# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

**ORNOVEL 500 mg / 200 mg film-coated tablets**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ornidazole ..... 500 mg
Ofloxacin ..... 200 mg

For a film-coated, scored tablet.

Excipients with known effects: starch

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

ORNOVEL film-coated tablets are a combination of an antibiotic from the quinolone family and an antibacterial, indicated for the treatment of the following bacterial infections.
Particular attention should be paid to available information on bacterial resistance to ofloxacin before initiating treatment. Official recommendations regarding the appropriate use of antibacterial agents should be taken into account.

This medication is indicated in the following cases:

•Certain urinary tract infections (bladder and kidney infections),

•Certain infections of the genital tract in men and women (for example: gonorrhea, a sexually transmitted disease),

•Certain infections of the bones and joints,

•Certain respiratory tract infections,

•Certain sinus infections,

•Certain skin infections,

•In case of exposure to anthrax.

•Amoebiasis (parasitic disease with diarrhea and abdominal pain);

• Urogenital trichomoniasis (parasitic urinary tract infection);

• Lambliasis (parasitic disease with diarrhea and asthenia );

•Infection with susceptible germs linked to a medical-surgical procedure;

•As a preventative measure against infection with susceptible germs related to a surgical procedure;

•As a follow-up to injectable treatments.

More generally, ORNOVEL film-coated tablets will be indicated in the following cases:

•Certain infections of the genital tract in men and women
-Gonorrhea
-Cystitis
-Urinary tract infection

-Pyelonephritis
-Prostatitis
-Amoebiasis (parasitic disease with diarrhea and abdominal pain)
-Urogenital trichomonas (parasitic urinary tract infection)
-Glyphaly (parasitic disease with diarrhea and asthenia)
-Infection with susceptible organisms linked to a medical-surgical procedure
-As a preventative measure against infection with susceptible organisms related to a surgical procedure
-As a follow-up to injectable treatments.

## 4.2. Posology and method of administration

**Posology ORNOVEL 500 mg / 200 mg**

Amoebiasis: 2 tablets per day for 3 days

Trichomoniasis : 2 tablets per day for 5-7 days

Giardiasis: 2 tablets per day for 5-7 days

Treatment of anaerobic bacterial infections (as first-line or follow-up treatment): 2 tablets for 7-10 days

Prevention of postoperative anaerobic bacterial infections (as first-line or follow-up treatment): preoperative: 1 tablet approximately 12 hours before the procedure; postoperative: 1 tablet every 12 hours for 3 days

Prostatitis: 2 tablets per day for 2-4 weeks

Cystitis: 2 tablets per day for 3 days

Urethritis: 2 tablets per day for 7 days

Gonorrhea: 2 tablets in 1 dose

Pyelonephritis: 2 tablets for 7-10 days

Pelvic inflammatory disease: 2 tablets per day for 2 weeks

Orchi-epididimyte : 2 tablets per day for 2 weeks

**Method of administration**

Oral route.
Swallow the tablets with a glass of water.
Do not take ORNOVEL at the same time as antacids (see section 4.5)

**Populations particulars**

*In the elderly:*
Age alone does not necessitate a dose adjustment of ofloxacin. However, the dose should be adjusted according to the degree of renal impairment (see section 4.4 QT interval prolongation).

*In patients with renal insufficiency:*
The dosage should be adjusted according to the degree of renal insufficiency by spacing out the doses:

- mild or moderate renal insufficiency (creatinine clearance greater than 20 ml/min ): one dose of 200 mg ofloxacin every 24 hours;

- severe renal insufficiency (creatinine clearance less than or equal to 20 ml/min ): one dose of 200 mg of ofloxacin every 48 hours.

In hemodialysis patients, it is recommended to adjust the dosage.
It is advisable to monitor serum levels of the active ingredient in patients with renal insufficiency and those undergoing hemodialysis.

*In patients with hepatic insufficiency (e.g., cirrhosis with ascites)*
In patients with severe hepatic impairment, a dose reduction and/or an extension of the dosing interval are recommended (see section 5.2).

## 4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

This medication should never be used:

 in patients with hypersensitivity to ornidazole or to another active substance in the imidazole family

- in patients with hypersensitivity to ofloxacin, other quinolones or to any of the excipients listed in section 6.1;
- in epileptic patients;
- in patients with a history of tendinopathy related to quinolone administration;
- in children or adolescents during their growth period* (see section 4.4);
- in pregnant or breastfeeding women* (see section 4.6).

* Based on data observed in animal experimentation, a risk of cartilage damage in growing beings cannot be completely excluded.

## 4.4. Special warnings and precautions for use

The use of ORNOVEL should be avoided in patients who have experienced serious adverse reactions with previous use of quinolone or fluoroquinolone-containing drugs (see section 4.8). Treatment of these patients with ORNOVEL should only be initiated when no alternative treatment is available and after a thorough benefit-risk assessment (see also section 4.3).

**Discontinue treatment in case of ataxia, dizziness or mental confusion.**

**Risks of resistance**

The prevalence of acquired resistance to ofloxacin may vary geographically and over time for certain species. Information on local resistance prevalence is useful; microbiological diagnosis with isolation of the pathogen and confirmation of its susceptibility should be sought, especially for the treatment of severe infections or in cases of inadequate response to treatment.

**Streptococcal and pneumococcal infections**

Given the level of sensitivity of streptococci and pneumococcus to ofloxacin, ORNOVEL is not the first-line treatment for infections due to streptococci and pneumococcus.

***Escherichia coli* infections**

*Escherichia coli* resistance to fluoroquinolones (the most common pathogen responsible for urinary tract infections) varies within the European Union. Prescribers should take into account the local prevalence of *Escherichia coli resistance* to fluoroquinolones.

**Methicillin-resistant Staphylococcus aureus (MRSA)** often exhibits co -resistance to fluoroquinolones, including ofloxacin. Therefore, ORNOVEL is not recommended for the treatment of known or suspected MRSA infections unless bacteriological results have confirmed the bacteria's susceptibility to ofloxacin (and antibiotics commonly recommended for the treatment of MRSA infections are deemed inappropriate).

**Osteoarticular infections**

For osteoarticular infections, the need for treatment in combination with other antibiotics must be considered.

***Neisseria gonorrhoeae* infections**

Due to increased resistance in *Neisseria gonorrhoeae* , ofloxacin should not be used as an empirical treatment in cases of suspected gonococcal infection ( gonococcal urethral infection , pelvic inflammatory disease and orchitis - epididymitis), unless the pathogen has been identified and confirmed to be susceptible to ofloxacin.

If no clinical improvement is obtained after 3 days of treatment, the choice of treatment should be reconsidered.

**Pelvic inflammatory disease**

For pelvic inflammatory disease, ofloxacin should only be considered in combination with anaerobic coverage.

**In children and adolescents**

Ofloxacin should not be used in children and adolescents until the end of the growth period due to joint toxicity: severe arthropathies preferentially affecting the large joints (see section 4.3). However, in exceptional cases, after microbiological documentation and after reviewing the benefit-risk ratio, ORNOVEL may be prescribed in children from the age of 6 years (this age limit is due to the pharmaceutical form, considering that any tablet administration is not recommended in children under 6 years of age because it can lead to choking) and in adolescents, for the exceptional treatment of certain severe infections that have not responded to conventional treatment and for which the results of bacteriological tests may justify the use of ofloxacin.

**Severe bullous reactions**

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell's syndrome) have been reported with ofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately before continuing treatment if any skin and/or mucous membrane reactions occur.

**Hypersensitivity**

Hypersensitivity and allergic reactions have been reported with fluoroquinolones after the first administration. Anaphylactic and anaphylactoid reactions can be life-threatening, even after the first dose. In these cases, ORNOVEL should be discontinued and appropriate treatment (e.g., treatment for shock) should be initiated.

***Clostridium difficile* -associated diarrhea**

Diarrhea, particularly if severe, persistent, and/or bloody, occurring during or up to 10 weeks after treatment with ofloxacin, may be a sign of *Clostridium difficile -associated colitis* (CDAC). The severity of CDAC can range from mild to life-threatening, with pseudomembranous colitis being the most severe form (see section 4.8). Therefore, it is important to consider this diagnosis in patients who develop severe diarrhea during or after treatment with ORNOVEL. If CDAC is suspected or confirmed, ORNOVEL should be discontinued immediately and appropriate treatment initiated without delay. Antiperistaltic drugs are contraindicated in patients who develop severe diarrhea.

**Patients predisposed to seizures**

Quinolones can lower the seizure threshold and trigger seizures. ORNOVEL is contraindicated in patients with a history of epilepsy (see section 4.3).
As with other quinolones, ofloxacin should be used with great caution in patients predisposed to seizures.
pre-existing lesions of the central nervous system, and may receive concomitant treatment with fenbufen , comparable non-steroidal anti-inflammatory drugs or drugs lowering the seizure threshold such as theophylline (see section 4.5).
In case of seizures, treatment with ORNOVEL should be stopped.

**Serious, long-lasting, disabling and potentially irreversible side effects**

Very rare cases of serious, persistent (lasting months or years), disabling, and potentially irreversible adverse reactions affecting various organs, sometimes with multiple manifestations ( musculoskeletal , nervous, psychiatric, and sensory), have been reported in patients receiving quinolones and fluoroquinolones, regardless of their age or pre-existing risk factors. Treatment with ORNOVEL should be stopped immediately at the first sign or symptom of a serious adverse reaction, and patients should be advised to contact their doctor for medical advice.

**Tendonitis and tendon ruptures**

Tendonitis and tendon rupture (particularly, but not exclusively, affecting the Achilles tendon), sometimes bilateral, can occur as early as the first 48 hours of treatment with quinolones and fluoroquinolones, and have been reported up to several months after discontinuation of treatment. The risk of tendonitis and tendon rupture is increased in elderly patients, patients with renal impairment, patients who have received solid organ transplants, and those receiving concomitant corticosteroid therapy. Therefore, concomitant use of corticosteroids should be avoided.

At the first signs of tendinitis (e.g., painful swelling, inflammation), treatment with ORNOVEL should be discontinued and alternative treatment considered. The affected limb(s) should be treated appropriately (e.g., immobilization). Corticosteroids should not be used if signs of tendinopathy appear.
The risk of developing arthropathy should be monitored, particularly in children.
Regarding children more specifically, if joint pain occurs during treatment with ofloxacin, the treatment should be stopped and the affected joint rested; specialist advice will be required.

**Patients with kidney failure**

Because ofloxacin is mainly excreted by the kidneys, the dosage should be adjusted in subjects with impaired renal function ( see section 4.2 ).

**Patients with a history of psychotic disorders**

Psychotic reactions, including suicidal ideation and suicide attempts, have been reported in patients taking fluoroquinolones, including ofloxacin, sometimes after only a single dose (see section 4.8). If a patient develops these reactions, ofloxacin treatment should be stopped immediately at the first signs or symptoms, and patients should be advised to contact their prescribing physician for advice. Alternative antibacterial treatment without a fluoroquinolone should be considered, and appropriate measures should be implemented .

**ORNOVEL should be used with caution in patients with or who have had psychiatric disorders.**

**Patients with liver failure / with severe liver damage**

ORNOVEL should be used with caution in patients with impaired liver function, as treatment may cause liver damage. Cases of fulminant hepatitis leading to liver failure (including fatal cases) have been reported with ofloxacin. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of liver disease occur, such as anorexia, jaundice, dark urine, pruritus, or abdominal tenderness (see section 4.8).

It is recommended to adjust the dosage in patients with severe hepatic impairment and in hemodialysis patients.

**Patients treated with vitamin K antagonists**

Given the possible increase in coagulation test results (Quick Time/INR) and/or bleeding in patients treated with fluoroquinolones including ofloxacin, in combination with vitamin K antagonist treatments (e.g. warfarin), coagulation tests should be monitored when these drugs are administered concomitantly with ofloxacin (see section 4.5).

**Hematological disorders**

In cases of a history of hematological disorders, high-dose treatment and/or prolonged treatment, it is recommended to have regular blood tests, particularly monitoring of the leukocyte differential.

In cases of leukopenia, the opportunity to continue treatment depends on the severity of the infection.

**Myasthenia**

Fluoroquinolones, including ofloxacin, have neuromuscular blocking activity and can exacerbate muscle weakness in patients with myasthenia gravis. During post-marketing surveillance, serious adverse events, including deaths and the need for respiratory support, have been associated with the use of fluoroquinolones in patients with myasthenia gravis.
ORNOVEL is not recommended for patients with a known history of myasthenia gravis.

**Prevention of photosensitivity**

Photosensitivity reactions have been reported with ofloxacin (see section 4.8). Patients should avoid unnecessary exposure to strong sunlight or artificial ultraviolet radiation (tanning lamps, solariums) during treatment and for 48 hours after stopping treatment to prevent photosensitivity.

**Secondary infections**

As with other antibiotics, the use of ofloxacin, particularly for a prolonged period, may promote the growth of non-susceptible strains. Repeated assessment of the patient's condition is essential. If a secondary infection develops during treatment, appropriate measures should be taken.
An emergence of resistance or a selection of resistant strains is possible in particular during long-term treatments and/or nosocomial infections, especially among staphylococci and *Pseudomonas* .

**QT interval prolongation**

Caution is advised when treating patients with fluoroquinolones, including ofloxacin, who have known risk factors for QT interval prolongation, such as:

- congenital long QT syndrome;

- concomitant treatment with drugs known to prolong the QT interval (e.g., class IA and III antiarrhythmics , tricyclic antidepressants, macrolides, antipsychotics);

- an uncorrected electrolyte imbalance (e.g., hypokalemia, hypomagnesemia);

- cardiac manifestations (such as heart failure, myocardial infarction or bradycardia).

Elderly patients and women may be more susceptible to treatments that prolong the QTc interval . Therefore, caution is advised when treating these populations with fluoroquinolones, including ofloxacin (see sections 4.2, 4.5, 4.8 and 4.9).

**Risk of aortic aneurysm and aortic dissection and regurgitation/incompetence of the heart valves**

Epidemiological studies report an increased risk of aortic aneurysm and aortic dissection, particularly in the elderly, as well as regurgitation of the aortic and mitral valves after taking fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal rupture), and regurgitation/incompetence of one of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).
Therefore, fluoroquinolones should only be used after careful evaluation of the potential benefits and risks, and after considering other therapeutic options in cases of a confirmed family history of aneurysm or congenital heart valve disease, or in cases of aortic aneurysm and/or aortic dissection or pre-existing heart valve disease diagnosed, or in the presence of other risk factors or predisposing conditions:

- both to aortic aneurysm or dissection and to regurgitation/incompetence of the heart valves (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet's disease, high blood pressure, rheumatoid arthritis) or even;

- to aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis [Horton's disease], known atherosclerosis, or Sjögren 's syndrome ) or even;

- to regurgitation/incompetence of the heart valves (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, as well as rupture of the aortic valves, may also be increased in patients treated concurrently with systemic corticosteroids.
In case of sudden abdominal, chest or back pain, patients should be advised to contact an emergency medical service immediately.
Patients should be advised to seek immediate medical attention in the event of acute dyspnea, the onset of new heart palpitations, or the development of edema of the abdomen or lower limbs.

**Dysglycemia**

As with all quinolones, blood glucose disturbances, including both hypoglycemia and hyperglycemia, have been reported, occurring more frequently in the elderly, generally in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or insulin. Cases of hypoglycemic coma have been reported. In diabetic patients, close monitoring of blood glucose is recommended (see section 4.8).
Treatment with ORNOVEL should be stopped immediately if a patient reports blood glucose disturbances and alternative antibacterial treatment without fluoroquinolones should be considered.

**Peripheral neuropathy**

Cases of sensory or sensorimotor polyneuropathy, manifesting as paresthesia, hypoesthesia, dysesthesia, or muscle weakness, have been reported in patients treated with quinolones and fluoroquinolones. To prevent progression to a potentially irreversible condition, patients treated with ORNOVEL should be advised to contact their doctor before continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or muscle weakness occur (see section 4.8).

Consider the risk of worsening neurological condition in patients with severe, fixed or progressive central and peripheral neurological disorders.

**Vision problems**

In the event of visual disturbances or any other ocular manifestation, an ophthalmologist should be consulted immediately (see sections 4.7 and 4.8).

**Patients with glucose-6-phosphate dehydrogenase deficiency**

Patients with latent or diagnosed glucose-6-phosphate dehydrogenase deficiency may be predisposed to hemolytic reactions if treated with quinolones. Therefore, if ofloxacin is to be used in these patients, the potential for hemolysis should be monitored.

**Interference with laboratory tests**

Testing for opiates or porphyrins in urine may produce false-positive results during treatment with ofloxacin. It may be necessary to confirm the presence of opiates or porphyrins using more specific detection methods.
Ofloxacin activity against *Mycobacterium tuberculosis* may cause negative results in TB testing, particularly in cases of pulmonary or osteoarticular tuberculosis.

**Avoid consuming alcoholic beverages and medications containing alcohol (disulfiram-like reaction).**

## 4.5. Interactions with other medicinal products and other forms of interaction

**Association not recommended** :

- **Alcohol**

Avoid consuming alcoholic beverages and medications containing alcohol: antabuse effect (heat, redness, vomiting, tachycardia).

- **Antacids, sucralfate, metallic cations**

Antacids containing aluminum (including sucralfate) and magnesium hydroxides, aluminum phosphate, zinc, iron, are responsible for reducing the absorption of ofloxacin tablets.
Ofloxacin should be administered approximately 2 hours after antacids.

- **Theophylline, fenbufen , or comparable non-steroidal anti-inflammatory drugs**

No pharmacokinetic interaction was found between ofloxacin and theophylline in a clinical study. However, a pronounced decrease in the seizure threshold may occur when quinolones are administered concomitantly with theophylline, non-steroidal anti-inflammatory drugs, or other drugs that lower the seizure threshold.

- **Drugs known to prolong the QT interval**

As with other fluoroquinolones, ofloxacin should be used with caution in patients receiving drugs known to prolong the QT interval (e.g., Class IA and III antiarrhythmics , tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

- **Vitamin K antagonists**

An increase in coagulation tests (PT/INR) and/or bleeding, which may be severe, has been reported in patients treated with ofloxacin in combination with VKAs (e.g., warfarin).
More frequent INR monitoring. Possible adjustment of the vitamin K antagonist dosage during and after fluoroquinolone treatment (see section 4.4).

- **Glibenclamide**

Ofloxacin may cause a slight increase in serum concentrations of glibenclamide if administered concomitantly. Therefore, it is recommended that patients treated concurrently with ofloxacin be monitored particularly closely.

- **Probenecid, cimetidine, furosemide or methotrexate**

Probenecid decreases the total clearance of ofloxacin by 24% and increases the AUC by 16%. The proposed mechanism is competition or inhibition of active transport during renal tubular excretion.
Caution is advised when ofloxacin is administered concurrently with other drugs that affect renal tubular secretion (including probenecid, cimetidine, furosemide or methotrexate), particularly in the case of high-dose treatment.

- **Strontium**

Decreased gastrointestinal absorption of strontium. Take strontium separately from fluoroquinolones (more than 2 hours apart if possible).

**Associations to consider:**

- **Fluorouracil** (and by extrapolation, tegafur and capecitabine )

Increased toxicity of fluorouracil due to decreased clearance.

- **Glucocorticoids (except hydrocortisone for replacement therapy)**

Possible increased risk of tendinopathy, or even tendon rupture (rare), particularly in patients receiving prolonged corticosteroid therapy.

- **Mycophenolate mofetil**

mycophenolic acid concentrations of approximately one third, with a potential risk of decreased effectiveness.

**Specific problems related to INR imbalance**

Numerous cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics.
A marked infectious or inflammatory context, the patient's age, and general condition appear to be risk factors. In these circumstances, it is difficult to distinguish between the infectious pathology and its treatment as the cause of the INR imbalance. However, certain classes of antibiotics are more frequently implicated: these include fluoroquinolones, macrolides, tetracyclines, cotrimoxazole, and some cephalosporins.

## 4.6. Pregnancy and breastfeeding

**Pregnancy**
Based on limited human data, the use of fluoroquinolones during the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse effects on pregnancy outcome. Animal studies have shown articular cartilage damage in immature animals, but no teratogenic effects.
There is limited data on the use of ornidazole in pregnant women.

Animal studies have not shown any teratogenic risk. One animal study demonstrated peri/postnatal toxicity (see section 5.3).

Therefore, ORNOVEL should not be used during pregnancy (see section 4.3).
Joint damage has been described in children treated with quinolones, but to date, no cases of arthropathy secondary to *in utero exposure* have been reported.

**Breastfeeding**

Ofloxacin is excreted in breast milk in small amounts. Due to the risk of arthropathy and other serious toxicities in the breastfed infant, breastfeeding should be discontinued during treatment with ORNOVEL (see section 4.3).

**Fertility**
No fertility studies have been conducted with ornidazole in humans. A reversible decrease in fertility has been reported in male rats (see section 5.3).

## 4.7. Effects on the ability to drive vehicles and use machinery

ORNOVEL has a significant influence on the ability to drive vehicles and operate machinery.
Reactions (e.g. dizziness/vertigo, drowsiness, visual disturbances) can impair the patient's ability to concentrate and react and therefore pose a risk in situations where these abilities are of particular importance (e.g., driving a vehicle or operating machinery).
In patients suffering from dizziness and confusion, driving and operating machinery should be avoided.

## 4.8. Undesirable effects

| **Organ system class** | **Uncommon (≥ 1/1000 to < 1/100)** | **Rare (≥ 1/10,000 (at < 1/1000)** | **Very rare (< 1/10,000)** | **Frequency not known (cannot be estimated from the available data)** |
|---|---|---|---|---|
| **Infections and infestations** | Fungal infections, Bacterial resistance | | | |
| **Hematological and lymphatic system disorders** | | | Anemia, Hemolytic anemia, Leukopenia, Eosinophilia, Thrombocytopenia | Agranulocytosis, Bone marrow failure |
| **Immune system disorders** | | Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema * | Anaphylactic shock*, Anaphylactoid shock* | |
| **Metabolism and nutrition disorders** | | Anorexia Hypoglycemic coma (see section 4.4). | | Hypoglycemia in diabetic patients treated with hypoglycemic agents* Hyperglycemia |
| **Psychiatric disorders°** | Hustle, Sleep disorders, Insomnia | Psychotic disorders (e.g., hallucinations), Anxiety, State of confusion Nightmares, Depression, Delirium, Memory problems. | | Psychotic disorders and depression that endanger the patient, including suicidal ideation or suicide attempts (see section 4.4) Nervousness |
| **Disorders of the nervous system°** | Sensations dizzying , Headaches | Drowsiness, Paresthesias, Dysgeusia, Parosmia | Peripheral sensory neuropathy*, Peripheral sensorimotor neuropathy*, Seizures, Extrapyramidal symptoms or other disorders of muscle coordination | Tremor, Dyskinesia, Ageusia, Syncope, Benign intracranial hypertension ( pseudotumor) cerebri ) |
| **Eye conditions°** | Eye irritation | Visual disturbances | | Uveitis |
| **Ear and labyrinth disorders°** | Dizziness | | Tinnitus, Hearing loss | Hearing difficulties |

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| **Heart conditions**** | | Tachycardia | | Arrhythmias ventricular , Torsades de pointes (events observed mainly in patients with risk factors for QT interval prolongation), QT interval prolongation confirmed by ECG (see sections 4.4 and 4.9). |
| **Vascular disorders**** | | Hypotension | | |
| **Respiratory, thoracic and mediastinal disorders** | Cough, Rhinopharyngitis | Dyspnea, Bronchospasm | | Allergic pneumonia, severe dyspnea |
| **Gastrointestinal disorders** | Abdominal pain, Diarrhea, Nausea, Vomiting | Enterocolitis sometimes hemorrhagic | Pseudomembranous colitis | Dyspepsia, Flatulence, Constipation, Pancreatitis |
| **Hepatobiliary disorders** | | Elevated liver enzymes (ALT, AST, LDH, gamma-GT and/or alkaline phosphatases), Increased blood bilirubin | Cholestatic jaundice<br><br>Hepatitis | Hepatitis, which can be severe<br>Cases of severe liver damage, including cases of acute liver failure, sometimes fatal, have been reported with ofloxacin, mainly in patients with underlying liver disease. |
| **Skin and subcutaneous tissue disorders** | Itching<br>Rash | Urticaria,<br>Hot flashes,<br>Hyperhidrosis<br>Pustular eruption | Erythema multiforme,<br>Bullous epidermal necrolysis<br>Photosensitivity reaction*,<br>Drug-induced rash,<br>Vascular purpura,<br>Vasculitis, which can exceptionally lead to skin necrosis | Stevens-Johnson syndrome,<br>Acute generalized exanthematous pustulosis , Drug eruption<br>Lyell's syndrome,<br>Stomatitis<br>Exfoliative dermatitis |
| **Musculoskeletal and systemic disorders° and bone disorders** | | Tendinitis | Arthralgia,<br>Myalgia,<br>Tendon rupture (e.g., Achilles tendon) can occur within 48 hours of starting treatment and may be bilateral. | Rhabdomyolysis and/or myopathy,<br>Muscle weakness,<br>Muscle tear, Muscle rupture<br>Ligament rupture,<br>Arthritis,<br>Possible worsening of myasthenia gravis * |

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| **Kidney and urinary tract disorders** | | Increase in serum creatinine | Acute renal failure | Acute interstitial nephritis |
| **Congenital, familial, and genetic disorders** | | | | Porphyria attacks in patients with porphyria |
| **General problems and conditions related to the administration site°** | | | | Fatigue, fever, pain (including back, chest and extremity pain) |

* see section 4.4.
° Very rare cases of serious, persistent (lasting months or years), disabling and potentially irreversible adverse effects affecting various, sometimes multiple, sensory organ systems (including tendinitis-like effects, tendon rupture, arthralgia, pain in the extremities, gait disturbances, neuropathies associated with paresthesia, depression, fatigue, memory impairment, sleep disturbances and disturbances of hearing, sight, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones, sometimes independently of pre-existing risk factors (see section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal), and regurgitation/incompetence of one of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

**Pediatric population**

In children: arthropathies ( see section 4.4 )

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals report any adverse effects suspected unwanted substance via the FRILAB declaration form available under the tab Pharmacovigilance information from the website: www.frilab.ch

## 4.9. Overdose

Analysis of the collection of overdose cases in humans shows that most often it involves elderly patients and that the cause of overdose in 1/3 of cases is the failure to adjust the dose to renal function.
The most frequent signs observed following an overdose of ofloxacin are central nervous system symptoms such as confusion, dizziness, impaired consciousness and seizures, QT interval prolongation, and gastrointestinal reactions such as nausea and gastric mucosal erosion.
CNS effects including confusion, seizures, hallucinations, and tremors have been reported since the drug was marketed.
In case of overdose, symptomatic treatment should be implemented.
Antacids can be used to protect the gastric mucosa.
It is helpful to know the kidney function (serum creatinine) to assess the drug's elimination potential. It is recommended to avoid strenuous muscle and tendon activity for the following days and then gradually resume normal physical activity. A portion of ofloxacin can be removed from the body by hemodialysis. Peritoneal dialysis and continuous ambulatory peritoneal dialysis are not effective in removing ofloxacin. There is no specific antidote.
Electrocardiographic (ECG) monitoring should be performed due to the possibility of QT interval prolongation.
Neurological clinical monitoring should be performed.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

**Class Pharmacotherapeutic: fluoroquinolone, ATC code: J01MA01 and Other Antibacterials, ATC code P01AB03**
ORNOVEL film-coated tablets are a combination of an antibiotic from the quinolone family and an antibacterial.

Ofloxacin is a synthetic antibiotic belonging to the quinolone family, in the fluoroquinolone group.

Ornidazole is an anti-infective drug belonging to the 5-nitroimidazole family.
Ornidazole has anti-infective properties against certain Gram-negative anaerobic bacteria such as various species of Bacteroides ( B. fragilis , P. melaninogenica , ...), Clostridium and Fusobacterium , as well as anaerobic cocci .
Ornidazole is also active against Trichomonas vaginalis, Entamoeba histolytica and Giardia intestinalis, and inactive against Candida albicans .

**Mechanism of action**

Its activity is strongly bactericidal by inhibiting bacterial DNA gyrase, preventing the synthesis of bacterial chromosomal DNA.

The mechanism of action of ornidazole is identical to that of other nitroimidazole derivatives : it involves selective toxicity towards anaerobic or microaerophilic microorganisms, as well as hypoxic cells. The nitrate group acts as an electron acceptor; the reduced form of the drug, under oxygen-deficient conditions, produces biochemical lesions in the helical structure of DNA, leading to cell death.

**Critical concentrations of ofloxacin**

The critical concentrations separate susceptible strains from strains with intermediate susceptibility, and the latter from resistant strains.
The critical minimum inhibitory concentrations (MICs) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) is presented below.

| **EUCAST established critical concentrations for ofloxacin (2012.01.01, v.2.0)** | | |
|---|---|---|
| **Organizations** | **Sensitive (S) (mg/l)** | **Resistant (R) (mg/l)** |
| *Enterobacteriaceae* | ≤ 0.5 | > 1 |
| *Staphylococcus spp .* | ≤ 1 | > 1 |
| *Streptococcus pneumoniae* | ≤ 0.12 | > 4 |
| *Haemophilus influenzae* | ≤ 0.5 | > 0.5 |
| *Moraxella catarrhalis* | ≤ 0.5 | > 0.5 |
| *Neisseria gonorrhoeae* | ≤ 0.12 | > 0.25 |
| Species-unrelated critical concentrations* | ≤ 0.5 | > 1 |
| * Species-non-critical concentrations were determined primarily on the basis of PK/PD data and are independent of the MIC distribution of specific species.<br>They apply only to species for which no species-specific critical concentration has been defined and not to those for which a sensitivity test is not recommended. | | |

Fluoroquinolones have concentration-dependent bactericidal activity with a moderate post-antibiotic effect. For this class of antibiotics, the ratio of the area under the curve (AUC) to the minimum inhibitory concentration (MIC), or the ratio of the maximum serum concentration (Cmax) to the MIC, is predictive of clinical success.
The prevalence of resistance can vary depending on geographic location and time period for certain species. Information on local resistance prevalence is useful, especially when treating severe infections. If necessary, expert advice should be sought, particularly when the drug's effectiveness in treating certain infections may be compromised by the level of local resistance.
Resistance to ofloxacin is acquired in successive steps through mutations in the target sites of the two types of type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as membrane mechanisms (common in *Pseudomonas aeruginosa* ) and efflux mechanisms can also affect sensitivity to ofloxacin.

**Critical concentrations of ornidazole**

The critical concentrations separate susceptible strains from strains with intermediate susceptibility, and the latter from resistant strains.
The critical minimum inhibitory concentrations (MICs) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) is presented below.

| **Critical concentrations established by EUCAST (based on EUCAST recommendations for metronidazole - V2.0 May 2019)** | | |
|---|---|---|
| Organizations | Sensitivity (S) (mg/l) | Resistance (R) (mg/l) |
| Gram-positive anaerobes | 4 | 4 |
| Gram-negative anaerobes ( *bacteriodes ) fragilis and other species)* | 4 | 4 |

**Classification of species according to sensitivity to ofloxacin:**

| **CLASS** |
|---|
| **SPECIES THAT ARE USUALLY SENSITIVE**<br>*including species with intermediate sensitivity<br>*Bacillus anthracis*<br>*Bordetella pertussis*<br>*Campylobacter*<br>*Chlamydia*<br>***Chlamydophila pneumoniae***<br>*Corynebacteria*<br>*Enterobacter*<br>*Haemophilus influenzae*<br>*Legionella pneumophila*<br>*Moraxella catarrhalis*<br>*Morganella morganii*<br>*Mycoplasma hominis*<br>*Mycoplasma pneumoniae*<br>*Proteus vulgaris*<br>*Salmonella*<br>*Shigella*<br>Streptococci<br>*Ureaplasma urealyticum*<br>*Yersinia* |
| **SPECIES WITH VARIABLE SENSITIVITY**<br>Inconstantly susceptible microorganisms (possibility of acquired resistance ):<br>*Citrobacter freundii*<br>***Escherichia coli***<br>*Klebsiella oxytoca*<br>*Klebsiella pneumoniae* |
| *Neisseria gonorrhoeae*<br>*Proteus mirabilis*<br>*Pseudomonas aeruginosa*<br>*Serratia*<br>*Staphylococci* coagulase negative<br>*Staphylococcus aureus* ( methicillin -sensitive)<br>*Streptococcus pneumonia*<br>**NATURALLY RESISTANT SPECIES**<br>*Acinetobacter baumannii*<br>*Bacteroides* spp . |

| |
|---|
| *Clostridium difficile* |
| *Enterococci* |
| *Listeria monocytogenes*<br>*Staphylococci* methi -R<br>*Nocardia* |

**Spectrum of antimicrobial activity of ornidazole**

The prevalence of acquired resistance can vary geographically and over time for certain species. Therefore, information on local resistance prevalence is useful, especially for treating severe infections. This data can only provide guidance on the likelihood of a bacterial strain's susceptibility to that antibiotic.
When the variability in resistance prevalence in France is known for a bacterial species, it is indicated in the table below.
Classification of species according to their sensitivity to anti-infectives:

| **Classes** |
|---|
| **Bacteria generally sensitive** |
| *Bacteroides fragilis*<br>*Bilophila*<br>*Clostridium*<br>*Clostridium difficile*<br>*Clostridium perfringens*<br>*Fusobacterium*<br>*Peptostreptococcus*<br>*Porphyromonas*<br>*Prevotella*<br>*Veillonella* |
| **Bacteria with varying susceptibility - Acquired resistance in France ~ 10%** |
| **Anaerobes**<br>*Bifidobacterium* ( resistance in France ~ 50%)<br>*Eubacterium* |
| **Bacteria naturally resistant** |
| **Gram-positive aerobes**<br>*Actinomyces*<br>**Anaerobes**<br>*Mobiluncus*<br>*Propionibacterium acne* |
| **Protozoa** |
| *Entamoeba histolytica*<br>*Giardia intestinalis*<br>*Trichomonas vaginalis* |

Cross-resistance exists between ornidazole and other 5- nitroimidazoles; cross-resistance with other chemically unrelated substances is not known.

## 5.2. Pharmacokinetic properties

**Absorption**

After oral administration of ofloxacin in fasting subjects, absorption is significant and rapid, with the serum peak appearing after an average of one hour.

After oral administration, the absorption of ornidazole is rapid and almost complete, with a tmax between 2 and 4 hours and a bioavailability greater than 90%.
Following oral administration of single doses of 750 mg of ornidazole , the mean maximum plasma concentration is 10.9 µg/ mL (9.1 to 14.8 µg/ mL ).

**Distribution**

The maximum serum concentration, after a single dose of 200 mg, is between 2.5 and 3 micrograms/ml on average.

The serum elimination half-life is 6 to 7 hours. This elimination is linear.
The apparent dispensing volume is 120 litres.

After repeated administrations, the serum concentration is not significantly increased (multiplicative factor of the order of 1.5).

Concentrations of ofloxacin in urine and at the site of urinary tract infection are 5 to 100 times higher than those measured in serum.

The plasma protein binding rate is low, approximately 10 %. The apparent volume of distribution is high: approximately 1.5 l/kg.

Ofloxacin exhibits a strong tissue affinity, with tissue levels exceeding serum concentrations, particularly in lung parenchyma, salivary glands, oropharyngeal mucosa, skin, muscle, bone, prostate, lymph nodes, gynecological tissues, as well as in saliva and bronchial mucus.

Following intravenous administration of a single 1-gram dose of ornidazole , the plasma concentrations are as follows:
- 1 hour: 17.7 µg/ml
- 24 hours: 4.9 µg/ml

single 20 mg/kg dose of ornidazole , the plasma concentrations are as follows: Cmax: 18.7 µg/ ml; 24 hours: 7.32 µg/ml.
Ornidazole diffuses well throughout the body, passes into the cerebrospinal fluid and crosses the placental barrier.

The distribution volume varies from 0.73 to 0.90 L/kg.
Plasma protein binding is less than 15%.

**Biotransformation**
The biotransformation of ofloxacin is very low (less than 5% of metabolites found in the urine).
Ornidazole is extensively metabolized by the liver (95%). Five free or glucuronide- and sulfate -conjugated metabolites have been identified.

**Elimination**
Ornidazole is eliminated primarily via the renal (63%) and biliary (22%) routes.
Urinary excretion is primarily in the form of metabolites. Less than 4% of the administered dose is eliminated unchanged in the urine.
The elimination half-life is 12 to 14 hours.

Ofloxacin is primarily excreted by the kidneys (80% of the administered dose is recovered in the urine in unchanged form).

**Pharmacokinetic properties in specific populations**

*In the elderly*

After a single dose of 200 mg or 400 mg ofloxacin, the half-life is prolonged without significant change in the maximum serum concentration.

*In patients with renal insufficiency*

The half-life of ofloxacin is prolonged and total and renal clearances are decreased depending on the degree of renal impairment.

Due to its low molecular weight and low plasma protein binding, ornidazole is eliminated by hemodialysis. Therefore, dosage adjustment is recommended in hemodialysis patients (see section 4.2).

*In subjects with liver failure*

Due to decreased total clearance (35 versus 51 mL /min, on average), the elimination half-life of ornidazole is increased (22 h versus 14 h, on average) in patients with hepatic cirrhosis compared to normohepatic subjects.
To avoid very marked systemic overexposure to ornidazole and its metabolites, it is recommended to adjust the dosage in patients with severe hepatic impairment (see section 4.2).

## 5.3. Preclinical safety data

No conventional safety pharmacology studies have been reported.

Oral administration of ornidazole in repeated-dose toxicity studies showed ataxia in dogs at 100 mg/kg. However, considering the short duration of administration in humans, these results can generally be considered of limited clinical relevance.

A reversible decrease in fertility was observed in male rats at an oral dose of 400 mg/kg/day (corresponding to 3 times the maximum recommended dose in humans expressed in mg/m2 ).

Limited studies have not shown any teratogenic effects up to oral doses of 400 mg/kg/day in mice and rats, and 100 mg/kg/day in rabbits (corresponding to 1-3 times the maximum recommended dose in humans expressed in mg/m² ).

A peri- and postnatal toxicity study conducted in rats showed an increase in postnatal mortality and a decrease in the weight gain of the pups at the oral dose of 400 mg/kg/day (corresponding to 3 times the maximum recommended dose in humans expressed in mg/m2 ).

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. List of excipients

Microcrystalline cellulose, Cross caramellose sodium, HPMC (50 CPS) starch, colloidal silicon dioxide , magnesium stearate , PVP K-30, talc, titanium dioxide , lauryl Sodium sulfate , Propylene glycol, Purified water

## 6.2. Incompatibilities

Not applicable.

## 6.3. Shelf life

3 years.

## 6.4. Special precautions for storage

Store at a temperature below 30°C.

## 6.5. Nature and contents of container

10 film-coated tablets in blister packs (PVC/ Aluminium ).

## 6.6. Special precautions for disposal and handling

No special requirements.

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

# 7. OPERATOR

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SWISS

# 8. MANUFACTURER

Helios Pharmaceuticals Pvt . Ltd.
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Tehsil : Nalagarh , Dist : Solan , HP, India

# 9. DATE OF REVISION OF THE TEXT

October 2024

## 10. DOSIMETRY

Not applicable

## CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I