SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Itrafungol 10 mg/ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

		mg/ml
Active substance(s):	Itraconazole	10
Excipients:	Caramel (E150)	0.2
	Propylene glycol (E1520)	103.6
	Sorbitol 70% Non-crystallising Solution	245.1

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution
Yellow to slightly amber, clear solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cat.

4.2 Indications for use, specifying the target species

Treatment of dermatophytosis caused by *Microsporum canis.*

4.3 Contraindications

Do not administer to cats with hypersensitivity to itraconazole or one of the other ingredients.
Do not administer to cats with impaired liver or kidney function.
For use in pregnant and lactating queens: see section 4.7

4.4 Special warnings <for each target species>

Some cases of feline dermatophytosis can be difficult to cure, especially in catteries.
Cats treated with itraconazole can still infect other cats with *M. canis* as long as they are not mycologically cured. It is therefore advised to minimise the risk of re-infection or spread of infection by keeping healthy animals (including dogs as they can also be infected by *M. canis*) separate from cats that are being treated. Cleaning and disinfection of the environment with appropriate fungicidal products is highly recommended – especially in case of group problems.

When clipping the hair of infected cats, the advice of the veterinarian should be sought first.

Clipping of the hair coat is considered useful because it removes infected hairs, stimulates new hair growth and hastens recovery. It is strongly recommended that clipping is performed by a veterinarian. In cases with limited lesions, hair clipping can be limited to the lesions only, whereas in cats with generalized dermatophytosis it is recommended to clip the entire hair coat. Care should be taken not to cause trauma to the underlying skin during clipping. It is recommended that disposable, protective clothing and gloves are worn during the clipping of the affected animals. The clipping of the hair should be performed in a well ventilated room which can be disinfected after clipping. The hairs should be disposed of appropriately and all instruments, clippers etc. should be disinfected.

Treatment of dermatophytosis should not be limited to treatment of the infected animal(s). It should also include disinfection of the environment with appropriate fungicidal products, since *M. canis* spores can survive in the environment for up to 18 months. Other measures such as frequent vacuuming, disinfection of grooming equipment and removal of all potentially contaminated material that cannot be disinfected will minimize the risk of re-infection or spread of infection. Disinfection and vacuuming should be continued for an extended period after the cat is clinically cured, but vacuuming should be limited to surfaces, which may not be cleaned with a damp cloth. All other surfaces should be cleaned with a damp cloth. Any cloth used for cleaning should be washed and disinfected or disposed of and the used vacuum cleaner bag should be disposed of.

Measures to prevent introduction of *M.canis* into groups of cats may include isolation of new cats, isolation of cats returning from shows or breeding, exclusion of visitors and periodic monitoring by Wood's lamp or by culturing for *M.canis*.

In refractory cases the possibility of an underlying disease should be considered.

Frequent and repeated use of an antimycotic may result in the induction of resistance to antimycotics of the same class.

Refer to section 4.5 ii) for Operator warnings.

4.5 Special precautions for use

i) Special precautions for use in animals

Cats suffering from dermatophytosis, but also in poor general condition and/or suffering from additional diseases or impaired immunological response should be monitored closely during treatment. Because of their condition, this category of animals may be more sensitive to the development of adverse effects. In case of a serious adverse effect, treatment should be interrupted and supportive care therapy (fluid therapy) should be initiated if necessary. If clinical signs suggestive of liver dysfunction develop, treatment should be discontinued immediately. It is very important to monitor liver enzymes in animals showing signs of liver dysfunction.

In humans, itraconazole has been associated with heart failure due to a negative inotropic effect. Cats suffering from heart diseases should be carefully monitored and the treatment should be withdrawn if the clinical signs deteriorate.

ii) Special precautions to be taken by the person administering the veterinary medicinal product to animals

If a suspected lesion occurs on a human, consult a physician, since *M.canis* dermatophytosis is a zoonotic disease. Therefore, wear latex gloves when clipping hair of infected cats, when handling the animal during treatment or when cleaning the syringe.

Wash hands and exposed skin after use. In case of accidental contact with eyes, rinse thoroughly with water. In case of pain or irritation, seek medical advice. In case of accidental ingestion, rinse mouth with water.

4.6 Adverse reactions (frequency and seriousness)

In clinical studies, some form of adverse reaction possibly related to the administration of the product were noted. Common adverse reactions were vomiting, diarrhoea, anorexia, salivation, depression and apathy. These effects are usually mild and transient. In very rare cases a transient increase in liver enzymes may occur. In very rare cases this was associated with icterus. If clinical signs suggestive of liver dysfunction develop, treatment should be discontinued immediately.

4.7 Use during pregnancy, lactation or lay

Do not use in pregnant or lactating queens. Malformations and foetal resorptions were seen in overdose studies in laboratory animals.

4.8 Interaction with other medicinal products and other forms of interaction

Vomiting, hepatic and renal disorders were seen after concomitant treatment of Itrafungol and cefovecin. Symtoms like motor incoordination, faecal retention and dehydration are observed when tolfenamic acid and Itrafungol are given simultaneously. Co-administration of the product and these drugs, in absence of data in cats, should be avoided.

In human medicine, interactions between itraconazole and certain other drugs have been described, resulting from interactions with cytochrome P450 3A4 (CYP3A4) and P-glycoproteins (PgP). This may result in increased plasma concentrations of e.g. oral midazolam, cyclosporin, digoxin, chloramphenicol, ivermectin, or methylprednisolone. The increased plasma levels can prolong the duration of effects as well as side effects. Itraconazole may also increase the serum level of oral antidiabetic agents, which may result in hypoglycaemia..
On the other hand, some drugs, e.g. barbiturates or phenytoin can increase the rate of metabolism of itraconazole, resulting in a decreased bioavailability, hence a decreased efficacy. As itraconazole requires an acidic environment for maximal absorption, antacids cause a marked reduction in absorption. Concomitant use of erythromycin can increase the plasma concentration of itraconazole.
Interactions in humans between itraconazole and calcium antagonists have also been reported. These drugs might have additive negative inotropic effects to the heart.

It is not known to what extent these interactions are relevant for cats, but in the absence of data, co-administration of the product and these drugs should be avoided.

4.9 Amounts to be administered and administration route

The solution is administered orally directly into the mouth by means of a dosing syringe.
The daily dosage is 5 mg/kg or 0.5 ml/kg/day.
The dosage regime is 0.5 ml/kg/day for 3 alternate periods of 7 consecutive days, each time with 7 days without treatment in between.

7 days	7 days	7 days	7 days	7 days
treatment	no treatment	treatment	no treatment	treatment

The dosing syringe shows graduations per 100 gram of body weight. Fill the syringe by pulling the plunger until it reaches the graduation corresponding to the correct body weight of the cat.

When administering the product to kittens, the administrator should be careful not to administer more than the recommended dose/weight. For kittens weighing less than 0.5 kg, a 1 ml syringe which allows proper dosing should be used.

Treat the animal by slowly and gently injecting the liquid into the mouth, allowing the cat to swallow the product.

After dosing, the syringe should be removed from the bottle, washed and dried and the cap should be screwed back on tightly.

Data in humans shows that food intake may result in lower drug absorption. Therefore, it is recommended to administer the product by preference between meals.

In some cases, a prolonged time between clinical and mycological cure may be observed. In cases where a positive culture is obtained 4 weeks after the end of administration, the treatment should be repeated once at the same dosage regimen. In such cases where the cat is also immunosuppressed, treatment should be repeated and the underlying disease addressed.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After a 5x overdose of itraconazole administered for 6 consecutive weeks, reversible clinical side effects were: rough hair coat, decreased food intake and reduced body weight. A 3x overdose for 6 weeks did not result in clinical side effects. Both after a 3x and a 5x overdose for 6 weeks, reversible change in serum biochemical parameters indicating liver involvement occur (increased ALT, ALP, bilirubin and AST). At 5 times overdose a slight increase in segmented neutrophils and a slight decrease in lymphocytes were observed.

No studies on overdose in kittens have been performed.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivates
ATCvet code: QJ02AC02

Itrafungol contains itraconazole, a synthetic broad spectrum triazole antimycotic with a high activity against dermatophytes (*Trichophyton* spp, *Microsporum* spp.), yeasts (*Candida* spp., *Malassezia* spp.), various dimorphic fungi, zygomycetes and eumycetes (e.g. *Aspergillus* spp.).

5.1 Pharmacodynamic properties

The mode of action of itraconazole is based on its highly selective binding ability to fungal Cytochrome P-450 iso-enzymes. This inhibits the synthesis of ergosterol and affects membrane-bound enzyme function and membrane permeability. This effect is irreversible and causes structural degeneration.

5.2 Pharmacokinetic particulars

Laboratory animals rapidly absorb orally administered itraconazole. It binds very extensively to plasma proteins (>99 %) and distributes to tissues. More than 30 metabolites are formed, from which hydroxy-itraconazole has an antifungal activity as the parent. Excretion is rapid and mainly via the faeces.

In cats a single oral dose of 5 mg/kg results in maximum plasma concentrations of on average
0.525 mg/l attained 2 hours after dosing. The $AUC_{0\text{-}24\ h}$ is 5 mg.h/l. The half-life in plasma is about 12 hours. After repeated administration for one week at 5 mg/kg/day, the maximum plasma concentration is more than doubled. The $AUC_{0\text{-}24\ h}$ is increased 3 times to 15 mg.h/l and the plasma half-life is also increased 3 times to 36 hours.

In the therapeutic treatment schedule, itraconazole is almost completely cleared from plasma after each wash-out. In contrast to what happens in other animals, hydroxy-itraconazole remains near or below the quantification limit in plasma after a single dose of itraconazole at 5 mg/kg. Concentrations in cat's hair vary; an increase occurs during treatment to a median value of 3.0 μg/g (mean 5.2 μg/g) at the end of the third dosing week and concentrations drop slowly to 1.5 μg/g (mean 1.9 μg/g) at 14 days after the end of treatment. Concentrations of hydroxy-itraconazole in hair are insignificant.

Bioavailability of the oral solution of itraconazole in humans is higher when administered in fasted conditions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

caramel (E150)
propylene glycol (E1520)
sorbitol 70 % non-crystallising solution
hydroxypropyl-b-cyclodextrin

concentrated hydrochloric acid
sodium hydroxide
sodium saccharin
cherry flavour
purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening of the container: 5 weeks.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed

6.5 Nature and composition of immediate packaging

Amber glass bottle (type III) containing 52 ml oral solution, closed with a child resistant polypropylene screw cap with a LDPE insert packed in a cardboard box with a graduated dosing syringe.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

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

7. MARKETING AUTHORISATION HOLDER

VIRBAC
1ère avenue 2065m LID
06516 Carros
France

8. MARKETING AUTHORISATION NUMBER

Vm 05653/4228

9. DATE OF FIRST AUTHORISATION

13 December 2002

10. DATE OF REVISION OF THE TEXT

July 2021

Approved: 13/07/21