Summary of Products Characteristics

1- Name of the Medicinal Product:

1.1 Product Name

- Generic Name or International Non-Proprietary Name (INN)

Azithromycin Tablets USP 500 MG

- Brand Name

Topsea Azithromycin 500

1.2 Dosage Strength

Each Film coated Tablets contains:

Azithromycin Dihydrate USP

Eq.to Azithromycin……500 mg

Excipients…….q.s

Colour : Titanium Dioxide

1.3 Dosage Form

Film coated Tablets

2- Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each Film coated Tablets contains:

Azithromycin Dihydrate USP

Eq.to Azithromycin……500 mg

Excipients…….q.s

Colour : Titanium Dioxide

2.2 Quantitative Declaration

Description: White Colour, Capsule Shape, film coated tablets having one side break line and other side plain.

Batch Size: 162.00 kg / 2.00 Lac Tablets

Reference. MFR No: MFR/T-E210, Version No: 00

Sr No	Ingredients	A.R No.	Specification	Overages	Quantity/ Tablet in mg	Standard Qty in kg
Mixing						
1.	Azithromycin Dihydrate	RM200397	USP	Nil	524.000	104.800
2.	Colloidal Silicon Dioxide	RM200377	BP	Nil	4.000	0.800
3.	Maize Starch	RM200228	BP	Nil	65.500	13.100
4.	Microcrystalline Cellulose	RM200588	BP	Nil	90.000	18.000
5.	Sodium Starch Glycolate	RM200338	BP	Nil	18.000	3.600
Paste Preparation						
6.	Maize Starch	RM200228	BP	Nil	36.000	7.200
7.	PVPK-30	RM200329	USP	Nil	4.000	0.800
8.	Sodium Benzoate	RM200483	BP	Nil	1.500	0.300
9.	*Purified Water	W220218	BP	Nil	Q.S.	Q.S.
Lubrication						
10.	Talc	RM200211	BP	Nil	7.000	1.400
11.	Magnesium Stearate	RM200248	BP	Nil	12.000	2.400
12.	Colloidal Silicon Dioxide	RM200390	BP	Nil	4.000	0.800
13.	Sodium Starch Glycolate	RM200034	BP	Nil	30.000	6.000
14.	Sodium Lauryl Sulphate	RM200414	BP	Nil	4.000	0.800
Coating						
15.	HPMC	RM200398	BP	Nil	7.500	1.500
16.	Titanium Dioxide	RM200381	BP	Nil	1.100	0.220
17.	Talc	RM200541	BP	Nil	1.400	0.280
18.	Isopropyl alcohol	RM200221	BP	Nil	74.700	14.940
19.	Methylene chloride	RM200411	BP	Nil	91.300	18.260
Average wt. of Tablet (810.000 mg ± 5.0 %)						

Note:

Active material was calculated on assay or Potency Basis.

BP = British Pharmacopoeia

USP= United State Pharmacopoeia

3. Pharmaceutical Form

'Film coated Tablet White, caplet shaped film coated tablets, having break line on one side and plain on other side.'

4. Clinical Particulars

4.1 Therapeutic indications

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin:

Acute bacterial sinusitis (adequately diagnosed), Acute bacterial otitis media (adequately diagnosed), Pharyngitis, tonsillitis, Acute exacerbation of chronic bronchitis (adequately diagnosed), Mild to moderately severe community acquired pneumonia, Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas, Uncomplicated Chlamydia trachomatis urethritis and cervicitis Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration Posology

Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below. Adults, children and adolescents with a body weight of 45 kg or over: The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5. In the case of uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dosage is 1000 mg as a single oral dose. Children and adolescents with a body weight below 45 kg: Azithromycin are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients. Elderly patients: For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes. Patients with renal impairment: Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Patients with hepatic impairment: Dose adjustment is not required for patients with mild to moderate hepatic dysfunction.

Method of administration

For oral use.

The tablets can be taken with or without food. The tablets should be taken with ½ glass of water.

4.3 Contraindication

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients use in formulation.

4.4 Special warnings and special precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued, and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued. 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. Superinfections: As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with non-susceptible micro-organisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to

overgrowth of C. difficile. C. difficile produces toxins A and B which 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. 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 antibacterial agents. In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed. 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, including azithromycin. Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients: - With congenital or documented acquired QT prolongation. - Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin. - With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia - With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency. Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

The following should be considered before prescribing azithromycin:

Azithromycin is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed. The selection of azithromycin to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the bacterial etiology of the infection in the approved indications and the prevalence of resistance to azithromycin or other macrolides. In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics. As for other macrolides, high resistance rates of Streptococcus pneumoniae have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by Streptococcus pneumoniae. In bacterial pharyngitis the use of azithromycin is recommended only in cases where first line therapy with beta-lactams is not possible. Skin and soft tissue infections: The main causative agent of soft tissue infections, Staphylococcus aureus,

is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin. Infected burn wounds: Azithromycin is not indicated for the treatment of infected burn wounds. Sexually transmitted disease: In case of sexually transmitted diseases a concomitant infection by T. pallidium should be excluded. Neurological or psychiatric diseases: Azithromycin should be used with caution in patients with neurological or psychiatric disorders. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids. Cetirizine: Azithromycin with cetirizine 20 mg at in no pharmacokinetic interaction and no

significant changes in the QT interval. Didanosins (Dideoxyinosine): Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine. Digoxin (P-gp substrates): Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, increased serum levels of the Pglycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered. Zidovudine: Single 1000 mg doses and multiple doses of 600 mg or 1200 mg azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients. Azithromycin 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. Ergotamine derivatives: Due to the theoretical possibility of ergoti sm, the concurrent use of azithromycin with ergot derivatives is not recommended. Astemizole, alfentanil: Caution is advised in the co-administration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin. Atorvastatin: Coadministration of atorvastatin (10 mg daily)

and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductaseinhibition assay). Carbamazepine: No significant effect on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin. Cisapride: Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes. Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen. Coumarin-Type Oral Anticoagulants: Azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin. There have been potentiated anticoagulation subsequent to coadministration of azithromycin and coumarintype oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants. Cyclosporin: Caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly. Efavirenz: Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions. Fluconazole: Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed. Indinavir: Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days. Methylprednisolone: Azithromycin had no significant effect on the pharmacokinetics of methylprednisolone. Midazolam: Coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam. Nelfinavir: Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required. Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in sub jects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established. Sildenafil: There was no evidence of an effect of

azithromycin (500 mg daily for 3 days) on the AUC and Cmax of sildenafil or its major circulating metabolite. Terfenadine: There is no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred. Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered 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. Triazolam: Coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo. Trimethoprim/sulfamethoxazole: Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies. 4.6 Pregnancy and lactation Pregnancy: The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore, Azithromycin should only be used during pregnancy if the benefit outweighs the risk. Breast-feeding: It is not known whether azithromycin may have adverse effects on the breastfed 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. 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. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities. 4.8 Undesirable effects Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100 to to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare(<1/10,000), not known (cannot be estimated from the available data). Within each frequency
grouping, undesirable effects are presented in order of decreasing seriousness.

4.9 Overdose Adverse

events experienced in higher than recommended doses were similar to those seen at normal doses. Symptoms: The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. Treatment: In the event of overdose, general symptomatic and supportive measures are indicated as required 5.

Pharmacological Properties 5.1 Pharmacodynamics properties Pharmacotherapeutic group: Antibacterials for systemic use, macrolides. ATC code : J01 FA10 Azithromycin is a macrolide antibiotic belonging to the azalide group. 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. Pharmacokinetic/pharmacodynamic 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, betahaemolytic 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:

Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 μg/ml. Distribution: Orally administered azithromycin is widely distributed throughout the body. At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 μg/g, 0,6-2,3 μg/g, 2,0-2,8 μg/g and 0-0,3 μg/ml have been measured in resp. lung, prostate, tonsil and serum. Binding of azithromycin to serum proteins is variable and varies from 52% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration. Elimination: The terminal plasma elimination half-life clos ely reflects the elimination half-life from tissues of 2-4 days. Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 μg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin. 5.3 Preclinical safety data In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated

toxicological consequences. 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 body weight/ 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 Data

6.1. List of excipients

- Maize Starch BP
- Colloidal Silicon Dioxide BP
- Sodium Starch Gycolate BP
- Microcrystalline Cellulose BP
- PVPK-30 USP
- Sodium Benzoate BP
- Purified Water BP
- Talc BP
- Magnesium Stearate BP
- Colloidal Silicon Dioxide BP
- Sodium Starch Glycolate BP
- Sodium Lauryl Sulphate BP
- HPMC BP
- Titanium dioxide BP
- Talc BP
- Isopropyl alcohol BP
- Methylene Chloride BP

6.2 Shelf life

3 Years from the date of manufacture.

6.3 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.4 Nature and contents of container

Pack 3 Tablet in a Blister with the help of Alu-Clear PVC foil in the arrangement of 1x3. Pack such 1 Blister in a printed Inner carton along with its package insert in the arrangement of 1x3's. Pack Such 10 Inner Cartons in an Outer Carton in the arrangement of 10x1x3's.

7- Marketing Authorization Holder:

SURMOUNT LABORATORIES PVT. LTD.

Plot No A-2/4003, GIDC Ind. Estate,
Ankleshwar-393002, Gujarat, India

Email: surmountlaborat@gmail.com

8- Marketing Authorization Number (s):

-Product license / registration Number (s) -------

9-Manufacturer Name:

SURMOUNT LABORATORIES PVT. LTD.

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