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**No. UA/10672/01/02**

# INSTRUCTION
## for medical use

## ZIOMYCIN®

***Composition:***
*active substance*: azithromycin;
1 tablet contains azithromycin dihydrate equivalent to 250 mg or 500 mg of azithromycin;
*excipients:* microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, povidone K 90, talc, magnesium stearate, coating Opadry 04B52069 Yellow: hypromellose, titanium dioxide (E 171), quinoline yellow (E 104), polyethylene glycols.

**Pharmaceutical form.** Film coated tablets.
*Basic physicochemical properties:*
*tablets 250 mg:* capsule-shaped, film-coated, yellow tablets, with logo "A 250" on one side and smooth on the other.
*tablets 500 mg:* capsule-shaped, film-coated, yellow tablets, with logo "A 500" on one side and smooth on the other.

**Pharmacotherapeutic group.**
Antibacterial agents for systemic use. Macrolides, lincosamides and streptogramins. Azithromycin. ATC code J01F A10.

***Pharmacological properties.***
*Pharmacodynamics.*
Azithromycin is a macrolide antibiotic of azalide group. The molecule is formed as a result of the introduction of nitrogen atom into the lactone ring of erythromycin A.
Azithromycin mechanism of action is a result of protein synthesis inhibition due to binding with 50S-subunit of ribosomes and inhibition of peptides translocation.
The mechanism of resistance.
The complete cross-resistance exists among *Streptococcus pneumoniae*, group A beta-hemolytic streptococci, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), to erythromycin, azithromycin, other macrolides and lincosamides.
The prevalence of acquired resistance may vary depending on location and time for selected species; local information on resistance is desirable, particularly when treating severe infections. If necessary, expert advice should be sought when the local prevalence of resistance is such as efficacy of the agent in at least some types of infections is questionable.
*The spectrum of azithromycin antimicrobial activity.*

| **Usually sensitive species** |
|---|
| **Aerobic gram-positive bacteria** |

| |
|---|
| *Staphylococcus aureus* methicillin-sensitive<br>*Streptococcus pneumoniae* penicillin-sensitive<br>*Streptococcus pyogenes* |
| **Aerobic gram-negative bacteria** |
| *Haemophilus influenzae*<br>*Haemophilus parainfluenzae*<br>*Legionella pneumophila*<br>*Moraxella catarrhalis*<br>*Pasteurella multocida* |
| **Anaerobic bacteria** |
| *Clostridium perfringens*<br>*Fusobacterium spp.*<br>*Prevotella spp.*<br>*Porphyriomonas spp.* |
| **Other microorganisms** |
| *Chlamydia trachomatis*<br>*Chlamydia pneumoniae*<br>*Mycoplasma pneumonia* |
| **Species for which acquired resistance may be a problem** |
| **Aerobic gram-positive bacteria** |
| *Streptococcus pneumonia* with intermediate penicillin resistance and penicillin-resistant |
| **Congenitally resistant organisms** |
| **Aerobic gram-positive bacteria** |
| *Enterococcus faecalis*<br>Staphylococci **MRSA, MRSE*** |
| **Anaerobic bacteria** |
| *Bacteroides fragilis* group |

*Methycillin-resistant staphylococcus has a very high prevalence of acquired resistance to macrolides and has been mentioned here because it is rarely susceptible to azithromycin.

*Pharmacokinetics.*
Bioavailability after oral administration is approximately 37%. Peak blood serum concentration is attained 2–3 hours after taking the medicinal product. 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 blood plasma, which indicates that the agent strongly binds to tissues.
Binding to blood serum proteins varies according to plasma concentrations and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram/ml in blood serum. Apparent volume of distribution at steady state ($VV_{ss}$) has been calculated to be 31.1 l/kg.
The terminal plasma elimination half-life closely reflects the elimination half-life from tissues within 2–4 days.
Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following 3 days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, 10 metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

**Clinical characteristics.**
***Indications.***

Infections caused by microorganisms, sensitive to azithromycin:
• ENT-organs infections (bacterial pharyngitis/tonsillitis, sinusitis, otitis media);
• respiratory tract infections (bacterial bronchitis, community acquired pneumonia);
• skin and soft tissues infections: erythema migrans (initial stage of Lyme disease), erysipelas, impetigo, secondary pyoderma, minor forms of acne vulgaris;
• sexually transmitted infections: uncomplicated genital infections, caused by *Chlamydia trachomatis*.

***Contraindications.***
Hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics, as well as to any other excipients.

***Interactions with other medicinal products and other forms of interaction.***
*Antacids.* In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations of azithromycin were reduced by approximately 25%. Azithromycin and antacids should not be taken at the same time.
*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.
*Didanosine*. Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive volunteers had no effect on the steady state pharmacokinetics of didanosine as compared with placebo.
*Digoxin and colchicine*. It was reported that concomitant use of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine leads to increased substrate of P-glycoprotein in blood serum. Consequently, in a case of the concurrent use of azithromycin and P-glycoprotein substrates such as digoxin the possibility of increased blood serum concentration of digoxin should be considered.
*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 metabolites. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of these findings is unclear, but they can be useful in treating 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.
*Ergots.* 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 below mentioned drugs known to undergo significant cytochrome P450 mediated metabolism.
*Atorvastatin.* Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the blood plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition analysis). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.
*Carbamazepine*. In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolites.
*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 observed.

*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 is data on potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal connection 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.
*Cyclosporine.* 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 $C_{max}$ and $AUC_{0-5}$ were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporine levels should be monitored and the dose adjusted accordingly.
*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.
*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 $C_{max}$ (18%) of azithromycin was observed.
*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 midazolam administered as a single dose of 15 mg.
*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*. Co-administration of azithromycin and rifabutin did not affect the serum concentrations of these drugs. 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. In some cases 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*. Co-administration of azithromycin 500 mg on day 1 and 250 mg on day 2 with 0.125 mg of triazolam had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.
*Trimethoprim/sulfamethoxazole.* Co-administration of trimethoprim/sulfamethoxazole double concentration (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*. Azithromycin should be used with caution in patients receiving drugs that prolong the QT interval and may cause cardiac arrhythmia, such as hydroxychloroquine.

***Administration details.***

*Hypersensitivity.*
As with erythromycin and other macrolide antibiotics, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these azithromycin-induced reactions have resulted in recurrent symptoms and required a longer period of observation and treatment.
*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 a history of liver 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 investigations should be performed immediately.
In case of abnormal liver function azithromycin should be discontinued.
*Ergots.*
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-administrated.
*Prolongation of the QT interval.*
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and atrial fibrillation or flutter (*torsade de pointes*), have been seen in treatment with other macrolide antibiotics including azithromycin. Since conditions associated with an increased risk of ventricular arrhythmias (including *torsade de pointes*) may lead to cardiac arrest, azithromycin should be used with caution in patients with already existing proarrhythmic conditions (especially women and the elderly), including:
• with congenital or documented QT interval prolongation;
• currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA (quinidine and procainamide) and III (dofetilide, amiodarone, sotalol), cisapride and terfenadine, neuroleptics such as pimozide; antidepressants such as citalopram, and fluoroquinolones, such as moxifloxacin and levofloxacin;
• with electrolyte disturbance, particularly in case of hypokalemia and hypomagnesemia;
• 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 (CDAD).*
*Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora in the colon leading to overgrowth of *C. difficile.*
*C. difficile* produces the toxins A and B that develop CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be resistant to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients with diarrhoea associated with the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD occurs, azithromycin therapy should be discontinued and specific treatment for *C. difficile* should be used.

*Streptococcal infections*.
In the treatment of pharyngitis/tonsillitis caused by Streptococcus pyogenes, penicillin is usually the drug of choice, and it is also used prophylactically in 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 (glomerular filtrate rate <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.
*Other.*
Safety and efficacy for the prevention or treatment *Mycobacterium Avium Complex* in children have not been established.
*Excipients*
This medicinal product contains less than 1 mmol (23 mg) sodium/dose, i.e. practically sodium-free.

*Use during pregnancy or breastfeeding.*
Pregnancy
There are no adequate data on the use of azithromycin in pregnant women. Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of toxic effects on the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Therefore, azithromycin is prescribed during pregnancy only if the benefit outweighs the risk.
Breast feeding.
It has been reported that azithromycin is excreted in human milk, but adequate and well-controlled clinical studies have not been conducted to characterize the pharmacokinetics of azithromycin excretion in human milk.
Fertility.
Fertility studies were conducted in rats; reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

*Effects on the ability to drive and use machines.*
There is no evidence to suggest that azithromycin may impair the ability to drive a car or operate other mechanisms, but the possibility of developing side reactions such as delirium, hallucinations, dizziness, drowsiness, fainting, convulsions, which may affect the ability to drive vehicles or other mechanisms, should be considered.

***Administration and dosage.***
The drug should be used once daily regardless of meals. Swallow the tablets without chewing. If one drug dose has been missed it should be taken as soon as possible, and the next ones at intervals of 24 hours.
Adults and children weighing >45 kg.

| *Indications* | *Total dose* | *Treatment regimen* | | |
|---|---|---|---|---|
| | | *Period* | *Dose* | *Multiplicity* |
| ENT-organs infections, respiratory tract and skin and soft tissues infections | 1500 mg | Day 1 to day 3 | 500 mg | 1 time per day |

| | | | | |
|---|---|---|---|---|
| (except chronic migrating erythema) | | | | |
| Acne vulgaris | 6000 mg | Week 1 (day 1 to day 3) | 500 mg | 1 time per day |
| | | Week 2 to week 10 | 500 mg | 1 time per week * |
| Erythema migrans | 3000 mg | Day 1 | 1000 mg | 1 time per day |
| | | Day 2 to day 5 | 500 mg | 1 time per day |
| Genital infections | 1000 mg | Day 1 | 1000 mg | 1 time per day |

*The week 2 dose should be taken 7 days after the first taken tablet. Week 3 to week 10 doses should be taken in 7 days intervals.

Elderly patients.
Dose adjustment is not required in elderly patients.
Azithromycin should be used with caution in patients with a risk of cardiac conduction disease, because of the possibility of cardiac arrhythmias, including *torsade de pointes*.
Patients with renal failure.
In patients with slightly impaired renal function (glomerular filtration rate is 10–80 ml/min) the dose may be the same as for patients with normal renal function. Azithromycin should be used with caution in patients with severe renal impairment (glomerular filtration rate <10 ml/min).
Patients with hepatic failure.
Since azithromycin is metabolized 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.

*Children.*
The drug should be used in children >45 kg of body weight. For children under 45 kg of body weight an appropriate dosage of azithromycin may be used.

***Overdose.***
*Symptoms:* adverse events experienced in higher than recommended doses were similar to those seen at normal doses. They may include diarrhea, nausea, vomiting and reversible hearing loss.
*Treatment:* the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

***Adverse reactions.***
In the table below, in accordance with organ systems and frequency of occurrence, adverse reactions identified in clinical studies and in the period of post-marketing surveillance, which were observed with the use of all dosage forms of azithromycin, are indicated. Adverse reactions reported during post-marketing surveillance are highlighted in italics. Groups according to the frequency of manifestations were determined according to the following scale: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000); unknown (cannot be determined from available data). Within each group, adverse reactions are listed in order of decreasing severity by frequency of occurrence.

*Adverse reactions possibly or probably related to azithromycin based on data from clinical trials and post-marketing surveillance*

| **Class of systems and organs** | **Adverse reactions** | **Frequency** |
|---|---|---|

| | | |
|---|---|---|
| *Infections and infestations* | Candidiasis, oral candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, impaired respiratory function, rhinitis. | Uncommon |
| | *Pseudomembranous colitis* | Unknown |
| *Blood and lymphatic system disorders* | Leukopenia, neutropenia, eosinophilia | Uncommon |
| | *Thrombocytopenia, hemolytic anemia* | Unknown |
| *Immune system disorders* | Angioedema, hypersensitivity reactions | Uncommon |
| | *Anaphylactic reaction* | Unknown |
| *Metabolism disorders* | Anorexia | Common |
| *Psychiatric disorders* | Nervousness, anxiety | Uncommon |
| | Agitation | Rare |
| | *Aggression, unrest*, delirium, hallucinations. | Unknown |
| *Nervous system disorders* | Headache | Common |
| | Dizziness, drowsiness, dysgeusia, paresthesia | Uncommon |
| | *Fainting, convulsions,* hypoesthesia, *increased psychomotor activity, anosmia, ageusia, parosmia, myasthenia gravis* | Unknown |
| *Eye disorders* | Visual disturbances | Uncommon |
| *Ear disorders* | Hearing disorders, vertigo | Uncommon |
| | Hearing impairment, including deafness and/or tinnitus | Unknown |
| *Cardiac disorders* | Palpitation | Uncommon |
| | *Atrial fibrillation or flutter (torsade de pointes), arrhythmia, including ventricular tachycardia,* prolongation of the QT interval on the ECG | Unknown |
| *Vascular disorders* | Flushing | Uncommon |
| | *Arterial hypotension* | Unknown |
| *Respiratory system disorders* | Dyspnoea, nosebleeds | Uncommon |
| *Gastrointestinal tract disorders* | Diarrhoea | Very common |
| | Vomiting, abdominal pain, nausea | Common |
| | Constipation, meteorism, dyspepsia, gastritis, dysphagia, flatulence, sores in the mouth, belching, mouth ulcers, hypersecretion of saliva | Uncommon |
| | *Pancreatitis, tongue discoloration* | Unknown |
| *Hepatobiliary disorders* | Hepatic function impairment, cholestatic jaundice | Rare |
| | *Hepatic failure (rarely fatal), fulminant hepatitis, liver necrosis* | Unknown |
| *Skin and subcutaneous tissue disorders* | Rash, itching, urticaria, dermatitis, dry skin, hyperhidrosis | Uncommon |
| | Photosensitivity, *acute generalized exanthematous pustulosis (AGEP)* | Rare |

| | | |
|---|---|---|
| | Stevens-Johnson syndrome, *toxic epidermal necrolysis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms* | Unknown |
| *Musculoskeletal disorders* | Osteoarthritis, myalgia, back pain, neck pain | Uncommon |
| | Arthralgia | Unknown |
| *Urinary system disorders* | Dysuria, renal pain | Uncommon |
| | *Acute renal failure, interstitial nephritis* | Unknown |
| *Reproductive system and breast disorders* | Uterine bleeding, testicular disorders | Uncommon |
| *General disorders and administration site conditions* | Oedema, asthenia, malaise, fatigue, face swelling, chest pain, hyperthermia, pain, peripheral oedema | Uncommon |
| *Laboratory findings* | Reduced number of lymphocytes, increased number of eosinophils, reduced blood bicarbonate, increased basophils, increased monocytes, increased neutrophils | Common |
| | Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium changes, alkaline phosphatase increased, chloride increased, glucose increased, platelet increased, haematocrit level decreased, bicarbonate level increased, sodium level deviation | Uncommon |
| *Lesions and poisoning* | Post procedural complication | Uncommon |

Information on adverse reactions possibly related to the prevention and treatment of *Mycobacterium Avium Complex* is based on data from clinical studies and observations in the post-marketing period. These adverse reactions differ in type or frequency from those reported with the rapid-acting dosage forms and the long-acting dosage forms.

*Adverse reactions possibly related to the prevention and treatment of Mycobacterium Avium Complex*

| **Class of systems and organs** | **Adverse reactions** | **Frequency** |
|---|---|---|
| *Metabolism disorders* | Anorexia | Common |
| *Nervous system disorders* | Dizziness, headache, paresthesia, dysgeusia | Common |
| | Hypoesthesia | Uncommon |
| *Eye disorders* | Visual impairment | Common |
| *Ear disorders* | Deafness | Common |
| | Hearing impairment, ear buzzing | Uncommon |
| *Cardiac disorders* | Palpitation | Uncommon |
| *Gastrointestinal tract disorders* | Diarrhea, abdominal pain, nausea, flatulence, gastrointestinal discomfort, frequent loose stools | Very common |
| *Hepatobiliary disorders* | Hepatitis | Uncommon |
| | Rash, itching | Common |

| | | |
|---|---|---|
| *Skin and subcutaneous tissue disorders* | Stevens-Johnson syndrome, photosensitivity | Uncommon |
| *Musculoskeletal disorders* | Arthralgia | Common |
| *General disorders and administration site conditions* | Increased fatigue | Common |
| | Asthenia, malaise | Uncommon |

Reported suspected adverse reactions.
The reporting of adverse reactions after the registration of the medicinal product is of great importance. This makes it possible to monitor the benefit/risk ratio when using this medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives should be notified of all cases of suspected adverse reactions and lack of efficacy of the medicinal product through the Automated Pharmacovigilance Information System at the link: https://aisf.dec.gov.ua.

***Shelf-life.*** 3 years.

**Storage conditions.**
Store at the temperature below 25ºC.
Keep out of reach of children.

**Package.**
Tablets 250 mg: 6 or 21 tablets in a blister, 1 blister in a carton package.
Tablets 500 mg: 3 tablets in a blister, 1 blister in a carton package.

**Conditions of supply.**
By prescription.

**Manufacturer.**
KUSUM HEALTHCARE PVT LTD.

**Location of manufacturer and its address of its business activity.**
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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