SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Boflox 100 mg/ml solution for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Marbofloxacin 100 mg

Excipients:
Disodium edetate 0.10 mg
Monothioglycerol 1 mg
Metacresol 2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Yellow greenish to yellow brownish, clear solution

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and pigs (sows).

4.2 Indications for use, specifying the target species

In cattle:
- treatment of respiratory infections caused by strains of *Histophilus somni*, *Mannheimia haemolytica*, *Mycoplasma bovis*, *Pasteurella multocida* susceptible to marbofloxacin.
- treatment of acute mastitis caused by strains of *Escherichia coli* susceptible to marbofloxacin during the lactation period.

In pigs:
- treatment of Postpartum Dysgalactia Syndrome –PDS-(Metritis Mastitis Agalactia syndrome), caused by bacterial strains susceptible to marbofloxacin.

4.3 Contraindications

Do not use in cases of resistance to other fluoroquinolones (cross resistance).
Do not use in cases of hypersensitivity to the active substance, to any other quinolone or to any of the excipients.

4.4 Special warnings for each target species

The efficacy data showed that the product has insufficient efficacy for the treatment of acute forms of mastitis induced by gram-positive bacteria.

4.5 Special precautions for use

Special precautions for use in animals

Official and local antimicrobial policies should be taken into account when the 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.
Whenever possible, fluoroquinolones should only be used based on susceptibility testing.
Use of the product deviating from the instructions given in the SPC 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.

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

People with known hypersensitivity to (fluoro)quinolones should avoid contact with the veterinary medicinal product. Care should be taken to avoid accidental self-injection as it can induce a slight irritation.
In case of accidental self injection, seek medical advice immediately and show the package leaflet or the label to the physician
In case of contact with skin or eyes, rinse with plenty of water.
Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases, transitory inflammatory lesions can occur at the injection site, without clinical impact, when administered via the intramuscular or subcutaneous route.
In very rare cases. administration by the intramuscular route may cause transient local reactions such as pain and swelling at the injection site and inflammatory lesions which may persist for at least 12 days after injection.
However, in cattle, subcutaneous route was shown to be better tolerated locally than intramuscular route. Therefore, the subcutaneous route is recommended in heavy cattle.

The frequency of adverse reactions is defined using the following convention:
- Very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment).
- Common (more than 1 but less than 10 animals in 100 animals).
- Uncommon (more than 1 but less than 10 animals in 1,000 animals).
- Rare (more than 1 but less than 10 animals in 10,000 animals).
- Very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

Safety of the veterinary medicinal product at 2 mg/kg body weight has been established in pregnant cows or in sucking calves and piglets when used in cows and sows. Can be used

during pregnancy and lactation.

Safety of the veterinary medicinal product at 8 mg/kg body weight has not been established in pregnant cows or in sucking calves when used in cows. Therefore, this dose regimen should be used only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

Route of administration:
Cattle: Intramuscular, subcutaneous or intravenous.
Pigs: Intramuscular.

Cattle:
Respiratory infections:
The recommended dosage is 8 mg marbofloxacin/kg body weight (2 ml veterinary medicinal product/25 kg body weight) in a single injection by the intramuscular route. If the volume to be injected is more than 20 ml, it should be divided between two or more injection sites.
In cases of respiratory infections caused by *Mycoplasma bovis*, the recommended dose is 2 mg marbofloxacin/kg body weight (1 ml veterinary medicinal product/50 kg body weight), in a single daily injection for 3 to 5 consecutive days, by the intramuscular or subcutaneous route. The first injection may be given by the intravenous route.

Acute mastitis:
- *Intramuscular or subcutaneous use:*
The recommended dosage is 2 mg marbofloxacin/kg body weight (1 ml veterinary medicinal product/50 kg body weight) in a single daily injection, for 3 consecutive days.
The first injection may also be given by the intravenous route.

Pigs (sows):
- *Intramuscular use:*
The recommended dosage is 2 mg marbofloxacin/kg body weight (1 ml veterinary medicinal product/50 kg body weight) in a single daily injection, for 3 consecutive days.

To ensure administration of a correct dose, body weight should be determined as accurately as possible, to avoid underdosing.
In cattle and pig, the preferred injection site is the neck area.
The cap may be safely punctured up to 30 times. The user should choose the most appropriate vial size according to the target species to treat.

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

No signs of overdosage have been observed after administration of 3 times the recommended dose.
Signs such as acute neurological disorders may occur when the dose is exceeded. This signs should be treated symptomatically. Do not exceed the recommended dose.

4.11 Withdrawal period(s)

Cattle:

Indication	**Respiratory**	**Mastitis**

Dosage	2 mg/kg for 3 days (IV/IM/SC)	8 mg/kg on a single occasion (IM)	2mg/kg for 3 days (IV/IM/SC)
Meat and offal	6 days	3 days	6 days
Milk	36 hours	72 hours	36 hours

Pigs:
Meat and offal: 4 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, Fluoroquinolones.
ATCvet code: QJ01MA93

5.1 Pharmacodynamic properties

Marbofloxacin is a synthetic, bactericidal antimicrobial, belonging to the fluoroquinolone group which acts by inhibition of DNA gyrase and topoisomerase IV. It has a broad-spectrum activity *in vitro* against Gram-negative bacteria (*E. coli, Histophilus somni, Mannheimia haemolytica and Pasteurella multocida*) and against genus *Mycoplasma* (*Mycoplasma bovis*). It should be noted that some strains of *Streptococci*, *Pseudomonas* and *Mycoplasma* may not be sensitive to Marbofloxacin.

A monitoring programme conducted by Kroemer, S et al 2012 in Europe established the susceptibility of bacterial strains isolated from diseased cattle before any antibiotic treatment between 2002 and 2008. 1509 bacterial strains from bovine respiratory disease (BRD) cases and 2342 bacterial strains from mastitis milk samples were collected. These 3851 isolates were sampled in the eight European countries targeted by the study: 2161 came from France, 413 from UK, 16 from Ireland, 68 from Belgium, 92 from the Netherlands, 815 from Germany, 183 from Italy and 103 from Spain.

MIC values of marbofloxacin (µg/ml) calculated for bacterial species isolated between 2002-2008 and the percentage of susceptible isolates are presented in the table below:

Bacterial species	**Studied strains**	**% Susceptible**	**MIC_{50}**	**MIC_{90}**	**MICrange**
Pasteurella multocida	751	99.73	0.015	0.120	0.004- 1
Mannheimia haemolytica	514	98.25	0.030	0.250	0.008- 1
*Mycoplasma bovis**	171	-	1.000	2.000	0.500-1
Histophilus somni	73	100%	0.030	0.060	0.008-0.06
Escherichia coli	617	98.22	0.030	0.030	0.008-1

*There are no validated clinical breakpoints to calculate the percentage of susceptible isolates

Another monitoring programme was carried out by El Garch et al., 2017 to evaluate the susceptibility of porcine bacterial isolates in Europe (France, the Netherlands, Belgium, the UK Ireland, Germany, Italy and Spain), isolated from five pathologies, including metritis. For E. coli causing metritis (369 isolates), 92,7% per cent of the combined collections of E. coli strains were susceptible between 2005 and 2013 with a MIC ranging from 0.008 to 1 µg/ml, 0.3% of isolates exhibited intermediate susceptibility with a MIC of 2 and 7% exhibited resistance with a MIC of >4. MIC_{50} was determined to be 0.03 µg/ml and MIC_{90} was 0.5 µg/ml.

The above pan European studies by Kroemer, S et al 2012 and El Garch, F., et al 2017, established clinical breakpoints for marbofloxacin used in *P. multocida* and *M. haemolytica* associated bovine respiratory disease and *E. coli* in bovine mastitis and porcine metritis. Resistant strains were determined to have MIC ≥4 µg/ml, intermediate strains a MIC=2 µg/ml

and susceptible strains, a MIC ≤1 µg/ml. No clinical breakpoints have been established for *Mycoplasma* species.

Resistance to fluoroquinolones occurs by chromosomal mutations with following mechanisms: decrease of the bacterial cell wall permeability, expression change of genes coding for efflux pumps or mutations of in genes encoding enzymes responsible for molecule binding. Plasmid-mediated resistance to fluoroquinolones confer only decreased susceptibility of bacteria, however, it can facilitate development of mutations in genes of target enzymes and can be transferred horizontally. Depending on the underlying resistance mechanism cross-resistance to other (fluoro)quinolones and co-resistance to other antimicrobial classes can occur.

5.2 Pharmacokinetic particulars

After subcutaneous or intramuscular administration in cattle and intramuscular administration in pigs at the recommended dose of 2 mg/kg body weight, marbofloxacin is readily absorbed and reaches maximal plasma concentrations of 1.5 µg/ml within less than 1 hour. Its bioavailability is close to 100%.

It is weakly bound to plasma proteins (less than 10% in pigs, and 30% in cattle), extensively distributed and in most tissues (liver, kidney, skin, lung, bladder, uterus, digestive tract) it achieves a higher concentration than in plasma.

In cattle, marbofloxacin is eliminated slowly in pre-ruminating calves ($t_{½\beta}$ = 5-9 h) but faster in ruminant cattle ($t_{½\beta}$ = 4-7 h) predominantly in the active form in urine (3/4 in pre-ruminating calves, ½ in ruminants) and faeces (1/4 in pre-ruminating calves, ½ in ruminants).

After a single intramuscular administration in cattle at the recommended dose of 8 mg/kg body weight, the maximum plasma concentration of marbofloxacin (Cmax) is 7.3 µg/ml reached in 0.78 hours (Tmax). Marbofloxacin is eliminated slowly (T1/2 terminal = 15.60 hours).

After intramuscular administration in lactating cows, a maximum concentration in the milk of marbofloxacin of 1.02 µg/ml is reached (Cmax after the first administration) after 2.5 hours (Tmax after the first administration).

In pigs, marbofloxacin is eliminated slowly ($t_{½\beta}$ = 8-10 h) predominantly in the active form in urine (2/3) and faeces (1/3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gluconolactone
Disodium edetate
Metacresol
Monothioglycerol
Water for injections

6.2 Major 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

Store in the original package in order to protect from light.

6.5 Nature and composition of immediate packaging

Amber glass type II vial, closed with bromobutyl rubber stopper with aluminium tear off caps or aluminium/plastic flip-off caps.

Package sizes:
Carton box with 1 vial of 100 ml
Carton box with 1 vial of 250 ml
Carton box with 6 vials of 100 ml
Carton box with 6 vials of 250 ml
Carton box with 10 vials of 100 ml
Carton box with 10 vials of 250 ml
Carton box with 12 vials of 100 ml
Carton box with 12 vials of 250 ml

Not all pack sizes may be marketed.

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

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

7. MARKETING AUTHORISATION HOLDER

Industrial Veterinaria, S.A.
Esmeralda, 19
E-08950 Esplugues de Llobregat (Barcelona) Spain

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <{DD/MM/YYYY}><{DD month YYYY}>
Date of last renewal: <{DD/MM/YYYY}><{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Veterinary medicinal product subject to veterinary prescription.