TOPETFARMA

FUNGITRAXX®

THE FACTS

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FUNGITRAXX®

Fungitraxx® is the first European registered antifungal product for birds.

It contains 10 mg/ml of itraconazole.

Itraconazole is a static antifungal medicine, with activity against *Aspergillus* spp. and *Candida* spp, two common pathogens in birds.

Fungitraxx® is an oral medicine. It can be administered directly into the mouth of the bird with a dosing syringe. Another way of administering the product is by mixing the prescribed dose with some food: in this case, one must ensure that the medicated food is eaten within an hour.

It is recommended that food should be provided at around the time of administering the medicine, as data in birds show that concomitant food intake results in higher absorption of itraconazole. (Hsu 2013, Handbook of Veterinary Pharmacology)

The caramel-flavour present in Fungitraxx® ensures that most birds find the solution palatable, facilitating acceptance.

An important, distinctive ingredient of Fungitraxx® is a cyclodextrin. This is a ring of glucose molecules. Within this ring a molecule can be present (in this case itraconazole).

This enables solubilisation and enhances absorption of the itraconazole.(Tell et al. 2005, Smith et al. 2010) Steady state plasma levels of itraconazole are reached six (6) days after the start of treatment.

Adverse effects in birds, are usually mild and dose-related. If emesis or anorexia occurs, it is advisable to lower the dose.

Itraconazole is not well tolerated by African grey parrots (*Psittacus erithacus*). These birds may exhibit anorexia, vomiting and/or depression. The product should, therefore, be used in this species at the lowest recommended dose (for the whole of the recommended treatment period).

Dosage

Aspergillosis: 5 – 10 mg itraconazole per kg bodyweight per day for eight (8) weeks. This corresponds to 0.5 – 1.0 millilitres Fungitraxx® per kilogram bodyweight per day.

In some cases, a prolonged period between clinical and mycological cures is observed. In cases where clinical signs are still present, or endoscopy indicates a remaining fungal presence eight (8) weeks after the start of treatment, the whole eight (8) week course of treatment should be repeated (using the same dosage regimen).

In severe cases of aspergillosis, an extended duration of treatment is often necessary.

Candidiasis: 10 mg itraconazole per kg bodyweight per day over fourteen (14) days.

For treatment of candidiasis in African grey parrots use 5 mg itraconazole per kg bodyweight per day for fourteen (14) days.

The bodyweight of the bird should be determined as accurately as possible – and weighing of the bird repeated periodically during prolonged treatment - to avoid underdosing or overdosing.

Itraconazole

The active ingredient in Fungitraxx® is itraconazole.

Itraconazole has long been used as an antifungal drug in human medicine.

The mode of action of itraconazole is based on its highly selective binding ability for fungal cytochrome P-450 iso-enzymes. Itraconazole inhibits the synthesis of ergosterol. It also affects membrane-bound enzyme function and membrane permeability and, as this effect is irreversible, it results in structural degeneration of the fungus. Itraconazole is thereby a medicine with static activity.

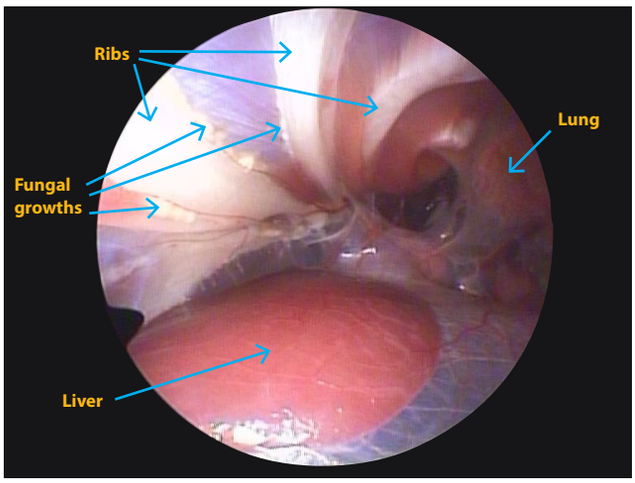
The minimum inhibitory concentrations of itraconazole for different *Aspergillus* isolates (*Aspergillus fumigatus, Aspergillus flavus* and *Aspergillus niger*) vary between 0.01 and 10 µg/ml; however, the normal range is 0.1 to 1.0 µg/ml. The minimum inhibitory concentrations (MICs) for different isolates of *Candida* range between 0.03 and >16 µg/ml, with most isolates having sensitivities of 0.25 to 2.0 µg/ml.

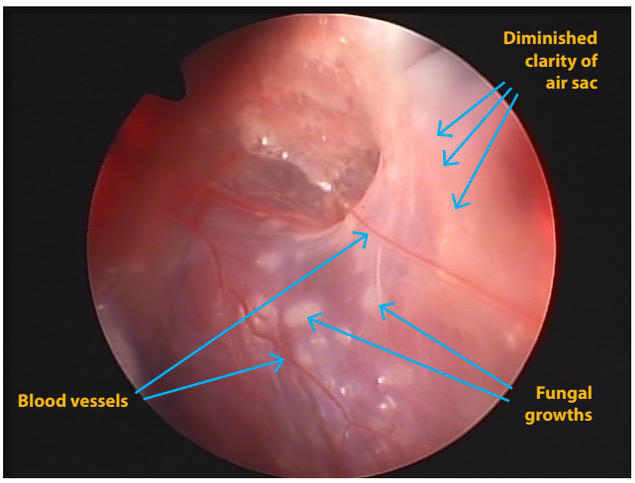
Pharmacokinetic properties

In birds, itraconazole plasma concentrations vary with the type of bird. The different target species consume different types of food and exhibit differing metabolism. One main metabolite, hydroxyitraconazole, has the same antifungal activity as the parent drug.

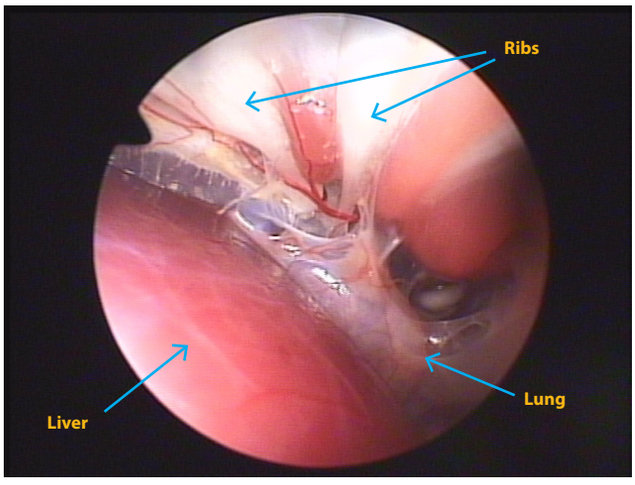
Itraconazole elimination may be a saturable process. Because of its long half-life, itraconazole does not reach

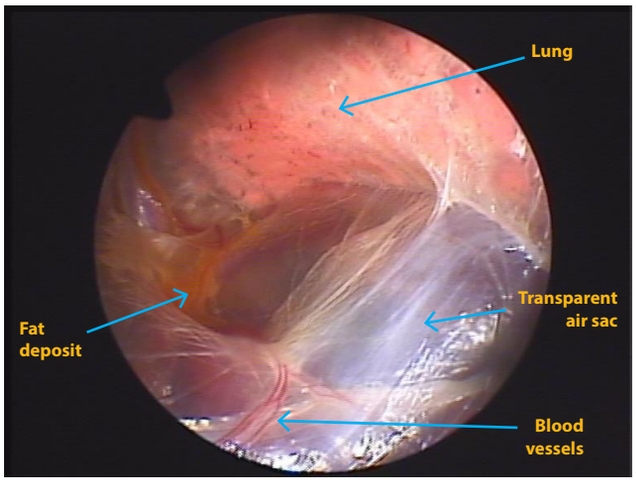
Before FUNGITRAXX® treatment





After FUNGITRAXX® treatment





steady state plasma levels for at least 6 days after the start of treatment.

Fungal infections in birds

Fungal infections are a frequent cause of illness and death in birds.

Two of the most common fungal pathogens are *Candida albicans* and *Aspergillus* spp.

Candida infection is usually associated with problems in the digestive tract, especially in ingluvitis ('sour crop'). It can, however, be either a primary cause of crop infections or a secondary pathogen.

Candida may be a normal inhabitant of the avian gastrointestinal tract. Problems occur when the presence of normal bacterial flora is disturbed (e.g. through the use of antibiotics). This can cause an increase in the number of *Candida* organisms.

In animals with a compromised or immature immune system, spontaneous primary candidiasis can occur.

Infection with *Aspergillus* spp. most frequently causes respiratory problems.
Respiratory disease is one of the most common findings in birds presented to veterinarians. An *Aspergillus* sp. may be the primary pathogen, or an opportunistic agent which complicates the already present condition.

The most common clinical findings in a bird suffering from *Aspergillus* infection include emaciation, respiratory distress, neuromuscular disease and abnormal droppings.

The total blood count will often show a chronic inflammatory white cell response. Radiographs can show cloudy air sacs and/or obvious granulomas, but sometimes a severely affected bird will exhibit no abnormality on radiographs.

Respiratory conditions caused by *Aspergillus* spp. can be present in both the upper and lower respiratory tract.

Upper respiratory aspergillosis can appear as granulomas. These can deform the nasal anatomy. The underlying tissue must be cultured to obtain a definitive diagnosis.

Lower respiratory aspergillosis is a more frequent problem and, unfortunately, more difficult to diagnose. Fungal growth can be present in lungs, air sacs and can also spread to other internal organs.

Currently the best method to diagnose lower respiratory aspergillosis is through endoscopy. Biopsies can be obtained and cultured to confirm the diagnosis.

In addition to respiratory problems, *Aspergillus* infection can cause other problems in birds.
In certain circumstances, *Aspergillus* organisms can cause disease in the entire body. On account of the unique anatomy of birds, lower respiratory aspergillosis is able to spread to other organs in the coelomic cavity. Examples of organs

commonly affected are the ovary and testis; this can result in poor breeding results. If the kidneys are involved, polyuria, polydipsia and gout may be observed. Aspergillosis can manifest itself by forming granulomas; the size and location of these granulomatous masses can cause problems because of their space-invading properties.

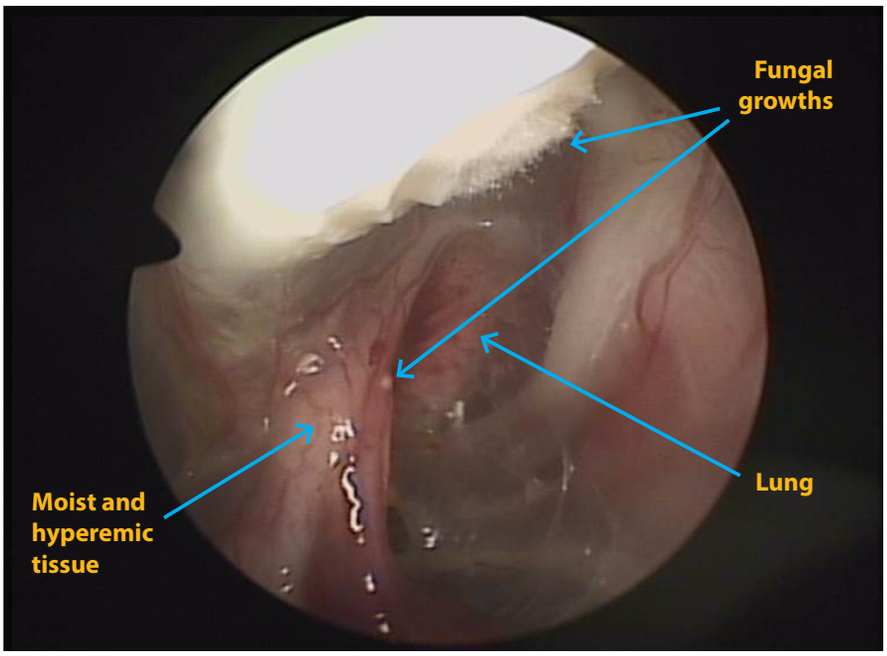
Aspergillus infections can also be found on the exterior of the bird. Fungal infections of the skin and beak are frequently encountered. These can be difficult to cure and (certainly in case of infections of the horny beak) often need long-term treatment.

In any infection associated with *Candida* or *Aspergillus* spp. in birds, it is wise to search for an underlying cause.

The infection in itself must be treated with the proper medication, but successful treatment also involves correcting the underlying conditions.

Some examples of predisposing conditions which can lead to fungal infections are:

- malnourishment or deficiencies in the regular diet of the bird.
- damp and unsanitary environment.
- contaminated food (peanuts, in particular, are known to be frequently contaminated with *Aspergillus* spores).
  In addition, insufficient hygiene in preparation of diets can predispose hand-fed baby parrots to *Candida* infections.
- concurrent infections with viruses, bacteria and/or parasites.
- use of antibacterial antibiotics
- stress



A severe case of lower respiratory aspergillosis

ITRACONAZOLE IN BIRDS -

SOME EARLIER (STANDARD) BOOK REFERENCES TO ITS USE

Cooper, JE (2002). Medicines and other Agents. *Birds of Prey: Health & Disease* Blackwell, Oxford.

Beynon, PH, Forbes, NA and Lawton, MPC (1996). Antifungals (Formulary) Eds. *Manual of Psittacine Birds*. British Small Animal Veterinary Association, Cheltenham, Glos. UK. Itraconazole (Sporanex, Janssen).

5-10 mg/kg twice a day for 3 weeks.

Beynon, PH, Forbes NA and Harcourt-Brown (1996). *Manual of Raptors, Pigeons and Waterfowl.* Antifungal agents (Formularies (Raptors) and Formularies (Waterfowl). Itraconazole (Sporanox Capsules, Janssen).British Small Animal Veterinary Association, Cheltenham, Glos. UK

Ritchie *et al* (1994). Treatment Regimens. Itraconazole (Sporanex, Janssen).*Avian Medicine: Principles and Applications*. Wingers, Lake Worth, Florida, USA.

Further literature

Tell LA et al Studies on itraconazole delivery and pharmacokinetics in mallard ducks (Anas platyrhynchos). Journal of Veterinary Pharmacology and Therapeutics2005 Jun;28(3):267-74.

Smith JA et al Effects of compounding on pharmacokinetics of itraconazole in black-footed penguins (Spheniscus demersus). Journal of Zoo and Wildlife Medicine 2010 Sep;41(3):487-95.

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