Fluoroquinolone Drug for External Otitis and Skin Infection in Dogs and Cats
Veterinary Drug
Prescription Legend Drug
Orbifloxacin MT Cream

Orbifloxacin MT Cream is a cream preparation in a hydrophilic ointment base patented by Toko Yakuhin Kogyo Co., Ltd. that was developed by Dainippon Sumitomo Co., Ltd. to treat external otitis and skin infections in dogs and cats. It contains the active ingredient orbifloxacin, a fluoroquinolone antimicrobial agent. Orbifloxacin has antibacterial activity against a broad spectrum of gram-negative and gram-positive bacteria. It does not demonstrate cross-resistance with other antimicrobial agents. It also contains miconazole nitrate, which is effective against fungus. It therefore exhibits excellent efficacy against external otitis and skin infections caused by single or mixed infections of gram-positive bacteria, gram-negative bacteria and fungus. It additionally contains the synthetic adrenal cortical hormone triamcinolone acetonide. It therefore rapidly reduces inflammatory symptoms such as itching, erythema and swelling at affected areas.

■ Composition
Each gram of Orbifloxacin MT Cream contains 10 mg of orbifloxacin, 10 mg of miconazole nitrate and 1 mg of triamcinolone acetonide.

■ Indications
Indicated Microorganisms
Dogs: Staphylococcus species, Streptococcus species, Pseudomonas species, Escherichia coli, Malassezia pachydermatis, dermatophyte fungi
Cats: Staphylococcus species, Psuedomonas species, Escherichia coli, Malassezia pachydermatis, dermatophyte fungi

Indicated Diseases
Dogs and cats: Bacterial and fungal external otitis, bacterial and fungal skin infection

■ Dosage and Administration
Apply the indicated amount to the affected area once daily.

■ Precautions
[General Precautions]
(1) Orbifloxacin MT Cream is a prescription legend drug dispensed by prescription or order of a veterinarian.
(2) The use of Orbifloxacin MT Cream is restricted to animals that have failed standard therapy.
(3) Orbifloxacin MT Cream should be used only for the indications listed in the Indications section.
(4) Orbifloxacin MT Cream should be used only as indicated.
(5) Treatment should not be continued beyond seven days.
(6) To prevent the development of resistant bacteria during the use of Orbifloxacin MT Cream, susceptibility should be determined and treatment should be discontinued at the minimum time necessary to treat the indication.
(7) Do not use Orbifloxacin MT Cream in severe cases due to limited efficacy.
(8) Take measures to ensure that animals do not lick affected areas after the application of Orbifloxacin MT Cream.
[User Precautions]
(1) Consult a physician immediately in case of accidental ingestion by humans.
(2) The effective ingredient triamcinolone acetonide has been reported to cause teratogenicity in laboratory animals. Orbifloxacin MT Cream should therefore be used with caution by women who are pregnant or may be pregnant.
(3) Orbifloxacin MT Cream should not be handled directly with bare hands by users with a history of hypersensitivity to adrenal corticoid hormone preparations.
(4) Wash with soap and water immediately after use or accidental skin contact.

[Precautions for Dogs and Cats]
1. Restrictions
(1) The effective ingredient triamcinolone acetonide has been reported to cause teratogenicity in laboratory animals. Orbifloxacin MT Cream should therefore be used with caution in animals that are pregnant or may be pregnant.

2. Adverse Reactions
(1) Consult a veterinarian immediately in case of adverse reaction.

3. Usage Precautions
(1) Orbifloxacin MT Cream is intended for external use only.

[Handling Precautions]
(1) Dispose of used containers according to local government regulations.

[Storage Precautions]
(1) Keep out of the reach of children.
(2) Store sealed in a cool location, away from direct sunlight and high temperatures.
(3) To avoid misuse and preserve quality, keep the preparation in the original package.

Therapeutic Efficacy and Pharmacology
1. Antibacterial Activity
(1) Orbifloxacin has a broad antibacterial spectrum. It exhibits potent antibacterial activity against a broad spectrum of bacteria, including gram negative bacteria, gram positive bacteria and mycoplasma.
(2) Orbifloxacin also exhibits antibacterial activity against bacteria that are resistant to such antibiotics as ampicillin, oxytetracycline and kanamycin.
(3) Miconazole nitrate exhibits potent antifungal activity. It exhibits stronger antifungal activity than Nystatin and good antifungal activity against strains with low susceptibility to Nystatin.

2. Anti-Inflammatory Effect
Triamcinolone is a glucocorticoid with a potent effect on carbohydrate metabolism. It has anti-inflammatory and anti-allergic effects, but has a relatively weak effect on mineral metabolism. An animal experiment (rats) evaluating corticoid activity showed that triamcinolone exhibits anti-inflammatory, thymus-involuting and liver glycogen storage activity. Triamcinolone acetonide has more potent glucocorticoid activity than triamcinolone, providing increased survival benefit in adrenalectomized rats, duration of action and cutaneous permeability.

3. Resistance
(1) Inherent bacterial resistance to orbifloxacin is uncommon.
(2) Orbifloxacin inhibits R-plasmid transfer. Resistance is not thought to be mediated by R-plasmids.

4. Mechanism of Action
(1) Orbifloxacin exhibits bactericidal activity by inhibiting the activity of bacteria-specific DNA gyrase, which prevents DNA replication.
(2) At low concentrations, miconazole nitrate exhibits antifungal activity primarily by acting on the membrane system (cell membranes and cell walls) to alter the permeability of cell membranes. At high concentrations, it exhibits bactericidal activity by producing necrotic changes in cells.

(3) Triamcinolone acetonide inhibits phospholipase A2 in the cell membrane, thereby blocking the synthesis of anti-inflammatory transmitters. It also stabilizes the lysosome membrane, which inhibits the release of hydrolase, thereby inhibiting the inflammation process. The inhibition of protein synthesis prevents capillary and fibroblast overgrowth and collagen deposition.

**In Vivo Pharmacokinetics**

1. Dermal Penetration

After repeated application of 0.02 g of Orbifloxacin MT Cream to a 1 cm² area of skin for seven days in dogs and cats, the concentrations of all three drugs, orbifloxacin, miconazole nitrate and triamcinolone acetonide, peaked and reached saturation on Day 5 in dogs. In cats, dermal concentrations of orbifloxacin and triamcinolone acetonide increased through Day 3 and remained at comparable levels subsequently. Miconazole nitrate concentrations remained approximately constant throughout the treatment period.

2. Elimination

To evaluate the elimination of Orbifloxacin MT Cream from the skin, a single dose equivalent to the dose used in the dermal penetration study was applied to dogs and cats. The concentrations of all three drugs decreased rapidly through Day 10 in dogs and Day 5 in cats, with gradual decrease thereafter. The results indicated that drug delivered into the skin is eliminated through skin turnover rather than metabolism or degradation in both dogs and cats.

**Toxicity**

1. Acute toxicity of Orbifloxacin MT Cream

<table>
<thead>
<tr>
<th>Animal Species</th>
<th>Sex</th>
<th>Administration Route</th>
<th>No. of Animals</th>
<th>LD₅₀ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (SD)</td>
<td>Male</td>
<td>Oral</td>
<td>10</td>
<td>&gt;2,000</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Oral</td>
<td>10</td>
<td>&gt;2,000</td>
</tr>
</tbody>
</table>

2. Subacute Toxicity

The NOAEL was 50 mg/kg/day in a 4-week repeated oral gavage study of orbifloxacin in rats. The NOAEL was 50 mg/animal/day in a 30-day repeated dermal study of miconazole nitrate in rats.

3. Chronic Toxicity

The NOAEL was 50 mg/kg/day in a 13-week repeated oral gavage study of orbifloxacin in rats. The NOAEL was 3 mg/kg/day in a 26-week repeated oral gavage study of miconazole nitrate in rats.

4. Teratogenicity

Teratogenicity was not observed with oral administration of orbifloxacin to rats. Teratogenicity was also not observed with oral or transvaginal administration of miconazole nitrate to rats.

**Safety**

A study evaluating the safety of repeated dermal application of Orbifloxacin MT Cream to the shaved dorsal skin of dogs and cats for seven days did not reveal any significant findings in any of the study parameters (local skin reaction, general clinical observations, food intake, body-weight gain, temperature, hematology tests and blood chemistry tests).
**Description**

1. **Formulation**
Orbifloxacin MT Cream is a pale yellow cream, with a slight distinctive odor.

2. **Effective Ingredients**
   
   **Generic name**: Orbifloxacin  
   **Chemical name**: 1-cyclopropyl-5, 6, 8-trifluoro-1, 4-dihydro-7-(cis -3, 5-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid  
   **Chemical formula**: C<sub>19</sub>H<sub>20</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>  
   **Molecular weight**: 395.38  
   **Melting point**: Approximately 263 °C (degradation)  
   **Description**: Orbifloxacin is a white to pale yellow, odorless, crystalline powder. It is soluble in acetic acid (100), very slightly soluble in water and methanol and practically insoluble in ethanol (95). It dissolves in dilute acetic acid and dilute sodium hydroxide reagent.

![Orbifloxacin structure](image)

**Generic name**: Miconazole nitrate  
**Chemical name**: 1-[(2RS)-2-(2,4 –dichlorobenzyloxy)-2(2-4-dichlorophenyl)ethyl]-1H-imidazole mononitrate  
**Chemical formula**: C<sub>18</sub>H<sub>15</sub>Cl<sub>4</sub>N<sub>3</sub>O<sub>4</sub>  
**Molecular weight**: 479.14  
**Description**: Miconazole nitrate is a white crystalline powder. It is freely soluble in N,N-dimethylformamide, sparingly soluble in methanol, slightly soluble in ethanol (95), acetone and acetic acid (100) and very slightly soluble in water and diethyl ether.

![Miconazole nitrate structure](image)

**Generic name**: Triamcinolone acetoniode  
**Chemical name**: 9-fluoro -11β, 21-dihydroxy-16α, 17 (1-methylethylidenedioxy)pregna-1,4-diene-3, 20-dione  
**Chemical formula**: C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>  
**Molecular weight**: 434.50  
**Description**: Triamcinolone acetate is a white, odorless, crystalline powder. It is sparingly soluble in ethanol (99.5), acetone and acetic acid (100) and very slightly soluble in water and diethyl ether.

![Triamcinolone acetoniode structure](image)
Packaging
Orbifloxacin MT Cream 5 g
20 g × 5
20 g

Marketing authorization holder
DS Pharma Animal Health Co., Ltd.
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