The following is an English translation of the package insert for the drug sold in Japan (as of April 2012).

Fluoroquinolone Antimicrobial Agent for Dogs and Cats
Veterinary Drug
Prescription Legend Drug
Orbifloxacin Injection 5%

Orbifloxacin Injection 5% is an injectable preparation for dogs and cats developed by Dainippon Sumitomo Pharma Co., Ltd. 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 also exhibits antibacterial activity against bacteria that are resistant to antibiotics.
Orbifloxacin Injection 5% is well absorbed after subcutaneous administration. Its other characteristics include high blood concentrations and good tissue penetration.

■Composition

Orbifloxacin Injection 5% contains 50 mg of orbifloxacin per milliliter. It also contains 20 mg per milliliter of the additive benzyl alcohol.

■Indications

Indicated Microorganisms
Staphylococcus species, *Streptococcus* species, *Enterococcus* species, *Escherichia coli*, *Klebsiella* species, *Proteus* species, *Pseudomonas aeruginosa*, *Pasteurella multocida*

Indicated Diseases
Dogs: Bacterial urinary tract infection, bacterial skin infection
Cats: Bacterial urinary tract infection, bacterial skin infection

■Dosage and administration

The dosage in dogs and cats is the following amounts of orbifloxacin per kilogram of body weight administered intravenously once daily.
Dogs: 2.5 to 5.0 mg (0.05 to 0.1 mL of solution), 2 to 7 days
Cats: 2.5 to 5.0 mg (0.05 to 0.1 mL of solution), 2 to 7 days

■Precautions

[General Precautions]

(1) Orbifloxacin Injection 5% is a prescription legend drug dispensed by prescription or order of a veterinarian.
(2) The use of Orbifloxacin Injection 5% is restricted to animals that have failed standard therapy.
(3) Orbifloxacin Injection 5% must be used only for the indications listed in the Indications section.
(4) Orbifloxacin Injection 5% should be used only as indicated. Do not repeat administration, even if administration does not exceed the number of days specified in the Dosage and Administration section.
(5) To prevent the development of resistant bacteria during the use of Orbifloxacin Injection 5%, susceptibility should be determined and treatment should be discontinued at the minimum time necessary to treat the indication.

[User Precautions]
(1) Consult a physician immediately in case of accidental ingestion by humans.

[Precautions for Dogs and Cats]
1. Restrictions
(1) The safety of Orbifloxacin Injection 5% has not been established in immature dogs less than four months of age.
(2) Orbifloxacin Injection 5% is effective against strains that are highly resistant to nalidixic acid, but it is not effective against strains that are highly resistant to fluoroquinolones.

2. Adverse Reactions
(1) Consult a veterinarian immediately in case of adverse reaction.
(2) Orbifloxacin Injection 5% may occasionally cause swelling, induration, mass formation and necrosis at the injection site.
(3) Orbifloxacin Injection 5% may occasionally cause vomiting, diarrhea, ischemia, edema, erythema and pruritus.

3. Interactions
(1) Rare instances of convulsion have been reported with concurrent administration of NSAIDs, which are analogous compounds.

4. Usage Precautions
(1) Orbifloxacin Injection 5% must be administered cautiously while closely monitoring the animal's condition.
(2) Use injection equipment that has been sterilized or sterilized by boiling. Do not use chemically disinfected equipment or equipment that was used for other drugs (gas-sterilized equipment is permitted). Allow equipment sterilized by dry heat, autoclave or boiling to reach room temperature prior to use.

[Handling Precautions]
(1) Use promptly if Orbifloxacin Injection 5% must be divided for use.
(2) Dispose of used equipment according to local government regulation.

[Storage Precautions]
(1) Keep out of the reach of children.
(2) Store Orbifloxacin Injection 5% away from direct sunlight and high humidity.
(3) To avoid misuse and preserve quality, keep in the original package.

■Therapeutic Efficacy and Pharmacology
1. Antibacterial Activity
(1) Orbifloxacin Injection 5% has a broad antibacterial spectrum. It exhibits potent antibacterial activity against a broad spectrum of gram negative and gram positive bacteria.
(2) Orbifloxacin Injection 5% also exhibits antibacterial activity against bacteria that are resistant to such antibiotics as ampicillin, oxytetracycline and kanamycin.

2. Resistance
Inherent bacterial resistance to Orbifloxacin Injection 5% is uncommon.

3. Mechanism of Action
Orbifloxacin Injection 5% exhibits bactericidal activity by inhibiting the activity of bacterial DNA gyrase and topoisomerase IV, which prevents DNA replication.

■***In Vivo* Pharmacokinetics**

1. Plasma Concentration

Following subcutaneous administration of a single dose of 5 mg/kg to dogs and cats, the plasma concentration peaked at two hours (dogs: 3.4 μg/mL, cats: 3.0 μg/mL). The half-life was 8.9 and 3.7 hours respectively.

2. Tissue Concentration

Orbifloxacin Injection 5% is widely distributed in organs and tissues after subcutaneous administration. The concentration is higher than or approximately equivalent to the plasma concentration in nearly all organs and tissues, including the kidneys, liver, lungs and skin, demonstrating good tissue penetration.

3. Metabolism and Excretion

Orbifloxacin Injection 5% is eliminated primarily through the urine. Urinary metabolite analysis has shown that unchanged drug accounts for the majority of urinary recovery (dogs ≥90%, cats ≥80%). Orbifloxacin Injection 5% therefore has limited *in vivo* metabolism, indicating that it possesses the antibacterial activity of the unchanged drug as it is distributed in the body.

■**Toxicity**

1. Acute toxicity LD_{50} (mg/kg)

Animal Species/Sex \ Administration Route		Intravenous	Intramuscular	Oral
Mouse (CD-1)	Male	250	>500	>2,000
	Female	283	>500	>2,000
Rat (CD)	Male	233	>200	>2,000
	Female	270	>200	>2,000

2. Chronic Toxicity

The NOAEL was 50 mg/kg in a 13-week oral study in rats.

3. Teratogenicity

In studies of oral administration during organogenesis in rats and rabbits, teratogenicity was not observed in rat or rabbit dams at the respective toxic doses of 500 mg/kg and 100 mg/kg.

4. Primary Palpebral Conjunctival Irritation

Evaluation of primary palpebral conjunctival irritation following injection of 0.1 mL of Orbifloxacin Injection 5% into the palpebral conjunctival sac of rabbits revealed transient congestion thought to be due to pH (acidity). The irritation was not, however, severe enough to be significant and improved with eye washing.

5. Primary Skin Irritation

Patches of lint containing 0.5 mL of Orbifloxacin Injection 5% were applied to the shaved dorsal skin of rabbits. Evaluation of primary skin irritation four hours after application did not reveal any erythema, eschar formation or edema.

■**Safety**

1. Safety in Dogs

A study evaluating the safety of once-daily repeated subcutaneous administration of 5 mg (recommended maximum dose), 10 mg (double dose) and 25 mg (quintuple dose) per kilogram of body weight for seven days was conducted in four-month-old beagles. Necropsy results showed mildly decreased total protein in the high dose group and a dose-dependent increase in CPK activity and mildly increased GPT activity attributed to degeneration and necrosis of the cutaneous muscle in the subcutaneous tissue at the injection site. All of the changes were transient, however. No other

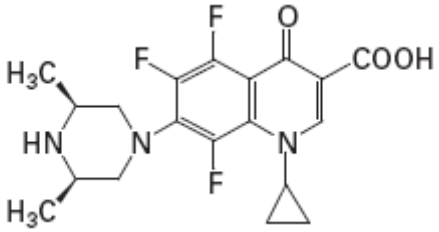
changes attributable to the administration of Orbifloxacin Injection 5% were noted. Administration of Orbifloxacin Injection 5% also did not result in upper gastrointestinal damage, CNS damage or arthropathy. It was therefore concluded that the subcutaneous administration of a 25 mg/kg dose of Orbifloxacin Injection 5%, equivalent to five times the recommended maximum dose, for seven days does not result in any significant safety issues.

2. Safety in Cats
A study evaluating the safety of once-daily repeated subcutaneous administration of 5 mg (recommended maximum dose), 10 mg (double dose) and 25 mg (quintuple dose) per kilogram of body weight for seven days was conducted in five-month-old laboratory mongrel cats. The results showed anorexia in some of the animals administered the double dose and all of the animals administered the quintuple dose and transient mild vomiting in some of the animals administered the quintuple dose. A dose-dependent increase in CPK activity attributed to damage and inflammatory changes in the muscle groups in the subcutaneous tissue at the injection site and mildly decreased total protein were also observed. All of the changes were transient, however. Arthropathy was not observed in any of the dosing groups. There were no significant findings, except trauma from scratching the injection site, at the recommended maximum dose. It was therefore concluded that repeated subcutaneous administration of a 10 mg/kg dose of Orbifloxacin Injection 5%, equivalent to twice the recommended maximum dose, for seven days does not result in any significant safety issues.

■Description

1. Formulation
Orbifloxacin Injection 5% is an off-white to pale yellow, clear, aqueous injectable solution containing 50 mg of orbifloxacin per milliliter.

2. Effective Ingredient
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: $C_{19}H_{20}F_3N_3O_3$
Molecular weight: 395.38
Melting point: Approximately 263 °C (degradation)
Description: Orbifloxacin is a white to pale yellow, odorless, crystalline powder, with a bitter taste. It is soluble in acetic acid, very slightly soluble in water, methanol and chloroform and practically insoluble in ethanol and ether. It dissolves in dilute acetic acid and dilute sodium hydroxide reagent



■Other Precautions

•Store at room temperature in a sealed opaque container.
•Ensure that the expiration date is visible.

■Packaging

Orbifloxacin Injection 5%: 20 mL × 1 vial

Marketing authorization holder
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