WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[NT020 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of azithromycin (as dihydrate).

Excipients with potential clinical effect

Each tablet contains 1.72 mg of lactose as lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets are plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[NT020 trade name] is indicated in adults, adolescents and children above 6 months of age for the treatment of yaws disease caused by *Treponema pallidum* subspecies *pertenue*.

[NT020 trade name] is also indicated in adults and adolescents for the treatment of other susceptible bacterial infections including:

- cholera
- enteric fever (typhoid and paratyphoid)
- gonorrhoea
- sexually transmitted infection and trachoma due to *Chlamydia trachomatis*
- acute dysentery.

Regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines, including official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Yaws disease

Adults, adolescents and children weighing at least 45 kg

The recommended dose of [NT020 trade name] is 2 g (4 tablets) as single dose.

Children ≥ 6 months weighing less than 45 kg

The recommended dose is 30 mg azithromycin per kg body weight as single dose. If paediatric formulations are not available, dosing recommendations based on age are provided in the table below:

Age	**Number of tablets of [NT020 trade name]**
6 months to less than 6 years	1 tablet crushed and mixed with water
6 to less than 10 years	2
10 to less than 15 years	3

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

15 years or older	4

The same doses are used for prevention and elimination of yaws disease as part of mass drug administration programmes.

Other bacterial infections

Recommended doses of [NT020 trade name] for other indications are shown in the following table:

Adults, adolescents and children weighing at least 45 kg

Indication	**Dose**
Acute dysentery	500 mg (1 tablet) daily for 3 days
Cholera Sexually transmitted infections due to *Chlamydia trachomatis* Trachoma	1g (2 tablets) as a single dose*
Enteric fever	500 mg (1 tablet) daily for 7 days
Gonorrhoea	2g (4 tablets) as a single dose in combination with a second antibiotic

*for chlamydial lymphogranuloma (including lymphogranuloma venereum) when doxycycline cannot be given, this dose may be repeated at weekly intervals for a total of 3 doses

Adolescents and children weighing less than 45 kg

[NT020 trade name] may not be suitable for paediatric patients ≥ 6 months and weighing less than 45 kg. Other formulations of azithromycin may be required to give suitable doses.

Missed dose

If a dose of [NT020 trade name] is missed within 12 hours of the time it is usually taken, patients should be instructed to take the dose of [NT020 trade name] as soon as possible.

If more than 12 hours have passed since the time the dose is usually taken, the patient should be advised to wait until the next scheduled dose.

Renal impairment

No dose adjustment is required in patients with GFR ≥10 ml/min. In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, azithromycin should be administered with caution in these patients (see section 4.4).

Elderly

No dose adjustment is required in elderly patients (see section 5.2). Since the elderly are more likely to experience proarrhythmic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

Method of administration

For oral use.

Tablets should be swallowed whole and may be taken with food or between meals. Administration immediately before a meal may enhance the gastrointestinal tolerability.

4.3 Contraindications

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Severe skin and hypersensitivity reactions

Rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with azithromycin treatment (see section 4.8).

QT interval prolongation

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 (see section 4.8). 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, especially women, with ongoing proarrhythmic conditions such as those:

- with congenital or documented QT prolongation
- currently receiving treatment with other active substances known to prolong QT interval (see section 4.5)
- with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
- who are elderly (may be more susceptible to drug-associated effects on the QT interval)

Hepatotoxicity

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. Hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have also been reported with azithromycin, some of which have resulted in death (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

Patients should be advised to stop any ongoing azithromycin administration and to contact their health care provider if signs and symptoms of liver dysfunction develop. These include any of the following: unexplained anorexia, nausea, vomiting, persistent fatigue or rash, when combined with abdominal tenderness, especially in the right upper quadrant, pruritus, icterus, dark urine or abnormally pale stools. If these symptoms appear or if other signs suggestive of hepatic damage such as bleeding tendency or hepatic encephalopathy are detected, liver function tests must be performed as soon as possible, and appropriate management instituted.

Antibiotic-associated colitis

Diarrhoea, particularly if severe, persistent or bloody, during or after treatment with [NT020 trade name], may be a symptom of antibiotic-associated colitis, which can be life-threatening. Therefore, if antibiotic-associated colitis is suspected or confirmed, any ongoing treatment with [NT020 trade name] must be stopped immediately, and diarrhoea should be appropriately managed without delay. Products inhibiting peristalsis are contraindicated in this situation.

Sexually transmitted infections

Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin. Therefore, national or local antimicrobial resistance data should determine the choice of treatment for gonorrhoea where available (see also section 5.1).

In addition, if single dose azithromycin is considered for the treatment of urethritis and cervicitis due to *N. gonorrhoeae* or *C. trachomatis* (see section 4.2), concomitant urogenital infection by *Mycoplasma genitalium* should be excluded due to the high risk of emergence of resistance in this organism.

Furthermore, a concomitant infection caused by *Treponema pallidum* should be excluded as symptoms of incubating syphilis could be masked, delaying diagnosis.

For all patients with sexually transmitted urogenital infections, appropriate antibacterial therapy and microbiological follow-up tests should be initiated.

Myasthenia gravis

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).

Non-susceptible organisms

The use of azithromycin may result in the overgrowth of non-susceptible organisms. If superinfection occurs, interruption of treatment or other appropriate measures may be required.

Potential for resistance

Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Azithromycin should be used in line with appropriate guidelines and local policies that take into account the prevalence of resistance (see also sections 4.1 and 5.1).

Excipients

This medicinal product contains lactose as lactose monohydrate. Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Although azithromycin is a weak CYP450 inhibitor and does not interact significantly with CYP450 substrates, CYP3A4 inhibition cannot be completely ruled out. Therefore, caution is recommended in case of co-administration with CYP3A4 substrates with narrow therapeutic index.

Azithromycin is an inhibitor of the transporter P-glycoprotein (P-gp). Co-administration of azithromycin with P-gp substrates, such as digoxin and colchicine, may increase their exposure. For narrow therapeutic index drugs, caution and clinical and/or therapeutic drug monitoring and dose adjustment as appropriate are advised. The relatively long half-life of azithromycin (see section 5.2) should be taken into account in this context.

Medicinal products that are known to prolong the QT interval

[NT020 trade name] should be used with caution in patients receiving medicinal products known to prolong the QT interval (see section 4.4), such as antiarrhythmics of Classes IA (e.g. quinidine and procainamide) and III (e.g. dofetilide, amiodarone and sotalol), antipsychotic agents (e.g. pimozide), antidepressants (e.g. citalopram), fluoroquinolones (e.g. moxifloxacin and levofloxacin), chloroquine and hydroxychloroquine.

Interaction table

Drug interaction information for azithromycin with potential concomitant medicinal products is summarised in the table and text below. The drug interactions described are based on clinical drug-drug interaction studies conducted with azithromycin or, where indicated, are potential drug interactions that may occur with azithromycin.

Drugs	**Interaction**	**Recommendation on co-administration**
Antiarrhythmic		

Digoxin	Increased digoxin exposure expected	Clinical monitoring, and possibly digoxin level monitoring, is needed during and after treatment with azithromycin.
Anticoagulant		
Dabigatran	Increased dabigatran exposure expected	Caution should be exercised since post-marketing data suggest an increased risk for haemorrhages in patients receiving azithromycin concomitantly with dabigatran.
Warfarin	No change in prothrombin time in clinical drug interaction study but post-marketing reports of potentiated anticoagulation of coumarin-type oral anticoagulants upon co-administration with azithromycin.	A higher frequency of prothrombin time monitoring should be considered during and after treatment with azithromycin.
Antigout		
Colchicine	colchicine AUC_{0-t} ↑ C_{max} ↑	Clinical monitoring is needed during and after treatment with azithromycin.
Ergot derivatives		
Dihydroergotamine Ergotamine Ergometrine Methylergometrine	Increased exposure to ergot alkaloids expected	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 ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered
HMG-CoA reductase inhibitor		
Atorvastatin	atorvastatin AUC ↔ C_{max} ↔	Caution should be exercised since post-marketing cases of rhabdomyolysis in patients receiving azithromycin concomitantly with statins have been reported.
Immunosuppressant		
Ciclosporin	ciclopsorin AUC ↔ C_{max} ↑	Clinical monitoring and therapeutic drug monitoring as appropriate should be performed during and after treatment with azithromycin. Ciclosporin dose should be adjusted if required.
↓ Decreased ↑ Increased ↔ No change	AUC area under the curve (bioavailability) C_{max} maximum (peak) concentration (in plasma or blood) C_{min} minimum (trough) concentration (in plasma or blood)	

No clinically relevant change in the exposure of azithromycin or the co-administered medicinal products was observed in clinical studies evaluating potential drug-drug interactions of azithromycin with oral antacids (aluminium hydroxide/magnesium hydroxide), carbamazepine, cetirizine, cimetidine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Azithromycin may be used where appropriate to treat infection during pregnancy, taking into account the importance of treatment and any potential risks.

There is a large amount of data from observational studies on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse fetal effects such as major congenital malformations or cardiovascular malformations. There are, however, no adequate and well-controlled studies in pregnant women.

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of teratogenic effects was found.

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3).

Breast-feeding

Azithromycin is excreted in human milk in substantial amounts. No serious adverse effects of azithromycin on the breast-fed infants have been observed, but effects such as diarrhoea, mucosal fungal infection and hypersensitivity could occur in breast-fed newborns/infants even at sub-therapeutic doses. A decision must be made whether to discontinue breast-feeding temporarily 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.

Fertility

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

Azithromycin can have a moderate influence on the ability to drive and use machines. Dizziness, drowsiness and convulsions have been reported in some patients taking azithromycin and some patients experienced visual and/or auditory impairment. This should be considered when assessing a patient's ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment include diarrhoea, headache, vomiting, abdominal pain, nausea and abnormal laboratory test values. Other important adverse reactions include anaphylactic reactions, torsade de pointes, arrhythmia including ventricular tachycardia, pseudomembranous colitis and hepatic failure (see section 4.4). Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with azithromycin treatment (see section 4.4).

List of adverse reactions

Adverse reactions identified through clinical trial experience and post marketing surveillance are listed below, by system organ class and frequency. Of note, some of these adverse reactions may relate to courses of treatment rather than single doses.

Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and Infestations

Uncommon	*Candida* infection, pneumonia, fungal infection, bacterial infection, vaginal infection, pharyngitis, gastroenteritis, rhinitis, oral candidiasis

Blood and lymphatic system disorders

Common	decreased lymphocyte count, increased eosinophil count, increased basophil count, increased monocyte count, increased neutrophil count
Uncommon	leukopenia, neutropenia, eosinophilia, increased platelet count, decreased haematocrit
Frequency not known	thrombocytopenia, haemolytic anaemia

Immune system disorders

Uncommon	angioedema, hypersensitivity
Not known	anaphylactic reaction

Metabolism and nutrition disorders

Uncommon	decreased appetite

Psychiatric disorders

Uncommon	nervousness, insomnia
Rare	agitation
Frequency not known	anxiety, delirium, hallucination, aggression

Nervous system disorders

Common	headache
Uncommon	dizziness, dysgeusia , paraesthesia, somnolence
Frequency not known	myasthenia gravis, seizure, anosmia, ageusia, hypoaesthesia, psychomotor hyperactivity, parosmia, syncope

Eye disorders

Uncommon	visual impairment

Ear and labyrinth disorders

Uncommon	ear disorder, vertigo
Frequency not known	deafness, hypoacusis, tinnitus

Cardiac disorders

Uncommon	palpitations
Frequency not known	torsades de pointes, arrhythmia including ventricular tachycardia, prolonged QT interval

Vascular disorders

Uncommon	hot flush

Frequency not known	hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon	dyspnoea, respiratory disorder, epistaxis

Gastrointestinal disorders

Very common	diarrhoea
Common	vomiting, abdominal pain, nausea
Uncommon	gastritis, constipation, dyspepsia, dysphagia, abdominal distension, dry mouth, mouth ulceration, salivary hypersecretion, eructation, flatulence
Frequency not known	pancreatitis, pseudomembranous colitis, tongue discoloration

Hepatobiliary disorders

Uncommon	increased aspartate aminotransferase, increased alanine aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase
Rare	abnormal hepatic function, jaundice cholestatic
Frequency not known	hepatic failure, hepatitis fulminant, hepatic necrosis

Skin and subcutaneous tissue disorders

Uncommon	rash. pruritus, urticaria, dermatitis, dry skin, hyperhidrosis
Rare	acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), photosensitivity reaction
Frequency not known	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Musculoskeletal and connective tissue disorders

Uncommon	osteoarthritis, myalgia, back pain, neck pain
Frequency not known	arthralgia

Renal and urinary disorders

Uncommon	dysuria, renal pain, increased blood urea, increased blood creatinine
Frequency not known	acute kidney injury, tubulointerstitial nephritis

Reproductive system and breast disorders

Uncommon	intermenstrual bleeding, testicular disorder

General disorders and administration site conditions

Uncommon	oedema, asthenia, malaise, fatigue, face oedema, chest pain, pyrexia, pain, peripheral oedema

Investigations

Common	blood bicarbonate decreased
Uncommon	abnormal blood potassium, increased blood chloride, increased blood glucose, increased blood bicarbonate, abnormal blood sodium

Adverse reactions associated with longer term use

When azithromycin has been used long-term, for example in the prophylaxis and treatment of *Mycobacterium avium* complex infections in people living with HIV, additional side effects have been reported including abdominal discomfort and hepatitis. However, [NT020 trade name] is not indicated for such use.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

Adverse reactions experienced with higher than recommended doses were similar to those seen at normal doses (see section 4.8). The typical symptoms of an overdose with azithromycin include gastrointestinal symptoms, i.e. vomiting, diarrhoea, abdominal pain and nausea.

Treatment

In the event of an overdose, general symptomatic treatment and support of vital functions are indicated and, if required, administration of medicinal charcoal or gastric lavage.

There are no data on the effects of dialysis on the elimination of azithromycin. However, due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antibacterials for systemic use, macrolides; ATC-code: J01FA10

Mechanism of action

The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides.

Pharmacokinetic/pharmacodynamic relation

The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC (minimum inhibitory concentration) of the causative organism.

Mechanisms of resistance

Resistance against azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).
- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA causing a resistance against macrolides (M), lincosamides (L) and streptogramins of

the B-group (SB) (so called MLSB-phenotype). Resistance-conferring methylases are encoded by *erm* genes. Affinity to ribosomal binding sites is also lowered by mutations in the 23S rRNA target structure or by mutations in the large subunit ribosomal proteins.

- Enzymatic inactivation of macrolides is only of minor clinical interest.

With the M-phenotype a complete cross-resistance between azithromycin, clarithromycin, erythromycin and roxithromycin is observed. The MLSB-phenotype shows an additional cross- resistance with clindamycin and streptogramin B. With the 16-ring-membered macrolide spiramycin a partial cross-resistance is exerted.

Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides.

Prevalence of acquired resistance

The prevalence of acquired resistance may vary geographically and with time for selected species. Thus local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought as necessary when the local prevalence of resistance is such that the utility of the agent may be questionable.

After therapeutic failure and in severe infections in particular, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to azithromycin should be sought.

5.2 Pharmacokinetic properties

Absorption of [NT020 trade name]

The absorption characteristics of [NT020 trade name] have been determined after administration of one Azithromycin 500 mg film-coated tablet in healthy volunteers under fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**
Maximum concentration (C_{max})	502 ± 173 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	4996 ± 1601 ng·h/mL
Time to attain maximum concentration (T_{max})	2.37 (±1.10) hours

Pharmacokinetics of azithromycin

* Information not available

Absorption	
Absolute bioavailability	37%
Oral bioavailability	NA*
Food effect	A similar exposure was obtained with high-fat meal vs. fasted conditions.
Distribution	
Volume of distribution (mean)	23 to 31 L
Plasma protein binding *in vitro*	Protein binding (mainly to alpha 1-acid glycoprotein) decreases with increasing concentrations: 50%, 23% and 7% protein binding at concentrations of 0.05, 0.1 and 1 mg/L, respectively.
Tissue distribution	Extensive distribution into tissue including tonsil, lung and gynaecological tissue was well as intracellular compartments, in particular polymorphonuclear leukocytes, macrophages and monocytes.
Metabolism	
	Azithromycin is minimally metabolised in the liver. The primary route of biotransformation is N-demethylation of the desosamine sugar. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring.
Active metabolite(s)	None
Elimination	
Elimination half life	68 h
Mean systemic clearance (Cl/F)	37.8 L/h
% of dose excreted in urine	<6% as unchanged drug
% of dose excreted in faeces	NA*
Pharmacokinetic linearity	Linear pharmacokinetic in the range of 250 mg to 1000 mg
Drug interactions *(in vitro)*	
Transporters	azithromycin is an inhibitor of P-gp
Metabolising enzymes	azithromycin is a weak inhibitor of CYP3A4

Renal impairment

Azithromycin pharmacokinetics was investigated in 43 adults (21 to 85 years of age) following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules) to subjects with GFR >80

ml/min (n =12), subjects with GFR between 10 and 80 ml/min (n = 12) and subjects with GFR <10 ml/min (n = 19).

The pharmacokinetics of azithromycin in subjects with GFR between 10 and 80 ml/min were not affected (mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with GFR <10 ml compared to subjects with GFR >80 ml/min.

No data are available for subjects undergoing dialysis, but due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

Hepatic impairment

Azithromycin pharmacokinetics was investigated in 22 adults following the oral administration of a single 500 mg dose of azithromycin (2 x 250 mg capsules) to subjects with normal hepatic function (n = 6), Child-Pugh A (n = 10) and Child-Pugh B (n = 6). The pharmacokinetics of azithromycin in subjects with Child-Pugh A and B were 3% and 19% lower on AUC_{0-inf} and 34% and 72% higher on C_{max}, respectively, compared to subjects with normal hepatic function.

Elderly

In elderly volunteers (> 65 years) given azithromycin 500 mg (2 x 250 mg capsules) on day 1 followed by 250 mg from days 2 to 5 in the fasted state the AUC_{0-24} on Days 1 and 5 were 3.0 and 2.7 μg•h/ml, respectively. A 29% higher AUC_{0-24}, a 8% higher C_{max} and a 37.5% higher T_{max} than in younger volunteers (<40 years) were observed at day 5. Since these differences are not considered clinically significant, no dose adjustment is required for elderly subjects with normal renal and hepatic function.

Paediatric population

The pharmacokinetics of azithromycin oral suspension have been characterised in 14 children aged 6 to15 years with pharyngitis and in 7 children aged 1 year to 5 years with otitis media. In these two studies, azithromycin oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5. Following 5 days of treatment, mean AUC_{0-24} values were 3.1 μg•h/ml and 1.8 μg•h/ml, respectively. The mean C_{max} value was 0.38 μg/ml and the corresponding mean T_{max} value was 2.4 hours in children aged 6 to 15 years and 0.22 μg/ml and 1.9 hours for children 1 to 5 years of age. The mean C_{max} and AUC_{0-24} values are 1.7 times greater in children 6 to 15 years of age than in children 1 to 4 years of age.

The PK of a 3-day course of azithromycin oral suspension at a dose of 10 mg/kg daily was also assessed in 16 children 6 months to 10 years with bacterial infections. The mean AUC_{0-24} for 7 children aged 2 to 4 years was 2.90 μg•h/ml while for the 8 children aged 5 to 10 years the value was 2.08 μg•h/ml. A low AUC_{0-24} value of 0.74 μg•h/ml was recorded for a single child in the 6 months to 2-year-old group.

Single dose pharmacokinetics of azithromycin in paediatric patients with given doses of 30 mg/kg have not been studied.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity did not indicate adverse reactions clearly relevant to humans not already considered in other sections of this document.

However, phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues 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 significance of this finding for humans is unknown.

In animal studies for embryotoxic effects performed up to moderately maternal toxic doses (2 to 3 times the maximum recommended adult daily dose of 500 mg based on body surface area), no teratogenic effect was observed in mice and rats. Azithromycin was shown to cross the placenta. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day (2 to 3 times the maximum recommended adult daily dose of 500 mg based

on body surface area) led to mild retardation of fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with azithromycin doses of 200 mg/kg/day (3 times the maximum recommended adult daily dose of 500 mg based on body surface area) was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Dicalcium phosphate
Pregelatinized starch
Croscarmellose sodium
Hypromellose
Sodium lauryl sulfate
Magnesium stearate
Lactose monohydrate

Film coat: Hypromellose
Titanium dioxide
Macrogol/PEG
Talc
Sodium lauryl sulphate

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per *tablet*.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC. Avoid excursions above 30ºC. Protect from light and moisture.

6.5 Nature and contents of container

Clear colourless plastic (PVC or PVC/PVDC) on aluminium foil blister cards, each containing 3 tablets. Available in cartons of 10 x 3 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

NT020

9. DATE OF PREQUALIFICATION

19 December 2025

10. DATE OF REVISION OF THE TEXT

March 2026

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