Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Zubinal (Metronidazole, Clindamycin & Clotrimazole Suppositories)

2. Qualitative and quantitative composition

Each suppository contains: Metronidazole 500mg, Clindamycin Phosphate Equivalent to Clindamycin 100 mg and Clotrimazole 100 mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Suppository

A white color, torpedo shaped Suppository

4. Clinical particulars

4.1 Therapeutic indications

Zubinal is recommended for the treatment of vaginal infections.

4.2 Posology and method of administration

Posology

Treatment of Bacterial Vaginosis and other gynecological infection: 1 suppository a day for 7 days before sleep.

Method of Administration

The suppositories should be inserted into the vagina, as high as possible. This is best achieved when lying back with legs bent up.

4.3 Contraindications

Hypersensitivity to the components of the preparation.

If you are suffering from any of the following diseases, you should not take Zubinal unless your doctor advises you to do so –

- Ulcerative Colitis
- Liver Disease
- Asthma
- Sexually transmitted diseases
- Abdominal Pain
- Diabetes
- AIDS Dysmorphic Syndrome
- Liver Disease
- Kidney Disease
- Heart Disease
- Diabetes
- Peripheral Neuropathy
- Calcium Deficiency
- Potassium Deficiency
- Coronary Artery Disease (CAD)

4.4 Special warnings and precautions for use

Metronidazole

Patients should be warned that metronidazole may darken urine.

Due to inadequate evidence on the mutagenicity risk in humans , the use of Flagyl for longer treatment than usually required should be carefully considered.

Neuropathy (central and peripheral)

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to the risk of neurological aggravation.

Cockayne syndrome

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Skin and subcutaneous tissue disorders

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, Flagyl treatment must be immediately discontinued.

Interference with laboratory tests

Metronidazole may interfere with certain types of blood test determinations in blood (aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to false negative or an abnormally low result. These analytical determinations are based on a decrease in ultraviolet absorbance, a fact that occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidised to nicotinamide adenine dinucleotide (NAD). The interference is due to the similarity in the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Clindamycin

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally and parenterally administered clindamycin has been associated with severe colitis, which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally

and parenterally administered clindamycin, as well as with topical (dermal) formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of Zubinal Vaginal Suppositories, because approximately 30% of the clindamycin dose is systemically absorbed from the vagina.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Clotrimazole

Before using Zubinal Vaginal Suppository which contains vaginal, medical advice must be sought if any of the following are applicable:

• more than two infections of candidal vaginitis in the last 6 months.
• previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.
• pregnancy or suspected pregnancy.
• aged under 16 or over 60 years.
• known hypersensitivity to imidazoles or other vaginal antifungal products.

Zubinal Vaginal Suppository should not be used if the patient has any of the following symptoms where upon medical advice should be sought:

• irregular vaginal bleeding.
• abnormal vaginal bleeding or a blood-stained discharge.
• vulval or vaginal ulcers, blisters or sores.
• lower abdominal pain or dysuria.
• any adverse events such as redness, irritation or swelling associated with the treatment.
• fever or chills.
• nausea or vomiting.
• diarrhoea.
• foul smelling vaginal discharge.

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of Zubinal.

Zubinal Suppository is to be used as per the label instructions or as suggested by your doctor. This medicine is only for vaginal application. You must wash your hands before and after using it. It is best to use this at bedtime regularly to get the most benefit. If there is any accidental exposure of the medicine to the eyes or mouth, you must

wash immediately. For better efficacy of the medicine, the course of the treatment should be completed even if you feel better. Do not use it more than the recommended dose.

4.5 Interaction with other medicinal products and other forms of interaction

Metronidazole

Alcohol: Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction.

Disulfiram: Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Oral anticoagulant therapy (warfarin type): Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.

Lithium: Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Phenytoin and phenobarbital: Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

5-fluorouracil: Metronidazole reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Ciclosporin: Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

Drugs that prolong QT interval: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval**.**

Clindamycin

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents (atracurium, cisatracurium, doxacurium, mivacurium, pancuronium, pipecuronium, rapacuronium, rocuronium, vecuronium, succinylcholine, tubocurarine, and metocurine) and respiratory drugs (budesonide, formoterol). Therefore, caution should be exercised with concomitant use**.**

Clotrimazole

Concomitant medication with Clotrimazole and oral tacrolimus (FK-506; immunosuppressant) might lead to increased tacrolimus plasma levels and similarly with sirolimus. Patients should thus be closely monitored for signs and symptoms of tacrolimus or sirolimus

overdosage, if necessary, by determination of the respective plasma levels.

4.6 Fertility, pregnancy, and lactation

Pregnancy:

Zubinal Suppository is generally considered safe to use during pregnancy. Animal studies have shown low or no adverse effects to the developing baby; however, there are limited human studies

Lactation:

Zubinal Suppository sheld until the treatment of the mother is completed and the drug is eliminated from her body

If a single dose of Zubinal Suppository is used, it is recommended to hold breastfeeding for 12- 24 hours to allow the removal of the drug.

4.7 Effects on ability to drive and use machines.

Patients should be warned about the potential for drowsiness, dizziness, vertigo, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Metronidazole

The frequency of adverse events listed below is defined using the following convention: *very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).*

Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

Blood and lymphatic system disorders:

Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia

Not known: leucopenia

Immune system disorders:

Rare: anaphylaxis

Not known: angioedema, urticaria, fever

Metabolism and nutrition disorders:

Not known: anorexia

Psychiatric disorders:

Very rare: psychotic disorders, including confusion and hallucinations

Not known: depressed mood

Nervous system disorders:

Very rare:

- encephalopathy (e.g. confusion, vertigo, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and

movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug
• drowsiness, dizziness, convulsions, headaches
Not known:
• during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.
• aseptic meningitis
• vertigo
Eye disorders:
Very rare: vision disorders such as diplopia and myopia, which in most cases, is transient
Not known: optic neuropathy/neuritis
Ear and labyrinth disorders:
Not known: hearing impaired/hearing loss (including sensorineural), tinnitus
Cardiac disorders:
Not known: QT prolongation has been reported (particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval)
Gastrointestinal disorders:
Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea
Hepatobiliary disorders:
Very rare:
• increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice and pancreatitis which is reversible on drug withdrawal
• cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs
Skin and subcutaneous tissue disorders:
Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis (AGEP), pruritis, flushing
Not known: erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), fixed drug eruption
Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia
Renal and urinary disorders:
Very rare: darkening of urine (due to metronidazole metabolite)

Clindamycin

Adverse events with possibility of being caused by clindamycin phosphate vaginal suppositories are as follows:
Urogenital system: Vulvovaginal disorder, vaginal pain, and vaginal moniliasis.
Body as a whole: Fungal infection (1%)

Other rare adverse effects events reported by <1% of patients include:
Urogenital system: Menstrual disorder, dysuria, pyelonephritis, vaginal discharge, and vaginitis/vaginal infection.
Body as a whole: Abdominal cramps, localized abdominal pain, fever, flank pain, generalized pain, headache, localized edema, and moniliasis.
Digestive system: Diarrhea, nausea, and vomiting.
Skin: Nonapplication-site pruritis, rash, application-site pain, and application-site pruritis.

Clotrimazole

Frequency not known. As the listed undesirable effects are based on spontaneous reports, assigning accurate frequency of occurrence for each is not possible.
Immune system disorders: Anaphylactic reaction, angioedema, hypersensitivity.
Vascular disorder: syncope, hypotension.
Respiratory, thoracic and mediastinal disorders: dyspnea.
Gastrointestinal disorders: abdominal pain, nausea
Skin and Subcutaneous Tissue Disorders: Rash, urticaria, pruritus.
Reproductive system and breast disorders:
Vaginal exfoliation, vaginal discharge, vaginal haemorrhage, vulvovaginal discomfort, vulvovaginal erythema, vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal pain.
General disorders and administration site conditions: application site irritation, oedema, pain.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

No risk of acute intoxication is seen as it is unlikely to occur following a single vaginal or dermal application of an overdose (application over a large area under conditions favorable to absorption) or inadvertent oral ingestion. There is no specific antidote.
Symptoms of overdose may include: severe headache, tiredness, dizziness, mental/mood changes (such as irritability, depression), vision changes (such as double vision, blurred vision), dry/peeling skin, bone/joint pain, loss of appetite, yellowing skin/eyes, dark urine, severe stomach/abdominal pain.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Clindamycin Phosphate:
Clindamycin works primarily by binding to the 50s ribosomal subunit of bacteria. This agent disrupts protein synthesis by interfering with the transpeptidation reaction, which thereby inhibits early chain

elongation. Clindamycin and the related drug lincomycin are often discussed along with the macrolides, but are not chemically related.
Clindamycin may potentiate the opsonization and phagocytosis of bacteria even at subinhibitory concentrations. By disrupting bacterial protein synthesis, clindamycin causes changes in the cell wall surface which decreases adherence of bacteria to host cells and increases intracellular killing of organisms.
Clotrimazole:
Clotrimazole is an antifungal medication commonly used in the treatment of fungal infections of both humans and animals such as vaginal yeast infections, oral thrush, and ringworm. It is also used to treat athlete's foot and jock itch.
Clotrimazole is a broad-spectrum antifungal which binds to phospholipids in the cell membrane altering cell wall permeability causing a loss in essential intracellular elements.
Metronidazole:
Metronidazole has antiprotozoal and antibacterial actions and is effective against Trichomonas vaginalis and other protozoa including Entamoeba histolytica and Giardia lamblia and against anaerobic bacteria.

5.2 Pharmacokinetic properties

Clindamycin Phosphate:
Absorption: ~10% of topically applied drug is absorbed systemically.No significant levels are seen in CSF, even with inflamed meninges; crosses the placenta; distributes into breast milk; high concentrations in bone and urine. Metabolism: Hepatic
Elimination: Most of drug eliminated by hepatic metabolism
Clotrimazole:
Absorption: Negligible through intact skin (topical); 3-10% (vaginal).
Metabolism: Hepatic; converted to inactive metabolites.
Excretion: Urine, faeces (as metabolites).
Metronidazole:
Metronidazole is rapidly and almost completely absorbed on administration of Metronidazole; peak plasma concentrations occur after 20 min to 3 hours.
The half-life of metronidazole is 8.5 ± 2.9 hours. Metronidazole can be used in chronic renal
failure; it is rapidly removed from the plasma by dialysis.
Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants

5.3 Preclinical safety data

Metronidazole
Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in

the hamster have given negative results. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans. Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro as well as in rodent or humans in vivo, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative.

Cindamycin
Long-term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative. Fertility studies in rats treated orally with up to300 mg/kg/day (31 times the human exposure based on mg/m2) revealed no effects on fertility or mating ability

Clotrimazole
Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.
Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced foetal weights and decreased pup survival.
In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0.4 by 24 hrs.

6. Pharmaceutical particulars

6.1 List of excipients
PEG-6000
Paraffin
Titanium dioxide

6.2 Incompatibilities
Not Applicable**.**

6.3 Shelf life
36 Months

6.4 Special precautions for storage:
Store below 30℃

6.5 Nature and contents of container
1 strips of 3 Suppositories in one carton.

6.6 Special precautions for disposal and other handling:

No special requirements.

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

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Company Name:	AVETINA LIFESCIENCES LTD
Address:	P.O Box 3328-00506,Nairobi
Country:	**Kenya**

Manufacturing site address:

Company name:	GALEN PHARMACEUTICALS LTD.
Address:	Plot No. 334/5 G.I.D.C. Estate Waghodia
Country	India

8. Marketing authorization number

CTD10156

9. Date of first registration

22/08/2023

10. Date of revision of the text:

15/09/2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable