SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ADVOCIN 180, 180 mg/ml, Solution for Injection for Cattle.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains.

Active substance:

Danofloxacin (Equivalent to 228.4mg Danofloxacin mesylate)	180 mg

Excipients:

Phenol	2.5 mg
Monothioglycerol	5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. Medium yellow to amber solution.

4. CLINICAL PARTICULARS

4.1. Target species

Cattle.

4.2. Indications for use, specifying the target species

In cattle: Treatment of bovine respiratory disease caused by *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* sensitive to danofloxacin.
For the treatment of acute bovine mastitis caused by *Escherichia coli* sensitive to danofloxacin.
In neo-natal calves: Treatment of enteric infections caused by *Escherichia coli* sensitive to danofloxacin.

4.3. Contraindications

Do not use in cases of hypersensitivity to the active substance, to other (fluoro)quinolones or to any of the excipients.

4.4. Special warnings for each target species

The safety of the product has not been assessed in breeding bulls.

4.5. Special precautions for use

Special precautions for use in animals

Use of fluoroquinolones should be based on susceptibility testing and take into account official and local antimicrobial use policies. It is prudent to reserve fluoroquinolones for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials. Efficacy against gram positive strains has not been established.

For fluoroquinolones as a class, over-dosage at multiples of the recommended dose has been shown to induce erosion of articular cartilage. Care should be taken to dose accurately and the product should be used with caution in animals with joint disease or cartilage growth disorders.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance.

Do not use in cases where the pathogen involved is resistant to other fluoroquinolones (due to the potential for cross resistance).

Special precautions to be taken by the person administering the medicinal products to animals

Persons with known hypersensitivity to (fluoro)quinolones should avoid contact with the product.
Care should be taken to avoid accidental self-injection, 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.
Do not eat, drink or smoke during application.

4.6. Adverse reactions (frequency and seriousness)

In very rare cases in sensitive animals, immediate or delayed anaphylactic shock may occur after the injection.
Subcutaneous injection of the product induces a moderate inflammatory response in the tissue around the injection site. The resultant lesions may persist for up to 30 days.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7. Use during pregnancy, lactation or lay

Studies in laboratory animals have shown adverse effects on reproduction. At high doses in rats (100 to 200 mg/kg/day), increase in foetal delayed ossification and in dilatation of the cerebral ventricles were observed. Dams given high dose produced fewer live pups per litter and pup weight and survival were adversely affected. The safety of the product has not been established during pregnancy in cows.
The use is not recommended during pregnancy.

4.8. Interaction with other medicinal products and other forms of interaction

When fluoroquinolones have been combined with bacteriostatic antimicrobials, such as tetracyclines and macrolides or phenicols, an antagonism was demonstrated *in vitro.*

4.9. Amounts to be administered and administration route

6 mg/kg body weight (1 ml/30 kg body weight) as a single injection by the subcutaneous or intravenous route.

If clinical signs of respiratory or enteric disease persist 48 hours after the first injection, an additional dose at 6 mg/kg body weight may be administered.

It is recommended to treat animals in the early stages of disease and to evaluate the response to treatment within 48 hours.

For the treatment of acute bovine mastitis, the product should be administered at 6 mg/kg body weight (1 ml/30 kg body weight) as a single injection by the subcutaneous or intravenous route. The clinical signs should be monitored carefully and supportive therapy should be given as appropriate. If clinical signs of acute bovine mastitis persist 36-48 hours after the first injection, the antibiotic treatment strategy should be reviewed. It is recommended to treat animals in the early stages of disease and to evaluate the response to treatment within 36-48 hours.

For treatment of cattle weighing more than 450 kg, divide the subcutaneous dose so that no more than 15 ml are injected at one site.

When dosing a large number of animals from a single vial, the use of an automatic syringe is recommended to avoid excessive broaching of the rubber stopper.

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

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

At doses of three times the therapeutic dose (18 mg/kg bw), erythema of the nasal and ocular mucosae was induced and food intake was reduced. At even higher doses and prolonged exposure, there was damage to the cartilage in the joints and some animals displayed paresis, ataxia or nystagmus.

4.11. Withdrawal period(s)

Meat and offal: 8 days
Milk: 4 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Fluoroquinolones,
ATCvet code: QJ01MA92

5.1. Pharmacodynamic properties

Danofloxacin is a synthetic fluoroquinolone antimicrobial agent that possesses potent *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Escherichia coli*, the bacterial pathogens most commonly associated with bovine respiratory, enteric disease and acute bovine mastitis.

The antimicrobial activity of danofloxacin is based upon the inhibition of microbial DNA gyrase and topoisomerase IV. The inhibitory effect is on the second step of the enzymatic process, uncoupling the breakage and reunion functions. Danofloxacin, in common with other fluoroquinolones, produces a stable complex between the enzyme and DNA. This results in the cessation of DNA replication and transcription. The bactericidal effect is also observed on bacteria in the stationary growth phase.

5.2. Pharmacokinetic particulars

The product is rapidly and extensively absorbed from the site of subcutaneous injection, bioavailability is around 90%. Danofloxacin is only poorly metabolised and subsequently eliminated via both the renal and hepatic routes. A difference in elimination kinetics is observed between pre-ruminant animals (half-life of 12 hours) and ruminant animals (half-life of 4 hours). High drug concentrations in lung, enteric and lymphatic tissues are observed. Following a single subcutaneous administration at 6 mg/kg body weight, peak plasma and tissue concentrations are achieved within one to two hours after treatment, with concentrations in lung and enteric tissues approximately four times greater than in plasma. The dose selected for the product was based on the optimisation of the concentration dependent bactericidal activity of danofloxacin against respiratory and enteric pathogens.

The mean milk concentrations of danofloxacin were 4.61 and 0.2 µg/ml at the 8 and 24 hour milking, respectively, following a single subcutaneous injection.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Phenol
Monothioglycerol
Povidone K 15
2-pyrrolidone
Magnesium oxide
Hydrochloric acid
Sodium hydroxide
Water for injection

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: 2 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.
Do not freeze.

6.5. Nature and composition of immediate packaging

Nature of Primary Packaging
- Type I amber glass vial
- Chlorobutyl rubber stopper
- Aluminium overseal with polypropylene cover

Market Presentations
- Box containing one 50 ml vial
- Box containing one 100 ml vial
- Box containing one 250 ml vial

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zoetis UK Limited
1st Floor, Birchwood Building
Springfield Drive
Leatherhead
Surrey
KT22 7LP

8. MARKETING AUTHORISATION NUMBER

Vm 42058/4000

9. DATE OF FIRST AUTORISATION

16 November 2001

10. DATE OF REVISION OF THE TEXT

January 2020

Approved 08 January 2020