1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

1.1 Name of the medicinal product:

1.2 Strength:

Each film coated tablet contains:
Azithromycin Dihydrate USP
Equivalent to Azithromycin ……. 250 mg
Excipients……q.s.
Colour: Titanium Dioxide

1.3 Pharmaceutical form:

Tablet

2. Qualitative and quantitative composition

NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

Each film coated tablet contains:

Azithromycin Dihydrate USP

Equivalent to Azithromycin ……. 250 mg

Excipients……q.s.

Colour: Titanium Dioxide

3. Pharmaceutical form

Tablet

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.

For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Children and adolescents with a body weight below 45 kg:

Azithromycin tablets 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). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min).

Patients with hepatic impairment:

Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

Method of administration

Azithromycin Film-coated Tablets are for oral administration only. The tablets can be taken with or without food. The tablets should be taken with ½ glass of water.

4.3 Contraindications

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient.

4.4 Special warnings and precautions for use

Hypersensitivity

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.

Hepatotoxicity

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 (see section 4.8). 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.

Ergot derivatives

In patients receiving ergot 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.

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 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 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.

Superinfection:

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended.

Clostridium difficile associated diarrhoea

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.

Strains of *C. difficile* producing hypertoxins 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 two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin 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 is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin 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 was observed.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Co-administration with hydroxychloroquine or chloroquine

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

Excipients

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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 concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

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

Didanosine (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 as compared with placebo.

Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

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.

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

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

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-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.

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: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg 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.

Ciclosporin*:* 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 ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Coadministration of a single dose of 600 mg 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 C_{max} (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: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam: In healthy volunteers, 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 was 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.

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 C_{max} of sildenafil or its major circulating metabolite.

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.

Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam: In 14 healthy volunteers, 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.

Hydroxychloroquine and chloroquine: Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine. Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (>7,300 first trimester exposures). While most studies do not suggest an association with adverse foetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.

Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the 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.

However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects:

Azithromycin is well tolerated with a low incidence of side effects.

The table below lists the adverse reactions identified through clinical trial 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); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

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** frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis, oral candidiasis, vaginal infection			Pseudomembranous colitis
Blood and lymphatic system disorders					
		Leukopenia, neutropenia			Thrombocytopenia, haemolytic anaemia
Immune system disorders					
		Angioedema, hypersensitivity			Anaphylactic reaction
Metabolism and nutrition disorders					
	Anorexia				
Psychiatric disorders					
		Nervousness	Agitation		Aggression anxiety
Nervous system disorders					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia somnolence, insomnia			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					

	Deafness	Hearing impaired, tinnitus	Vertigo		
Cardiac disorders					
		Palpitations			Torsades de pointes arrhythmia including ventricular tachycardia.
Vascular disorders					
					Hypotension
Gastrointestinal disorders					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation			Pancreatitis, tongue discoloration
Hepatobiliary disorders					
		Hepatitis	Hepatic function abnormal		Hepatic failure (which has rarely resulted in death) hepatitis fulminant, hepatic necrosis, jaundice cholestatic
Skin and subcutaneous tissue disorders					
	Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction, urticaria	Acute generalised exanthematous pustulosis (AGEP) *§, DRESS (Drug reaction with eosinophilia and systemic symptoms) *§		Toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal and connective tissue disorders					
	Arthralgia				
Renal and urinary disorders					
					Renal failure acute, nephritis interstitial
General disorders and administration site conditions					
	Fatigue	Chest pain, oedema, malaise, asthenia			
Investigations					

	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal			Electrocardiogram QT prolonged

*ADR identified post-marketing

§ ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

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, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. Pharmacological properties:

5.1 Pharmacodynamics properties:

General properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides. ATC code: J01FA10.

Mode of action

Azithromycin is a macrolide antibiotic belonging to the azalide group.

The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.

Mechanism of action

The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

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.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly in *Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B) streptococcus against other macrolides and lincosamides.

Breakpoints

Azithromycin susceptibility breakpoints for typical bacterial pathogens, as published by EUCAST are:

Organism	**MIC breakpoint (mg/L)**	
	Susceptible (S≤)	**Resistant (R>)**
Staphylococcus spp.	1	2
Streptococcus spp. (Group A, B, C, G)	0.25	0.5
Streptococcus pneumoniae	0.25	0.5
Haemophilus influenzae	0.12	4
Moraxella catarrhalis	0.25	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: Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus Methycillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms

Haemophilus influenzae *Haemophilus parainfluenzae*
Legionella pneumophila
Moraxella catarrhalis
Neisseria gonorrhoeae
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatis
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae Penicillin-intermediate Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE***
Anaerobic microorganisms
Bacteroides fragilis group

* Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

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 (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml.

Distribution

Orally administered azithromycin is widely distributed throughout the body.

In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

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.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Elimination

The terminal plasma elimination half-life closely 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.

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 > 80ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 35% 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.

In elderly volunteers (> 65 years) higher (29%) AUC values have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Infants, toddlers, children and adolescents

Pharmacokinetics has 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 in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. 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 as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in *in-vivo* and *in-vitro* test models.

Reproductive toxicity:

In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No	Ingredients	SPEC
1	Maize Starch	BP
2	Lactose	BP
3	Sodium Starch Glycolate	BP
4	Povidone K-30	USP
5	Isopropyl alcohol	BP
6	Microcrystalline Cellulose	BP

7	Sodium Methyl Paraben	BP
8	Sodium Propyl Paraben	BP
9	Purified Water	BP
10	Purified talc	BP
11	Magnesium Stearate	BP
12	Sodium Starch Glycolate	BP
13	Crosscarmellose Sodium	BP
14	Idealcoat IJ–MS-1011 (White) IH	IH

6.2 Incompatibilities

None

6.3 Shelf life

36 Months (3 Years) from date of manufacturing

6.4 Special precautions for storage

Store below 30°C in a dry place. |Protect from light.

Keep medicines out of reach of children.

6.5 Nature and contents of container

NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg) is Alu-Pvc blister of 6 tablet such 1 Blister packed in a carton along with pack insert.

6.6 Special precautions for disposal:

None

7. Registrant:

M/s NOMEDI PHARMACEUTICALS LTD
387, Agege Motor Road, Mushin,

P. O. Box 11623, Ikeja, Lagos, Nigeria.

8. MANUFACTURER

CORAL LABORATORIES LTD.
Plot No. 57/1 (16), Bhanslore, Dunetha,
Nani Daman-396210, India
E-mail: exports@corallab.com

9. Date of revision of the text: NA

2.16.2 PATIENT INFORMATION LEAFLET

Enclosed

NOMETHROMAX 250 TABLETS
(Nigeria)
Pack insert Artwork

Size :170 x 76 mm

Front

NOMETHROMAX TABLETS
Azithromycin Tablets USP 250 mg

PHARMACEUTICAL DOSAGE FORM: Tablets for oral use

DESCRIPTION:
NOMETHROMAX TABLETS: White, oval shaped film coated tablets plain on both sides

NOMETHROMAX TABLETS
COMPOSITION:
Each film coated tablet contains :
Azithromycin Dihydrate USP
equivalent to Azithromycin ..... 250 mg
Excipients .....q.s.
Colour : Titanium Dioxide

CLINICAL PHARMACOLOGY:
Pharmacodynamics:
Azithromycin is an azalide, a sub-class of the macrolide 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.

Pharmacokinetics:

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).
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.
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).

INDICATIONS:
Azithromycin tablets is indicated for the treatment of the following infections, when caused by microorganisms sensitive to Azithromycin
- Upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis
- Acute otitis media
- Lower respiratory tract infections: acute bronchitis and mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis

WARNINGS AND PRECAUTIONS:
As with erythromycin and other macrolide antibiotics serious allergic reactions are rarely reported, these include angio-oedema and anaphylaxis (rarely fatal). Some of these reactions have resulted in recurrence of symptoms whereby a longer period of observation and treatment was necessary.
As is true of all antibiotics, it is advisable to be alert to signs of super infection by non-sensitive micro-organisms including fungi.
Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should also be considered in patients who get diarrhoea after starting treatment with Azithromycin.
Due to the theoretical possibility of ergotism, Azithromycin and ergotamine derivatives should not be given at the same time.
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolide.
Therefore Azithromycin should not be used:
- In patients with congenital or documented acquired QT prolongation.
- With other active substances that prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.
- In patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- In patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

The following should be considered before prescribing Azithromycin:
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 macrolide, high resistance rates of Streptococcus pneumoniae (> 30 %) have

Back

been reported for Azithromycin in some European countries. This should be taken into account when treating infections caused by Streptococcus pneumoniae.

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

ADVERSE EFFECTS:
In this section undesirable effects are defined as follows:
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.

Cardiac disorders
Rare: Palpitations, arrhythmia (including ventricular tachycardia).
There is a potential risk of QT lengthening and torsades in predisposed patients.

Blood and lymphatic system disorders
Rare: Thrombocytopenia, haemolytic anaemia and transient episodes of mild neutropenia have been observed in clinical research. No causal connection with the use of Azithromycin could be established for this.

Nervous system disorders
Uncommon: Dizziness, convulsions, headache, somnolence, changes in smell and/or taste.
Rare: Paresthesia, syncope, insomnia, hyperactivity.

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, discolouration of the tongue, pancreatitis. Discolourations of the teeth and pseudomembranous colitis have been reported.

Renal and urinary disorders
Rare: Interstitial nephritis, acute renal failure.

DOSAGE AND ADMINISTRATION:
Administration: For Oral Use.
Dosage:
Adults: In uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dosage is 1000 mg in one single oral dose. For all other indications the dosage is 1500 mg, to be administered as 500 mg per day for three consecutive days. Alternatively the same total dosage (1500 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.

Elderly: 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

OVERDOSAGE :
The symptoms that occurred at higher than recommended dosages were equivalent to known undesirable effects at normal dosage. Characteristic symptoms of overdose with macrolide antibiotics are: reversible loss of hearing, serious nausea, vomiting and diarrhoea. In cases of overdose, gastric lavage and general supportive measures are indicated.

STORAGE :
Store below 30°C in dry place. Protect from light.
Keep medicine out of reach of children.

POM: Prescription only medicine.

PRESENTATION :
Alu-PVC Blister of 6 Tablets.

NAFDAC Reg. No.: B4-7858

Manufactured by:
Coral Laboratories Ltd.
Plot No. 57/1 (16), Bhenslore,
Dunetha, Nani Daman - 396 210. INDIA.
Email : exports@corallab.com
Website : www.corallab.com

For:
Nomedi Pharmaceuticals Limited.
RC: 871751 387, Agege Motor Road, Mushin,
P.O. Box 11623, Ikeja, Lagos - Nigeria.

NGA/I/DNZ/00

PANTONE 485 C

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor, health care provider or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)** is and what it is used for

2. What you need to know before you take **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)**

3. How to take **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)**

4. Possible side effects

5. How to store **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)**

6. Contents of the pack and other information

1. WHAT NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg) IS AND WHAT IT IS USED FOR

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.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg).

Do not take NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

- Do not take medicines for indigestion 2 hours before or after you take this medicine.
- Never take 2 doses at the same time. Never take an extra dose to make up for a forgotten one.

Warnings and precautions

Hypersensitivity

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.

Hepatotoxicity

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.

Ergot derivatives

In patients receiving ergot 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.

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 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 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.

Superinfection:

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended.

Clostridium difficile associated diarrhoea

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.

Strains of *C. difficile* producing hypertoxins 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 two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin 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 is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin 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 was observed.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Co-administration with hydroxychloroquine or chloroquine

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

Excipients

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Pregnancy and breast-feeding

Pregnancy

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (>7,300 first trimester exposures). While most studies do not suggest an association with adverse foetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.

Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Driving and using 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.

3. HOW TO TAKE NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg).

Always take **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)** exactly as your doctor has told you. You should check with your doctor, pharmacist or health care provider if you are not sure.

If you take more NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg) than you should

If you accidentally take a lot more tablets than the doctor prescribed, contact a doctor or the nearest hospital emergency department immediately, or make sure that someone else contacts them for you. If any of these symptoms occur, **stop the treatment and consult a doctor immediately.**

If you forget to take NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

Try to make sure that you do not miss any dose. However, if you do forget a dose, take the missed dose as soon as you realise that you have forgotten it. Then take the next dose after the prescribed interval. **Do not take a double dose to make up for a forgotten tablet.**

If you stop taking NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

To be effective the medicine must be taken regularly at the dose prescribed and for as long as your doctor has advised. The disappearance of fever or any other symptoms does not mean that you are completely cured. Any sensations of fatigue, nausea, vomiting might not be due to the drug but to the infection itself. Reducing or suspending your treatment would have no effect on these sensations or symptoms and would only delay your recovery.

If you have any further questions on the use of this product, ask your doctor, pharmacist or health care provider.

4. POSSIBLE SIDE EFFECTS

- Feeling sick (nausea) Stick to simple meals and do not eat rich or spicy food while you're taking this medicine.
- Diarrhoea. ...
- Being sick (vomiting) ...
- Losing your appetite. ...
- Headaches. ...
- Feeling dizzy or tired. ...
- Changes to your sense of taste.

5. HOW TO STORE NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

Keep this medicine out of the sight and reach of children.

Store below 30°C. Do not use **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)** after the expiry date which is stated on the blister and the outer packaging after EXP. The expiry date refers to the last day of that month. Do not throw away any medicines via

wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What **NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)** contains

The active ingredients are Azithromycin.

The other ingredients are: Maize Starch BP, Lactose BP, Sodium Starch Glycolate BP, Povidone K-30 USP, Isopropyl alcohol BP, Microcrystalline Cellulose BP, Sodium Methyl Paraben BP, Sodium Propyl Paraben BP, Purified Water BP, Purified talc BP, Magnesium Stearate BP, Sodium Starch Glycolate BP, Crosscarmellose Sodium BP, Idealcoat IJ–MS-1011 (White) IH.

What NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg) looks like and contents of the pack

NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg)

Description;

Off , White, Oval, shape Uncoated tablets plane on side.

Carton containing;

NOMETHROMAX TABLETS (Azithromycin Tablets USP 250 mg) is Alu-Pvc blister of 6 tablet such 1 Blister packed in a carton along with pack insert.