SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICATION DENOMINATION DU MEDICAMENT

AZITRINE 250 mg, coated tablet
AZITRINE 500 mg, coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AZITRINE 250 mg: Azithromycin (in the form of azithromycin dihydrate)……..……....250,00 mg
AZITRINE 500 mg: Azithromycin (in the form of azithromycin dihydrate)……..……....500,00 mg

For one coated tablet

Excipients: Microcrystalline cellulose, corn starch, sodium starch glycolate, sodium benzoate, purified talc, magnesium stearate, isopropyl alcohol, dichloromethane, wincoat WT-1001 white.

3. PHARMACEUTICAL FORM

Coated tablet.

4. CLINICAL DATA

4.1. Therapeutic indications

They derive from the antibacterial activity and pharmacokinetic characteristics of azithromycin. They take into account both the clinical studies conducted with this medication and its place in the range of antibacterial products currently available.
Their use is limited to infections caused by germs defined as susceptible:

· Documented beta-haemolytic streptococcal A angina, as an alternative to beta-lactam therapy, especially when beta-lactam therapy cannot be used,

· Superinfection of acute bronchitis,

· Exacerbation of chronic bronchitis,

· Stomatological infections,

· Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis*.

Official recommendations for the appropriate use of antibacterials should be taken into account.

4.2. Dosage and administration

Dosage

Adult

· Angina, stomatological infections: 500 mg per day for 3 days.

This 3-day regimen is explained by the particular pharmacokinetic properties of azithromycin and the maintenance of activity, in these indications, several days after the last dose.

· Superinfections of acute bronchitis, exacerbations of chronic bronchitis: 500 mg on the first day then 250 mg on the 4 following days. The treatment duration is 5 days.

· Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis*: 1000 mg in one single dose.

Elderly patients

The same dose as in adult patients is used for older people. Since elderly people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointe (see section 4.4).

Patients with hepatic impairment

Same dosage in patients with mild to moderate hepatic impairment (see section 4.4).

Administration

The tablets can be taken indifferently during meals or in one daily dose.

4.3. Contraindications

This medication MUST NEVER BE USED:

· In case of hypersensitivity to azithromycin, erythromycin, any other macrolide, ketolide or to any of the excipients listed in section 6.1,

· In combination with ergot alkaloids: dihydroergotamine, ergotamine (see sections 4.4 and 4.5),

· In combination with cisapride (see section 4.5),

· In combination with colchicine (see section 4.5),

· In case of severe hepatic impairment (see section 4.4).

4.4. Warnings and precautions

QT interval prolongation

Cases of cardiac repolarization prolongation and QT interval prolongation, implying a risk of cardiac arrhythmia and torsade de pointes, have been observed during treatment with macrolides, including azithromycin (see section 4.8). As the following conditions may lead to an increased risk of ventricular arrhythmia (including torsade de pointes), which may lead to death, caution should be exercised when treating the following patients with azithromycin:

· Patients with congenital or documented QT interval prolongation.

· Patients currently being treated with other active substances known to prolong the QT interval (see section 4.5).

· Patients with an electrolyte disorder, especially in cases of hypokalaemia and hypomagnesaemia.

· Patients with clinically significant bradycardia, cardiac arrhythmia, or severe heart failure.

Women and elderly patients may also be more sensitive to treatments that prolong the QT interval.

Hypersensitivity

As is the case with erythromycin and other macrolides, rare serious allergic reactions such as angioedema and anaphylactic reactions (rarely fatal) have been reported. As recurrence of symptoms is likely even after discontinuation of symptomatic treatment, prolonged monitoring and extended treatment may be required.

Skin reactions

Furthermore, serious life-threatening skin reactions such as cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome (drug hypersensitivity syndrome with eosinophilia and systemic symptoms) have been reported. Patients should be advised to monitor for skin effects

and suggestive signs and symptoms, which usually appear within the first weeks of treatment. In the event of suggestive symptoms (e.g. progressive rash often associated with mucosal lesions or blisters), azithromycin should be discontinued immediately. Treatment must not be reintroduced.

Hepatotoxicity

As the liver is the major route of elimination of azithromycin, patients with severe hepatic impairment or patients with severe cholestasis should not be treated with azithromycin.
Cases of fulminant hepatitis leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing liver disease or may have taken other hepatotoxic drugs.
Liver function tests should be performed immediately if signs or symptoms of impaired liver function occur, such as rapid onset of asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Azithromycin should be discontinued immediately if liver dysfunction occurs.

***Clostridium difficile* infection**

Cases of C Difficile Infections (CDI, formerly C. difficile associated diarrhoea or CDAD) have been reported with the use of virtually all antibiotics, including azithromycin. Their severity can range from mild diarrhoea to life-threatening pseudomembranous colitis. Antibiotic treatment alters the flora of the colon, leading to overgrowth of C. difficile.
C. *difficile* produces toxins A and B, which contribute to the development of CDI. These toxin-producing strains increase morbidity and mortality, as infections may be refractory to antibiotic treatment and require colectomy. CDI should be considered in all patients who develop diarrhoea after antibiotic use. It is important that this diagnosis is considered in patients who develop diarrhoea during or after antibiotic use, as cases have been reported up to 2 months after stopping the treatment.

Myasthenia

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

Superinfection

As with all antibiotics, it is recommended to monitor for signs of superinfection by non-susceptible organisms, including fungi.

Rye ergot derivatives

During treatment with ergot derivatives, some concomitant macrolide antibiotics have precipitated ergotism. There is no existing data on a possible interaction between ergot and azithromycin. However, given the theoretical risk of ergotism, ergot derivatives and azithromycin should not be co-administered (see sections 4.3 and 4.5).

Hypertrophic pyloric stenosis in infants

Cases of hypertrophic pyloric stenosis in infants have been reported with the use of azithromycin in new-borns (treatment up to 42 days of life). Parents and caregivers should be instructed to contact the physician if vomiting or hyper-reactivity to food occurs.

Renal insufficiency

In patients with severe renal impairment (glomerular filtration rate < 10 ml/min), a 33% increase in systemic exposure to azithromycin has been observed.
No dosage adjustment is required in patients with mild renal impairment (creatinine clearance > 40 ml/min). In patients with creatinine clearance below 40 ml/min, azithromycin should be prescribed with caution.

Due to excipients

This medication contains lactose. It should not be used in patients with galactose intolerance, Lapp lactase deficiency or glucose or galactose malabsorption syndrome (a rare hereditary disease).

4.5. Interactions with other medication and other forms of interactions

Contraindicated combinations

+ **Cisapride**
Increased risk of ventricular arrhythmias, in particular torsades de pointes.
+ **Colchicine**
Increase of colchicine side effects with potentially fatal consequences.
+ **Dihydroergotamine (see section 4.4)**
Ergotism with possible necrosis of the extremities (inhibition of hepatic elimination of ergot alkaloids).
+ **Ergotamine (see section 4.4)**
Ergotism with possible necrosis of the extremities (decreased hepatic elimination of ergot alkaloids).

Non-recommended combinations

+ **Ergot alkaloid dopamine**
(Bromocriptine, cabergoline, lisuride, pergolide)
Increased plasma concentrations of dopaminergic with possible increase in its activity or appearance of signs of overdose.

Combinations subject to precautions for use

+ **Atorvastatine**
Increased risk of adverse effects (concentration-dependent) such as rhabdomyolysis, due to a reduction in the hepatic metabolism of the cholesterol-lowering agent.
Use lower doses of cholesterol-lowering medication or another statin not affected by this type of interaction.
+ **Ciclosporin**
Risk of increased ciclosporin blood concentration and serum creatinine concentration.
Measure ciclosporin blood concentrations, monitor renal function and adjust dosage during the combination and after discontinuation of the macrolide.
+ **Digoxin**
Increased serum digoxin levels due to the increased absorption of digoxin.
Clinical and possibly blood digoxin monitoring during and after azithromycin therapy are required.

+ **Medications that may cause torsades de pointes:** especially class IA (e.g. quinidine) and class III (e.g. amiodarone, sotalol) antiarrhythmic medications, antipsychotics (e.g. phenothiazines, pimozide), tricyclic antidepressants (e.g. citalopram), certain fluoroquinolones (e.g. moxifloxacin, levofloxacin). Hypokalaemia (hypokalaemic medications) is a favourable factor, as well as bradycardia (bradycardic medication) or pre-existing QT interval prolongation, congenital or acquired (see section 4.4).
Increased risk of ventricular rhythm disorders, including torsades de pointes.
Clinical and electrocardiographic monitoring during combination
+ **Simvastatin**
Increased risk of rhabdomyolysis-like (concentration-dependent) adverse effects due to decreased hepatic metabolism of the cholesterol-lowering agent.
Use lower doses of cholesterol-lowering agent or another statin not affected by this type of interaction.
+ **Antivitamin K**
Increased effect of antivitamin K and increased risk of bleeding.
More frequent monitoring of INR. Possible adjustment of antivitamin K dosage during treatment with macrolide and after its discontinuation.

Special problems of INR imbalance

Many cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics. The infectious or inflammatory context, the age and the general condition of the patient appear to be risk factors. In these circumstances, it appears difficult to distinguish between the infectious pathology and its treatment in the occurrence of INR imbalance. However, certain classes of antibiotics are more likely to be the cause of this imbalance, these include: fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

4.6. Fertility, pregnancy and lactation

Pregnancy

1st trimester:
As a safety measure it is better not to use azithromycin during the first trimester of pregnancy. Indeed, though animal data in rodents do not show any malformative effect, clinical data are insufficient.

From the 2nd trimester:
Due to the expected benefit, the use of azithromycin may be considered from the second trimester of pregnancy if necessary. Indeed, although they are limited, the clinical data are reassuring in case of use beyond the first trimester.

Lactation

No data on the passage in human milk.
The safety and effectiveness of azithromycin in women breast-feeding has not been established, therefore, it should be used only if the benefits outweigh the risks.

4.7. Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery. However, patients should be made aware that they may experience side effects during treatment with azithromycin, such as dizziness, sleepiness, visual or hearing impairment. Therefore, caution should be used when driving or operating machinery.

4.8. Side effects

The table below lists the adverse reactions identified through clinical experience and post-marketing surveillance by system organ class and frequency. 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); unknown (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Side effects possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

	Very common (≥ 1/10)	**Common (≥ 1/100 à < 1/10)**	**Uncommon (≥ 1/1 000 à < 1/100)**	**Rare (≥ 1/10 000 à < 1/1 000)**	**Very rare (< 1/10 000)**	**Unknown**
Infections et infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis			Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopenia Neutropenia Eosinophilia			Thrombocytopenia Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity			Anaphylactic reaction (See section

						4.4)
Metabolism and nutrition disorders			Anorexia			
Psychiatric disorders			Nervousness Insomnia	Agitation		Aggression Anxiety Delirium Hallucination
Nervous system disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia			Syncope, convulsion Hypoesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4))
Eye disorders			Visual impairment			
Ear and labyrinth disorders			Ear disorder Vertigo			Hearing impairment including deafness and/or tinnitus
Cardiac disorders			Palpitations			Torsades de pointes Arrhythmia including ventricular tachycardia Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis			
Gastrointestinal disorders	Diarrhoea	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion			Pancreatitis Tongue discolouration

Hepatobiliary disorders				Hepatic function abnormal Jaundice cholestatic		Hepatic failure (which has rarely resulted in death) Hepatitis fulminant Hepatic necrosis (See section 4.4)
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction	DRESS (drug reaction with eosinophilia and systemic symptoms)	Steven-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain			Arthralgia
Renal and urinary disorders			Dysuria Renal pain			Renal failure acute Nephritis interstitial
Reproductive system and breast disorders			Metrorrhagia Testicular disorder			
General disorders and administration site conditions			Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema			
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline			

			phosphatase increased Chloride increased Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal sodium			
Injury and poisoning			Post procedural complication			

Reporting of suspected side effects

It is important to report suspected side effects after authorisation of the medicinal product. This allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

The side effects observed with higher dosage were similar to those observed with recommended dosage.
Treatment in case of overdose: gastric lavage and general symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIBACTERIALS FOR SYSTEMIC USE, ATC code: J01FA10 (J: Anti-infectious)
Macrolide antibiotic.
Azithromycin is the first molecule of the class of azalide antibiotics (macrolide family).
Azithromycin works by inhibiting bacterial protein synthesis by binding to the 50 S part of the ribosome and preventing peptide translocation.

Spectrum of antibacterial activity

Critical concentrations separate sensitive strains from strains of intermediate sensitivity and the latter from resistant ones.
S ≤0,5 mg/l and R > 4 mg/l
The prevalence of acquired resistance may vary geographically and over time for some species. It is therefore useful to have information on the prevalence of local resistance, especially for the treatment of severe infections. These data can only provide an orientation on the probabilities of the sensitivity of a bacterial strain to this antibiotic.
When the variability of the prevalence of resistance in France is known for a bacterial species, it is indicated in the table below:

Categories	**Frequency of resistance acquired in France (> 10 %) (extreme values)**
SUSCEPTIBLE SPECIES **Gram-positive aerobic** *Bacillus cereus* *Corynebacterium diphtheriae* Enterococci *Rhodococcus equi* *Staphylococcus meti*-S *Staphylococcus meti*-R* *Streptococcus* B	 50 – 70 % 70 – 80 %

Non-groupable *Streptococcus* *Streptococcus pneumoniae* *Streptococcus pyogenes* **Gram negative aerobic** *Bordetella pertussis* *Branhamella catarrhalis* *Campylobacter* *Legionella* *Moraxella* **Anaerobes** *Actinomyces* *Bacteroides* *Eubacterium* *Mobiluncus* *Peptostreptococcus* *Porphyromonas* *Prevotella* *Propionibacterium acnes* **Others** *Borrelia burgdorferi* *Chlamydia* *Coxiella* Leptospires *Mycoplasma pneumoniae* *Treponema pallidum*	30 – 40 % 35 – 70 % 16 – 31 % 30 – 60 % 30 – 40 %
Categories	Frequency of resistance acquired in France **(> 10 %) (extreme values)**
MODERATELY SUSCEPTIBLE SPECIES (intermediate sensitivity in vitro) **Gram-negative aerobes** *Haemophilus* *Neisseria gonorrhoeae* **Anaerobes** *Clostridium perfringens* **Others** *Ureaplasma urealyticum*	
RESISTANT SPECIES **Gram-positive aerobes** *Corynebacterium jeikeium* *Nocardia asteroids* **Gram-negative aerobes** *Acinetobacter* *Enterobacteriaceae* *Pseudomonas* **Anaerobes** *Fusobacterium* **Others** *Mycoplasma hominis*	

* The frequency of resistance to methicillin is approximately 30 to 50% of all staphylococci and is found mainly in hospitals.

Cardiac electrophysiology:

QTc interval prolongation was studied in a randomized, placebo-controlled, parallel-group study in 116 healthy volunteers receiving chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg and 1500 mg once daily). Concomitant administration of azithromycin resulted in dose- and concentration-dependent prolongation of the QTc interval. When comparing the results observed between healthy volunteers receiving chloroquine plus azithromycin and those receiving chloroquine alone, it was observed that the maximum means (upper limit of the 95% confidence interval) QTcF

interval were increased by 5 (10) ms, 7 (12) ms and 9 (14) ms respectively with azithromycin doses of 500 mg, 1000 mg and 1500 mg.

5.2. Pharmacokinetic properties

Absorption – distribution

Azithromycin is rapidly absorbed after oral administration.
Tablet absorption is not impacted by food intake.
The plasma peak is reached in 2 to 3 hours.
Kinetic studies have shown tissue levels of azithromycin much higher than plasma levels (up to 50 times the maximum plasma concentration), reflecting the strong tissue affinity of the molecule. It also shows that the overall exposure to 1.5 g of azithromycin administered over 3 or 5 days is similar.
The terminal plasma elimination half-life, a faithful reflection of the tissue depletion half-life, is 2 to 4 days.
Azithromycin is widely distributed in the body: after a single dose of 500 mg, the concentrations observed in the target tissues exceed the MIC90 of the germs most often involved in pulmonary, tonsillar or prostate infections. Macrolides penetrate and accumulate in phagocytes (neutrophils, monocytes, peritoneal and alveolar macrophages).
Intraphagocytic concentrations are high in humans. These properties explain the activity of azithromycin on intracellular bacteria.
In experimental infections, in the active phase of phagocytosis, the quantities of azithromycin released are greater than during the quiescent phase. In animals, this leads to the presence of high concentrations of azithromycin at the site of infection.
Binding to plasma proteins is around 20%.

Elimination

Azithromycin is found mainly in unchanged form in bile and urine.
The liver is the main route of bio-transformation of azithromycin, by N-demethylation. The main route of elimination is biliary.
There is also minor urinary elimination of the product. During a 5-day regimen treatment, the product could be found in the urine from 24 hours up to 3 weeks after intake.

5.3. Preclinical security data

In repeated dose toxicity studies conducted in rats and dogs, phospholipidosis (accumulation of intracellular phospholipids) was observed in several tissues (retina, liver, dorsal root ganglia, gallbladder, kidneys, choroid plexus, spleen, pancreas). Phospholipidosis was observed to a similar degree in the tissues of new-born rats and dogs. This effect was reversible after discontinuation of treatment. The significance of these findings in animals and humans is unknown.
Azithromycin has not been shown to be genotoxic in a battery of appropriate studies. Reproductive toxicity studies did not show any deleterious effect on embryo-foetal development in mice and rats, and on post-natal development in rats.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Microcrystalline Cellulose, Corn Starch, Sodium Starch Glycolate, Sodium Benzoate, Purified Talc, Magnesium Stearate, Isopropyl Alcohol, Dichloromethane, Wincoat WT-1001 White.

6.2. Incompatibilities

Non-applicable.

6.3. Shelf-life

3 years

6.4. Special precautions for storage

Keep away from light, in a dry cool place, below 30°C.

Keep out of reach and sight of children.

6.5. Nature and contents of outer package

AZITRINE 250mg: 6 coated tablets in blister pack (PVC/Aluminium)
AZITRINE 500mg: 3 coated tablets in blister pack (PVC/Aluminium)

6.6. Special precautions for disposal and other handling

No specific requirements.

7. MARKETING AUTHORISATION HOLDER

IMEX PHARMA
Rose Belle Building, Unit 3
Rose Belle Business Park
Mauritius

8. DATE OF REVISION OF THE TEXT

01/04/2022

PRESCRIPTION AND DELIVERY CONDITIONS

List I