potentially raised digoxin levels and these levels must be monitored.
Antacids: In a pharmacokinetic study into the effect of concurrent administration of antacids and Azithromycin, no effect was seen on the total biological availability, although peak serum levels were reduced by 30%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

4.6 Pregnancy and lactation
Pregnancy: There are no adequate and well controlled studies in pregnant women. Animal reproduction studies show passage across the placenta.
Lactation: Azithromycin passes into breast milk. Because it is not known whether Azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with Azithromycin.
Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitization is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter. Nursing Mothers: It is not known whether Azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Azithromycin is administered to a nursing woman

4.7 Effects on ability to drive and use machines
No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery

4.8 Undesirable effects
Cardiac disorders:
Rare: Palpitations, arrhythmia (including ventricular tachycardia). There is a potential risk of QT lengthening and torsades in predisposed patients.
Uncommon: Dizziness, convulsions, headache, somnolence, changes in smell and/or taste.
Rare: Paresthesia, syncope, insomnia, hyperactivity.
Ear and labyrinth disorders:
Rare: Loss of hearing including deafness and/or tinnitus has been reported in long-term use of high doses of azithromycin during clinical research.
In those cases where follow-up data were available, the majority of these undesirable effects proved to be reversible.
Gastrointestinal disorders:

Common: Nausea, vomiting, diarrhoea, gastrointestinal symptoms (pain/cramps).
Uncommon: Very watery faeces (as a consequence of infrequent dehydration of the system), flatulence, digestive disturbances.
Rare: Constipation, discoloration of the tongue, pancreatitis.
Discoloration of the teeth and pseudomembranous colitis have been reported.
Renal and urinary disorders:
Rare: Interstitial nephritis, acute renal failure.
Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia.
Metabolism and nutrition disorders Uncommon:
Anorexia.

4.9 Overdose

a) Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea

***b) Therapeutic measure*:**

In the event of overdose, general symptomatic and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolides; azithromycin, ATC code: J01FA10

Mechanism of action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50Sribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.
Complete cross resistance exists among Streptococcus pneumoniae, beta haemolytic streptococcus of group A, Enterococcus faecalis and Staphylococcus aureus, including methicillin resistant S. aureus (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

5.2 Pharmacokinetic properties

Absorption

The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution

After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities.

Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.

The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

Elimination

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days. Approximately 12% of an intravenously administered dose of azithromycin is, over a period of 3 days, excreted unchanged in the urine. High concentrations of unchanged azithromycin were found in human bile.

In this, ten metabolites were also detected (formed by N- and O- desmethylation, by hydroxylation of the desosamin and aglycon rings and by splitting the cladinose conjugate). A comparison of fluid chromatography and microbiological assessment methods shows that the metabolites are microbiologically inactive.

In animal models high concentrations of azithromycin were found in phagocytes. Also it has been shown that during active phagocytosis higher concentrations of azithromycin are released than during inactive phagocytosis. In animal models this process was shown to contribute to the accumulation of azithromycin in infectious tissue.

5.3 Preclinical safety data

In animal tests in which the dosages used amounted to 40 times the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule no true toxicological consequences were observed which were associated with this. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown. Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in in-vivo and invitro test models. ***Reproductive toxicity:***

Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above

6. PHARMACEUTICAL PARTICULARS:

6.1. List of excipients:

1. Microcrystalline cellulose

2. Maize Starch
3. Sodium Starch Glycolate
4. Poividone – K 30
5. Purified water
6. Colloidal Anhydrous Silica
7. Purified Talc
8. Magnesium stearate
9. Film coat universal white
10. Macrogols 6000
11. Dichloromethane 12. Isopropyl alcohol

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life:

36 months

6.4. Special precautions for storage:

Store in a dry place below 30°C Protected from light. Keep out of reach of children.

6.5. Nature and content of container:

3 tablets are packed in PVC blisters and such blisters are packed in a monocarton.

6.6. Special precautions for disposal and other handling: No special requirements

7. APPLICANT/ MANUFACTURER:

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