FORCYL 16 % Solution for Injection

VETERINARY MEDICINE

SCHEDULING STATUS **S4**

1. NAME OF VETERINARY MEDICINE

FORCYL ® 16% Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml sterile aqueous solution of FORCYL contains:
Active Ingredient: 160 mg marbofloxacin
Preservative: 15 mg Benzyl Alcohol (E 1519).

3. PHARMACEUTICAL FORM

Solution for injection
Clear yellow greenish to yellow brownish solution

4. CLINICAL PARTICULARS

4.1 Target Species

Cattle
Pigs (fattening pigs, weaned piglets, sows)

Indications for use, specifying the target species

Cattle: Therapeutic treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida* and *Mannheimia haemolytica*.
In lactating cows*:* Treatment of acute mastitis caused by sensitive strains of *Escherichia coli*

Pigs:
In fattening pigs: Treatment of respiratory tract infections caused by susceptible strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*
In weaned piglets: Treatment of intestinal infections caused by susceptible strains of *E. coli*
In post-partum sows: Treatment of Metritis-Mastitis-Agalactiae syndrome (form of postpartum dysgalactiae syndrome, PPDS) caused by susceptible strains of *E. coli*

4.2 Posology and method of administration

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.
Cattle: Therapeutic treatment of respiratory infections: **10 mg/kg** body weight i.e., 10 ml/160 kg body weight in a single intramuscular injection

- Treatment of acute mastitis caused by sensitive strains of *Escherichia coli*: 10 mg/kg body weight i.e., 10 ml/160 kg body weight in a single intramuscular or intravenous injection

If the volume to be injected in more than 20 ml, it should be divided between two or more injection sites.

Pigs: The recommended dose is **8 mg/kg** body weight i.e., 1 ml/20 kg body weight in a single intramuscular injection in the side of the pig neck.

4.3 Contraindications

- Do no use in animals with known hypersensitivity to fluoroquinolones or to any of the excipients
- Do not use in cases where the pathogen involved is resistant to other fluoroquinolones (cross resistance)

4.4 Special warnings and precautions for use

Special warnings < for each target species >
Piglets:

- To limit development of resistance, do not use fluoroquinolones as prophylaxis or metaphylaxis during weaning

Lactating cows:

- The efficacy of the product has not been tested on mastitis caused by Gram positive bacteria

Special precautions for use

i) Special precautions for use in animals

Official and local antimicrobial policies should be considered when this product is used.
Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.
Wherever possible, use of the product should only be based on susceptibility testing.
Use of the product deviating from the instructions given in this PI may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance.

ii) Special precautions to be taken by the person administering the veterinary medicine

People with known hypersensitivity to fluoroquinolones and benzyl alcohol should avoid any contact with the product.
Wash hands after use. Avoid contact of the skin and eyes with the product. If the product comes into contact with the skin or eyes, rinse with copious amounts of water.
Care should be taken to avoid accidental self-injection. In the event of accidental self-administration, the user should immediately seek professional medical care.
Accidental self-injection can induce a slight irritation.

4.5 Interactions with other medicinal products and other forms of interaction
None known

4.6 Fertility, pregnancy, and lactation
Studies in laboratory animals (rats, rabbits) did not show any evidence of a teratogenic, embryotoxic or maternotoxic effect associated with the use of marbofloxacin.

Safety of the product at:
- 10 mg/kg has not been determined in pregnant cows or in suckling calves when used in cows.
- 8 mg/kg in pregnant sows or in suckling piglets when used in sows.

Use only according to the benefit/risk assessment by the responsible veterinarian.

4.7 Adverse reactions (frequency and seriousness)
In Cattle: Very rare cases (less than 1 animal in 10,000 animals, including isolated reports), of administration by the intramuscular route may cause transient local reactions such as pain and swelling at the injection site which may persist up to 7 days after injection.
In very rare cases, anaphylactic-type reactions with a potentially fatal outcome might occur.
Fluoroquinolones are known to induce arthropathies. In cattle, such lesions were observed after a three day treatment with the 16% marbofloxacin solution. These lesions did not induce clinical signs and should be reversible, particularly if they were to be observed after a single administration.

In Pigs: Local reactions can be observed at the injection site, which disappear within 36 days. Pain at the injection site has been commonly reported (more than 1 but less than 10 animals in 100 animals).

4.8 Overdose (symptoms, emergency procedures, antidotes), if necessary
In Cattle: Lesions of the joint cartilage were observed in some animals treated at 10 mg/kg or 30 mg/kg for three times the recommended treatment duration but did not induce clinical signs. Moreover, no other signs of overdosage was observed throughout this study.

In Pigs: Lesions of the joint cartilage, potentially leading to difficulties in movement, were observed in some animals treated at three times the recommended dose and treatment duration.

4.9 Withdrawal period
Cattle: Meat and offal: 5 days
Milk: 48 hours
Pigs: Meat and offal: 9 days.

5. PHARMACOLOGICAL PROPERTIES
Pharmacological Classification
C17.1.6 Antimicrobials (Quinolones)

5.1 Pharmacodynamical properties
Marbofloxacin is a synthetic, bactericidal antimicrobial, belonging to the fluoroquinolone group which acts by the inhibition of DNA gyrase. It has a broad-spectrum activity in vitro against Gram-positive bacteria and, Gram-negative bacteria. The *in vitro* activity of

marbofloxacin has been demonstrated towards *Pasteurella multocida, Mannheimia haemolytica* and *Escherichia coli.*

The clinical breakpoints defined for marbofloxacin are S ≤ 1 µg/mL, I = 2 µg/mL, and R ≥ 4 µg/mL for Pasteurellaceae according to the "Comité de l'Antibiogramme de la Société Française de Microbiologie" (= French Society of Microbiology) (CA-SFM 2013).

In cattle: The marbofloxacin in vitro activity against pathogens isolated in 2007 from bovine respiratory diseases is good: MIC values are comprised between 0.008 and 0.5 µg/ml for *M. haemolytica* (MIC90 = 0.139 µg/ml; MIC50 = 0.021 µg/ml), between 0.004 and 0.5 µg/ml for *P. multocida* (MIC90 = 0.028 µg/ml; MIC50 = 0.012 µg/ml). In 2008, the marbofloxacin MIC50 for *E. coli* isolated from bovine mastitis was 0.021 µg/ml and the MIC90 was 0.038 µg/ml.

In swine: Between 2009 and 2013, the activity of marbofloxacin against Pasteurella multocida (n=444) and Escherichia coli (n=1226) isolated from swine diseases in Europe was for *P. multocida:* MIC range: 0,004-1 µg/ml, MIC50: 0.013µg/ml MIC90: 0,028µg/ml and for *E. coli* (digestive infections): MIC range 0,008-64µg/ml; MIC50:0,026µg/ml; MIC90:0,681µg/ml, for *E. coli* (MMA syndrome): MIC range 0,015-16µg/ml; MIC50:0,024µg/ml; MIC90:0,475µg/ml. Marbofloxacin MIC distribution among *E. coli* strains isolated from digestive or MMA syndrome are similar with a trimodal distribution**.**
Between 2009 and 2012, the activity of marbofloxacin against *Actinobacillus pleuropneumoniae* (n=157) isolated from swine diseases in Europe was: MIC range: 0.015-2µg/mL, MIC50: 0.03µg/mL, MIC90: 0.06µg/mL

The activity of marbofloxacin against the target bacterial species is bactericidal concentration-dependent.

A decrease of susceptibility of Campylobacter spp. against fluoroquinolones was observed since 1999.

Resistance to fluoroquinolones occurs by chromosomal mutation with three mechanisms: decrease of the bacterial wall permeability, expression of efflux pump or mutation of enzymes responsible for molecule binding. To date, only sporadic cases have been reported for plasmid mediated fluoroquinolone resistance in animals. Depending on the underlying resistance mechanism cross-resistance to other fluoroquinolones and co-resistance to other antimicrobial classes can occur.

5.2 Pharmacokinetic properties
In Cattle:
After a single intramuscular administration in cattle at the recommended dose of **10 mg/kg** body weight, the maximum plasma concentration of marbofloxacin (C_{max}) is 7.915 µg/ml reached in 1.28 h (T_{max}) for an exposure (AUC_{INF}) of 52.7 µg.h/mL. Bioavailability after intramuscular injection is complete (more than 90%). Marbofloxacin is extensively distributed. Binding to plasma proteins is about 30%.

In lactating cows: After intravenous or intramuscular administration, marbofloxacin concentrations in milk increase rapidly and the AUC_{INF}, T_{max} and C_{max} values obtained in plasma and milk after both administration routes are similar. Marbofloxacin is eliminated slowly (T1/2λz = 17.50 h) predominantly as the active form in urine and faeces.

In Pigs:
After administration of an intramuscular dose of **8 mg**/**kg**, the following mean plasmatic pharmacokinetic parameters were observed:

Parameter	*Fattening Pigs*	*Weaned Piglets*	*Sows*
T_{max}	0.95 h	0.93 h	1 h
C_{max}	6.295 µg/mL	5.550 µg/mL	5.809 µg/mL
AUC_{inf}	114.7 µg.h/mL	79.89 µg.h/mL	112.0 µg.h/mL
T ½lz	15.14 h	13.23 h	11.92 h
F	91.53%	89.57%	nc

T_{max} = mean observed occurrence time of C_{max}; C_{max} = maximum plasma concentration; AUC_{inf} = area under the concentration-time curve; T ½lz = mean elimination half-life; F= mean absolute bioavailability; nc = not calculated

Marbofloxacin is extensively distributed. Uterus tissue concentrations in sows reach C_{max} of 9.346 µg/g in the uterine body observed at T_{max} of 1.00 h after administration and the AUC_{last} was 105.4 µg.h/g.
Binding to plasma proteins is weak, about 4%. In pigs, the elimination is predominantly as the active form in urine and faeces.
Marbofloxacin is eliminated slightly faster in post-weaning piglets than in heavier animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzyl alcohol (E1519)
Glucono-delta-lactone
Water for injection

6.2 Incompatibilities
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life
Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: 28 days

6.4 Special precautions for storage
This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and content of container
Amber Type II glass vials.
Chlorobutyl rubber stoppers
Aluminum cap of flip-cap.

6.6 Special precautions for disposal of unused veterinary medicine or waste material derived from the use of such products.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Hazeldean, Pretoria, 0081

8. REGISTRATION NUMBER

19/17.1.6/25

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

12 October 2021