1.3.1 Summary of Product Characteristics (SmPC)

1- Name of the Medicinal Product:

1.1 Product Name

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

AZITHROMYCIN FOR ORAL SUSPENSION USP

-Brand Name

PYTHROCIN SUSPENSION

1.2 Dosage Strength

Each 5ml (After reconstitution) contains

Azithromycin Dihydrate USP	
Eq. to Azithromycin	200 mg
Excipients	q.s.

1.3 Dosage Form

Oral Suspension

2- Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each 5ml (After reconstitution) contains

Azithromycin Dihydrate USP	
Eq. to Azithromycin	200 mg
Excipients	q.s.

2.2 Quantitative Declaration

Sr. No:	Ingredients	Specification	Each 30 ml After Reconstitution	Overages %	Qty/Batch 10,000 nos. in Kg
Dry mixing					
1.	Azithromycin Dihydrate eq. to Azithromycin	USP	1296	--	12.960
2.	Methyl Paraben	BP	60	--	0.600
3.	Propyl Paraben	BP	6	--	0.060
4.	Sugar	BP	1953	--	19.530
5.	Xanthan gum	BP	56	--	0.560
6.	Colloidal Silicon Dioxide	BP	150	--	1.500
7.	Menthol	BP	5	--	0.050
8.	Flavor Banana	IHS	300	--	3.000
9.	Kyron 135	IHS	1560	--	15.600
10.	Aspartame	BP	90	--	0.900
Average weight of net content of powder			**5476 mg**	**Limit : 5476 mg ± 5%**	

Note: Active material was calculated on assay or Potency Basis.
IHS = In-house Specification
BP = British Pharmacopoeia
USP= United state pharmacopeia

3- Pharmaceutical Form:

A white to off white Colour granules powder with Banana flavor This on reconstitution with water gives off white Colour suspension.

4- Clinical Particulars:

4.1 Therapeutic indications

Azithromycin powder for oral suspension is indicated for the treatment of the following infections, when caused by microorganisms sensitive 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
- skin and soft tissue infections
- uncomplicated Chlamydia trachomatis urethritis and cervicitis

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis, the dosage is 1,000 mg in one single oral dose.
For all other indications the dosage is 1,500 mg, to be administered as 500 mg per day for three consecutive days. Alternatively the same total dosage (1,500 mg) can also be given over a period of 5 days with 500 mg on the first day and then 250 mg on days 2 to 5.
To treat these patients other pharmaceutical forms are also available.

Older people

The same dosage as in adult patients is used in the older people. Since older 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 (see section 4.4).

Children and adolescents (< 18 years)

The total dosage in children aged 1 year and older is 30 mg/kg administered as 10 mg/kg once daily for three days, or over a period of five days starting with a single dose of 10 mg/kg on the first day, followed by doses of 5 mg/kg per day for the following 4 days, according to the tables shown below. There are limited data on use in children younger than 1 year.

Weight (kg)	3-day therapy	5-day therapy		Contents of the bottle
	Day 1-3 10 mg/kg/day	Day 1 10 mg/kg/day	Day 2-5 5 mg/kg/day	
10 kg	2.5 ml	2.5 ml	1.25 ml	15 ml
12 kg	3 ml	3 ml	1.5 ml	15 ml
14 kg	3.5 ml	3.5 ml	1.75 ml	15 ml
16 kg	4 ml	4 ml	2 ml	15ml
17 – 25 kg	5 ml	5 ml	2.5ml	15ml
26 – 35 kg	7.5 ml	7.5 ml	3.75 ml	22.5 ml
36 – 45 kg	10 ml	10 ml	5 ml	30 ml
> 45 kg	12.5 ml	12.5 ml	6.25 ml	22.5 ml + 15 ml

The dosage for the treatment of pharyngitis caused by *Streptococcus pyogenes* is an exception: in the treatment of pharyngitis caused by *Streptococcus pyogenes* Azithromycin has proved to be effective when it is administered to children as a single dose of 10 mg/kg or 20 mg/kg for 3 days with a maximum daily dosage of 500 mg. At these two dosages a comparable

clinical effect was observed, even if the eradication of the bacteria was more significant at a daily dosage of 20 mg/kg.
Penicillin is however the drug of first choice in the treatment of pharyngitis caused by *Streptococcus pyogenes* and the prevention of subsequent rheumatic fever.

Patients with renal impairment:
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).
Patients with hepatic impairment:
A dose adjustment is not necessary for patients with mild to moderately impaired liver function
Method of administration
Before use the powder should be reconstituted with water into a white to off white, homogenous suspension, After reconstitution the drug can be administered using a PE/PP syringe for oral use.
After taking the suspension a bitter after-taste can be avoided by drinking fruit juice directly after swallowing. Azithromycin powder for oral suspension should be given in a single daily dosage. The suspension may be taken together with food.

4.3 Contraindications

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

4.4 Special warning and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneuroticoedema 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.
Azithromycin tablets contains soya lecithin which might be a source of soya protein and should therefore not be taken in patients allergic to soya or peanut due to the risk of hypersensitivity reactions.
Since 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. Liver function tests/investigations should be performed in cases where signs and symptoms of liver dysfunction occur such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.
In patients receiving ergotamine derivatives, ergotism has been precipitated by co-administration 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.

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 cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization. Therefore caution is required when treating patients:

- With congenital or documented acquired QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Clostridium difficile associated diarrhoea (CDAD) has been reported with the 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 antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Safety and efficacy for the prevention or treatment of MAC in children have not been established.

The following should be considered before prescribing azithromycin:

Azithromycin tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

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 (> 30 %) have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by Streptococcus pneumoniae.

Pharyngitis/ tonsilitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by Streptococcus pyogenes. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis
Often, azithromycin is not the substance of first choice for the treatment of sinusitis.
Acute otitis media
Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.
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. palladium should be excluded.
Neurological or psychiatric diseases
Azithromycin should be used with caution in patients with neurological or psychiatric disorders.
As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.
In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

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 and azithromycin, no effect on the total bio-availability was seen, although the peak serum concentrations were reduced by approximately 25%. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Fluconazole
Co-administration 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 co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.
Nelfinavir
Co-administration 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 subjects 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.

Terfenadine

Pharmacokinetic studies have reported 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.

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.

Effect of azithromycin on other medicinal products:

Ergotamine derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Digoxin

It is known that some macrolide antibiotics limit the metabolism of digoxin (in the gut). In patients treated concomitantly with azithromycin and digoxin the possibility of increased digoxin levels should be borne in mind, and digoxin levels monitored.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type 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

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporinCmax and AUC0-5 were found to be significantly elevated. Consequently, 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.

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 theoophylline leveis is advised.

Trimethoprim/sulfamethoxazole

Co-administration 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.

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of 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.

Astemizole, alfentanil

There are no known data on interactions with astemizole or 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

Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed 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.

Cetirizine

In healthy volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosins (Dideoxyinosine)

Co-administration 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 as compared with placebo.

Efavirenz
Co-administration 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.
Indinavir
Co-administration 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
In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.
Midazolam
In healthy volunteers, co-administration 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.
Sildenafil
In normal healthy male volunteers, 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.
Triazolam
In 14 healthy volunteers, co-administration 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

4.6 Fertility, Pregnancy and lactation

There are no adequate data from the use of Azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore Azithromycin tablets should only be used during pregnancy if definitely indicated.
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 tablets. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation 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 machine

There is no evidence to suggest that azithromycin may have an effect: on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: 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); not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are listed in order of decreasing seriousness.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance.

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Candidiasis, oral candidiasis, vaginal infection
	Not known	*Pseudomembranous colitis*
Blood and lymphatic system disorders	Common	Lymphocyte count decreased, eosinophil count increased
	Uncommon	Leukopenia, neutropenia
	Rare	Thrombocytopenia, haemolyticanaemia
Immune system disorders	Uncommon	Angioedema, hypersensitivity
	Not known	*Anaphylactic reaction*
Metabolism and nutrition disorders	Common	Anorexia
Psychiatric disorders	Uncommon	Nervousness
	Rare	Agitation, depersonalisation
	Not known	*Aggression, anxiety*
Nervous system disorders	Common	Dizziness, headache, paraesthesia, dysgeusia
	Uncommon	Hypoaesthesia, somnolence, insomnia
	Not known	*Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia,*

		parosmia, Myasthenia gravis (see section 4.4).
Eye disorders	Common	Visual impairment
Ear and labyrinth disorders	Common	Deafness
	Uncommon	Hearing impaired, tinnitus
	Rare	Vertigo
Cardiac disorders	Uncommon	Palpitations
	Not known	*Torsades de pointes, arrhythmia (including ventricular tachycardia, electrocardiogram QT prolonged*
Vascular disorders	Not known	*Hypotension*
Gastrointestinal disorders	Very common	Diarrhoea, abdominal pain, nausea, flatulence
	Common	Vomiting, dyspepsia
	Uncommon	Gastritis, constipation
	Not known	*\Pancreatitis, tongue discolouration*
Hepatobiliary disorders	Uncommon	Hepatitis, aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubine increased
	Rare	Hepatic function abnormal
	Not known	*Hepatic failure*, hepatitis fulminant, hepatic necrosis, jaundice cholestatic*
Skin and subcutaneous tissue disorders	Common	Rash, pruritus
	Uncommon	Steven-Johnson syndrome, photosensitivity reaction, urticaria
	Not known	*Toxic epidermal necrolysis, erythema multiforme*
Musculoskeletal and connective tissue disorders	Common	Arthralgia
Renal and urinary disorders	Uncommon	Blood urea increased
	Rare	Renal failure acute, nephritis

		interstitial
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Chest pain, oedema, malaise,asthenia
Investigations	Common	Blood bicarbonate decreased
	Uncommon	Blood potassium abnormal

* which has rarely resulted in death

4.9 Overdose and treatment

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of over dosage general symptomatic and general supportive measures are indicated as required.

5- Pharmacological Properties:

5.1 Pharmacodynamic Properties

General properties

Pharmacotherapeutic group: antibacterial for systemic use; macrolids; azithromycin,

ATC code: J01FA10

Mode of action:

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal 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*, betahaemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	**susceptible (mg/l)**	**resistant (mg/l)**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Gruppen A, B, C, G)	≤ 0,25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilusinfluenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.5	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Susceptibility:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms
*Haemophilusinfluenzae**
*Moraxella catarrhalis**
Other microorganisms
Chlamydophilapneumoniae
Chlamydia trachomatis

Legionella pneumophila
Mycobacterium avium
*Mycoplasma pneumonia**
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus *
Streptococcus agalactiae
*Streptococcus pneumoniae**
*Streptococcus pyogenes**
Other microorganisms
Ureaplasmaurealyticum
Inherently resistant organisms
Staphylococcus aureus – methicillin resistant anderythromycin resistant strains
Streptococcus pneumoniae – penicillin resistant strains
Pseudomonas aeruginosa
*Klebsiella*spp.

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

5.2 Pharmacokinetic Properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Excretion

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchangedform, is a major route of elimination.

The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR> 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension.. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety Data

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:

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

Mutagenic potential:

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6- Pharmaceutical Particulars :

6.1 List of excipients

Methyl Paraben
Propyl Paraben
Sugar
Xanthan gum
Colloidal Silicon Dioxide
Menthol
Flavour Banana
Kyron 135
Aspartame

6.2 Incompatibilities
None known

6.3 Shelf life
36 months from the date of manufacture.

6.4 Special precautions for storage
Store in a cool and dry place, protected from light

6.5 Nature and contents of container
HDPE bottle of 30 ml.
Not all pack sizes may be marketed
Note: All pack style may not be marketed.

7- Marketing Authorization Holder:

- **Name** : **GLOBELA PHARMA PVT. LTD.**
- **Address** : Plot No. 357, G.I.D.C.,
  Sachin,
  Surat – 394 230,
  Gujarat,
  India.
- **Phone** : +91– 261–2398058
- **Fax** : +91– 261–2398058
- **E-mail** : info@globclapharma.com

8- **Marketing Authorization Number (s) :**

-Product license / registration Number (s)

9- **Manufacturer Name:**

- **Name :** GLOBELA PHARMA PVT. LTD.
- **Address :** Plot No. 357, G.I.D.C.,
  Sachin,
  Surat – 394 230,
  Gujarat,
  India.
- **Phone :** +91– 261–2398058
- **Fax :** +91– 261–2398058
- **E-mail :** info@globelapharma.com

10- **Date of first authorization/renewal of the authorization :**

11- **Date of revision of the text:**
