**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 100 mg/ml oral solution for chickens and turkeys

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

**Active substance:**
Difloxacin (as hydrochloride) 100 mg

**Excipients:**
Benzyl alcohol 100 mg

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Oral solution

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Chickens (broilers and future breeders)
Turkeys (young turkeys up to 2 kg body weight).

### 4.2 Indications for use, specifying the target species

In chickens and turkeys: Dicural oral solution is indicated for treatment of chronic respiratory infections caused by sensitive strains of *Escherichia coli* and *Mycoplasma gallisepticum*.

In turkeys: Dicural oral solution is also indicated for the treatment of infections caused by *Pasteurella multocida*.

### 4.3 Contraindications

Since no studies were performed in clinically lame birds, Dicural should not be used in birds with existing leg-weakness or in birds suffering from osteoporosis.

### 4.4 Special warnings for each target species

None.

### 4.5 Special precautions for use

**Special precautions for use in animals**
Heavy reliance on a single class of antibiotics may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antibiotics.
Official and local antimicrobial policies should be taken into account when the product is used**.**

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 of cross resistance.

**Special precautions to be taken by the person administering the veterinary medicinal product to animals**
People with known hypersensitivity to quinolones should avoid any contact with the product.
In order to avoid irritation of skin and/or eyes, use gloves and a face-protecting device when handling this product.

**4.6 Adverse reactions (frequency and seriousness)**

None known.

**4.7 Use during pregnancy, lactation or lay**

Do not use in birds in lay and/or within 4 weeks before the onset of the laying period.

**4.8 Interaction with other veterinary medicinal products and other forms of interaction**

None known.

**4.9 Amounts to be administered and administration route.**

Dicural oral solution must be administrated daily via the drinking water in such a concentration that the dose is 10 mg/kg bodyweight. The administration must be continued for 5 days.

Taking into account the content of difloxacin in the oral solution (10%w/v), the following calculation should be made to determine the volume (ml) to be added for each 1000 litres of water:

$$\frac{\text{number of animals in the house X mean weight of individual animal(kg) X 100}}{\text{total water consumption of the house at the previous day (litres)}}$$

The medicated drinking water should be prepared freshly each day.

No other source of drinking water should be available during the medication period.

At concentrations in the water of 0.03% (= 300 ml in 1000 litres) or greater, palatability for turkeys may be affected.

**4.10 Overdose (symptoms, emergency procedures, antidotes)**

Target animal safety studies in chickens and turkeys demonstrated that, when administered in drinking water at 30 mg/kg (chickens) or 22 mg/kg (turkeys) for three times the recommended duration (15 consecutive days), difloxacin hydrochloride appeared to be safe for the birds.

**4.11 Withdrawal periods**

Meat and offal (chickens and turkeys): 24 hours.

Not permitted for use in laying birds producing eggs for human consumption.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: general anti-infectives for systemic use; antibacterials for systemic use, quinolone antibacterials.

ATC vet code: QJ01MA94

The fluoroquinolones exert their antibacterial effect against both replicating and non-replicating micro-organisms. Difloxacin hydrochloride is bactericidal in activity and acts by inhibition of bacterial DNA gyrase.

Strains of *Escherichia coli*, *Pasteurella multocida*, *Mycoplasma gallisepticum* isolated from broilers and turkeys have been shown to be sensitive to difloxacin.

### 5.2 Pharmacokinetic properties

Difloxacin is rapidly absorbed after oral administration to reach steady state plasma concentrations in a few hours after initiation of medication. Difloxacin is well distributed throughout the animal body, as was demonstrated by the tissue to plasma ratios. Difloxacin concentrations equal to or greater than the MICs for the relevant pathogens are achieved in all relevant tissues and maintained for as long as medication is continued.

Chickens:
In chickens difloxacin is nearly completely absorbed after oral administration (approx. 96%). It is well distributed in the body ($V_d$ = 4.7 l/kg) and has a plasma elimination half-life of approximately 7 hours. Following continuous oral dosing with Dicural oral solution at 10 mg/kg/day for five consecutive days the mean difloxacin steady state plasma concentrations are approximately 200 ng/ml. Tissue to plasma ratios range from 0.6 (abdominal fat), 2.4 (lung), 4.5 (muscle) to 14.1 (liver).

Turkeys:
In turkeys difloxacin has a moderate oral bioavailability (approx. 58%). It is very well distributed in the body ($V_d$ = 9.9 l/kg) and has a plasma elimination half-life of approximately 7 hours. Following continuous oral dosing of Dicural oral solution at 10 mg/kg/day for five consecutive days the mean difloxacin steady state plasma concentrations are approximately 60 ng/ml. Tissue to plasma ratios range from 2.5 (abdominal fat), 3.7 (muscle), 4.8 (lung) to 36.5 (liver).

In both species difloxacin may be conjugated (glucuronidated or sulphated), desmethylated into sarafloxacin or oxidised into N-oxide-difloxacin. The main metabolites are hydrolysable conjugates of difloxacin, the other metabolites are proportionally minor ones.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Edetic acid
Potassium hydroxide
Propylene glycol
Benzyl alcohol
Purified water

### 6.2 Incompatibilities

No additional chlorine, for example from the use of water chlorinators, or hydrogen peroxide should be added to the drinking water used with this product.

### 6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Medicated water must be freshly prepared daily.
Shelf life after first opening the container: 1 month.

### 6.4 Special precautions for storage

Do not store above 25 °C. Protect from light. Do not freeze.

### 6.5 Nature and composition of immediate packaging

White HDPE bottles with a screw cap containing 250ml or 1litre of Dicural oral solution.
The screw cap on the 1 litre bottle can be used as measuring device. If filled to the brim the measuring device provides 50ml. For the 250ml bottle a separate measuring device is placed on the screw cap. Measuring lines indicate the volume supplied.

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, if any

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

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/2/97/003/001-003

## 9. DATE OF RENEWAL OF THE AUTHORISATION

15.01.2008

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

## PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 15 mg coated tablets for dogs
Dicural 50 mg coated tablets for dogs
Dicural 100 mg coated tablets for dogs
Dicural 150 mg coated tablets for dogs

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance:**

Each tablet contains:

| | | |
|---|---|---|
| Dicural 15 mg | difloxacin (as the hydrochloride) | 15 mg |
| Dicural 50 mg | difloxacin (as the hydrochloride) | 50 mg |
| Dicural 100 mg | difloxacin (as the hydrochloride) | 100 mg |
| Dicural 150 mg | difloxacin (as the hydrochloride) | 150 mg |

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Coated tablets

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Dogs

### 4.2 Indications for use, specifying the target species

For the treatment of:
- Acute uncomplicated urinary tract infections caused by *Escherichia coli* or *Staphylococcus spp*
- Superficial pyoderma caused by *Staphylococcus intermedius.*

### 4.3 Contraindications

As for other quinolones, due to possible adverse effects on the articular cartilage of weight bearing joints difloxacin should not be used during the rapid growth phase, that is, do not use in small and medium-sized breeds of dogs up to and including 8 months of age, in large breeds up to 1 year of age and in giant breeds up to 18 months of age.

Do not use in epileptic dogs.

### 4.4 Special warnings

None known.

## 4.5 Special precautions for use

**Special precautions for use in animals**
Heavy reliance on a single class of antibiotics may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antibiotic.

**Special precautions to be taken by the person administering the veterinary medicinal product to animals.**
People with known hypersensitivity to quinolones should avoid any contact with the product.

## 4.6 Adverse reactions (frequency and seriousness)

Adverse reactions were rare in dogs treated with difloxacin. The observed reactions were inappetence, emesis, diarrhoea, and anal irritation. These adverse reactions were self-limiting within one or two days and did not require additional treatment.

## 4.7 Use during pregnancy, lactation or lay

The reproductive safety of the veterinary medicinal product has only been evaluated in laboratory animals, the use of difloxacin in pregnant or lactating bitches or male stud dogs is therefore not recommended.

## 4.8 Interaction with other veterinary medicinal products and other forms of interaction

The use of fluoroquinolones in combination with non-steroidal anti-inflammatory drugs (NSAIDs) may cause seizures.

Antacids may interfere with gastro-intestinal absorption.

Nitrofurantoin may impair quinolone efficacy if used concurrently in the treatment of urinary tract infections.

## 4.9 Amounts to be administered and administration route

The recommended dose of difloxacin is 5 mg/kg bodyweight per day. Dicural coated tablets should be given once a day for at least 5 days. Superficial pyoderma may require treatment for up to a maximum of 21 days. The tablets should be administered for at least 2 days beyond the cessation of clinical signs.

Therapy should be re-evaluated if no improvement is seen within 5 days, or 10 days in the case of superficial pyoderma.

## 4.10 Overdose (symptoms, emergency procedures, antidotes)

Dogs treated orally with difloxacin (as hydrochloride) at 10 times the recommended dose for 10 days occasionally showed mild adverse reactions such as orange/yellowing discoloration of the faeces, emesis and hypersalivation.

Histopathological changes were noted in the articular cartilage of weight bearing joints of young (3.5 months old) beagle dogs after the oral administration of difloxacin at doses of greater than 5 mg/kg/day (as the hydrochloride) for 90 days.

No specific antidotes for difloxacin (or other quinolones) are known, therefore, in case of overdose symptomatic treatment should be given.

### 4.11 Withdrawal period

Not applicable.

## 5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: general anti-infectives for systemic use; antibacterials for systemic use, quinolone antibacterials.

ATC vet code: QJ01MA94

Difloxacin is an aryl-fluoroquinolone with a broad spectrum of antimicrobial activity. Difloxacin can be bactericidal against many Gram-negative micro-organisms and a selection of Gram-positive micro-organisms.

### 5.1 Pharmacodynamic properties

The fluoroquinolones exert their antibacterial effects against both replicating and dormant micro-organisms. Difloxacin acts primarily through inhibition of bacterial DNA gyrase.

The following organisms were tested and found to be susceptible to difloxacin *in vitro*:

*Escherichia coli*
*Klebsiella spp.*
*Pasteurella spp.*
*Pseudomonas spp.*
*Staphylococcus intermedius*

The following organisms were found to be of intermediate susceptibility:

*Proteus spp.*
*Staphylococcus spp.*
*Streptococcus canis (beta)*
*Streptococcus spp.*

### 5.2 Pharmacokinetic properties

Following an oral dose (a plain tablet) in dogs of 5 mg/kg bodyweight, difloxacin reached its average peak plasma concentration of 1.8 µg/ml in approximately 3 hours. Approximately 95 % of the oral dose was absorbed. The elimination half-life averaged 9.3 hours.

Long term daily oral treatment over 180 days at 5 mg/kg bodyweight did not influence difloxacin kinetics, neither by accumulation nor by increased drug metabolism.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium starch glycollate
Microcrystalline cellulose
Magnesium stearate
Colloidal silicon dioxide
Sodium lauryl sulphate

Lactose
Sodium croscarmellose
Micronised brewer's yeast
Aromatic liver flavour

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in a dry place.

### 6.5 Nature and contents of container

PVC/aluminium blisters with 10 tablets per blister. Cardboard boxes of 1, 2 or 10 blisters.

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, if any

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

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/2/97/003/004-015

## 9. DATE OF RENEWAL OF THE AUTHORISATION

15.01.2008

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

## PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg/ml solution for injection for cattle and dogs.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance:**
Difloxacin (as hydrochloride) 50 mg/ml

**Excipients:**
Benzyl alcohol 50 mg/ml

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Solution for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Cattle (calves and young cattle)
Dogs.

### 4.2 Indications for use, specifying the target species

In cattle: Dicural 50 mg/ml solution for injection is indicated for the treatment of bovine respiratory disease (shipping fever, calf pneumonia) caused by single or mixed infections with *Pasteurella haemolytica*, *Pasteurella multocida*, and/or *Mycoplasma spp*.

In dogs: Dicural 50 mg/ml solution for injection is indicated for the treatment of:
- Acute uncomplicated urinary tract infections caused by *Escherichia coli* or *Staphylococcus spp*
- Superficial pyoderma caused by *Staphylococcus intermedius.*

### 4.3 Contraindications

Cattle:
None.

Dogs:
As for other quinolones, due to possible adverse effects on the articular cartilage of weight bearing joints difloxacin should not be used during the rapid growth phase. Therefore, do not use in small and medium-sized breeds of dogs up to and including 8 months of age, in large breeds up to 1year of age and in giant breeds up to 18 months of age.

Do not use in epileptic dogs.

### 4.4 Special warnings for each target species

None known.

## 4.5 Special precautions for use

**Special precautions for use in animals**
Heavy reliance on a single class of antibiotics may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antibiotic.

Whenever possible, fluoroquinolones should only be used based on susceptibility testing.

Official and local antimicrobial policies should be taken into account when the product is used.

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 of cross resistance**.**

**Special precautions to be taken by the person administering the veterinary medicinal product to animals**
People with a known hypersensitivity to quinolones should avoid any contact with the product.

## 4.6 Adverse reactions (frequency and seriousness)

Cattle:
In target animal safety studies, subcutaneous administration was generally well tolerated. Transient swelling at the injection site following administration may occur.

Dogs:
In target animal safety studies, subcutaneous administration was generally well tolerated. Pruritis and/or local swellings and occasionally a slight pain reaction on injection have been observed. In general the pruritis disappears within a few minutes and the local swelling within a few days.

## 4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

## 4.8 Interaction with other veterinary medicinal products and other forms of interaction

The use of fluoroquinolones in combination with non-steroidal anti-inflammatory drugs (NSAIDs) may cause seizures.

Antagonism may be observed with nitrofurantoin.

## 4.9 Amounts to be administered and administration route

Subcutaneous use

Cattle:
The recommended dose is 2.5mg difloxacin/kg bodyweight/day for 3 days (i.e. 5ml/100 kg bodyweight/day). If there is insufficient improvement after 3 days, the treatment can be continued for another 2 days.

For complicated respiratory disease the dose can be doubled to 5 mg/kg bodyweight/ day.

The volume administered per injection site in cattle should not exceed 7 ml. A new injection site should be used each day

Dogs:
The recommended dose is a single injection of 5.0 mg difloxacin/kg bodyweight Treatment must be continued with Dicural coated tablets (see that SPC)

The volume administered per injection site in dogs should not exceed 5 ml.

### 4.10 Overdose (symptoms, emergency procedures, antidotes)

Cattle:
At very high doses adverse effects on the nervous system (ataxia, unsteadiness, twitching, tremors, convulsions, etc) may occur in cattle. Overdosage may also give rise to oedema and swelling in the knee joints.

Dogs:
The oral administration of difloxacin at up to 5 times the recommended dose rate for 30 days did not result in any adverse reactions.
In another study, dogs treated orally with difloxacin at 10 times the recommended dose for 10 days showed occasionally mild adverse reactions such as orange/yellowing discoloration of the faeces, emesis and hypersalivation.

No specific antidotes for difloxacin (or other quinolones) are known, therefore in case of overdosage symptomatic treatment should be given.

### 4.11 Withdrawal period

Cattle:
Meat and offal: 46 days

Dogs:
Not applicable

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: general anti-infectives for systemic use; antibacterials for systemic use, quinolone antibacterials.

ATC vet code: QJ01MA94

The fluoroquinolones exert their antibacterial effect against both replicating and dormant micro-organisms. Difloxacin hydrochloride can be bactericidal in activity and acts primarily through inhibition of bacterial DNA gyrase.

The following organisms were tested and found to be susceptible to difloxacin *in vitro*:

*Pasteurella spp*.
*Mycoplasma spp*.
*Escherichia coli*
*Staphylococcus intermedius*

The following organism was found to be of intermediate susceptibility:

*Staphylococcus spp.*

Induction of resistance against quinolones can develop by mutations in the gyrase gene of bacteria and by changes in cell permeability towards quinolones

### 5.2 Pharmacokinetic properties

Cattle:
After subcutaneous administration of difloxacin peak plasma levels of 1.7 µg/ml are achieved at 6 hours post dosing. After subcutaneous administration the bioavailability is 88% and the volume of distribution is 2.5 l/kg.
The parent compound difloxacin is the major component in the faeces and tissues. In the urine, liver, fat and kidneys the metabolites desmethyl-difloxacin and difloxacin N-oxide can be found in small amounts in addition to the major (parent) compound.
The clearance of difloxacin after subcutaneous administration to cattle is 229 ml/h/kg. A half-life time of 7.7 hours has been observed. The majority of difloxacin (i.e. 68 - 82%) is excreted via the faeces. A fraction of difloxacin (i.e. 7 - 18%) is eliminated via the urine.

Dogs:
After subcutaneous administration of difloxacin peak plasma levels of 1.4 -1.9 µg/ml are achieved in 3.1 hours post dosing. After subcutaneous administration the bioavailability is 96%. The volume of distribution is 2.6 l/kg. A half-life time of 5.8 hours has been observed. The majority of difloxacin is excreted via the faeces. A fraction of difloxacin is eliminated by the urine.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Ethanol
Benzyl alcohol
Propylene glycol
Arginine
Water for injections

### 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: 2 years

Shelf life after first use of the product: 28 days

### 6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.
Keep the container in the outer carton.

### 6.5 Nature and composition of immediate packaging

Dogs:
Cardboard box with one glass vial of 50ml with a rubber stopper and aluminium cap.

Cattle:
Cardboard box with one glass vial of 50ml, 100ml or 250 ml with a rubber stopper and aluminium cap.

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, if any

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

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/2/97/003/016-018

## 9. DATE OF RENEWAL OF THE AUTHORISATION

15.01.2008

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

## PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

# ANNEX II

**A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION REGARDING SUPPLY AND USE**

**C. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION WITH REGARD TO SAFE AND EFFECTIVE USE**

**D. STATEMENT OF THE MRLs**

## A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release:

*For all three pharmaceutical forms:*

Pfizer Olot, S.L.U.
Ctra. Camprodón, s/n°, Finca La Riba,
Vall de Bianya, 17813 Girona
Spain

## B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION REGARDING SUPPLY AND USE

To be supplied only on veterinary prescription.

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

## C. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION WITH REGARD TO SAFE AND EFFECTIVE USE

Not applicable.

## D. STATEMENT OF THE MRLs

which are accepted in accordance with Council Regulation (EEC) No 2377/90 and in accordance with Article 31 (3b) of Council Regulation (EEC) No 2309/93 of 22 July 1993, as amended.

Annex I of Council Regulation (EEC) No 2377/90

| Pharmacologically active substance | Marker residue | Animal Species | MRLs | Target tissues | Other provisions |
|---|---|---|---|---|---|
| Difloxacin | Difloxacin | Poultry[1] | 300 µg/kg<br>400 µg/kg<br>1900 µg/kg<br>600 µg/kg | Muscle<br>Skin + fat<br>Liver<br>Kidney | Not for use in animals from which eggs are produced for human consumption |
| Difloxacin | Difloxacin | Bovine[2] | 400 µg/kg<br>100 µg/kg<br>1400 µg/kg<br>800 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | Not for use in animals from which milk is produced for human consumption |

Annex II of Council Regulation (EEC) No 2377/90

***Oral solution:***

| Pharmacologically active substance | Animal Species | Other provisions |
|---|---|---|
| Edetic acid[3] | All food-producing species | |
| Potassium Hydroxide[4] | | |
| Propylene glycol[5] | | |
| Benzyl alcohol[6] | | For use as excipient |
| Hydrochloric acid[7] | | For use as excipient |

***Solution for injection:***

| Pharmacologically active substance | Animal Species | Other provisions |
|---|---|---|
| Ethanol [8]<br>Propylene glycol [9]<br>Benzyl alcohol [10]<br>Arginine [11] | All food-producing species | For use as excipient |



1 OJ No. L 172 of 02.07.02
2 OJ No. L 172 of 02.07.02
3 OJ No. L 290 of 5.12.95
4 OJ No. L 272 of 25.10.96
5 OJ No. L 45 of 15.02.97
6 OJ No. L 143 of 27.06.95
7 OJ No. L 143 of 27.06.95
8 OJ No. L 143 of 26.06.95
9 OJ No. L 45 of 15.02.97
10 OJ No L 143 of 26.06.95
11 OJ No. L 240 of 10.09.99

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**
**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE**
**Dicural oral solution**
**CARTON LABEL - 1 X 250 ML BOTTLE / 1 X 1000 ML BOTTLE / 6 X 1000 ML BOTTLE**
**VIAL LABEL 250 ml bottle / 1000 ml bottle**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 100 mg/ml oral solution for chickens and turkeys

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

| | |
|---|---|
| Difloxacin (as hydrochloride) | 100 mg/ml |
| Benzyl alcohol | 100 mg/ml |

## 3. PHARMACEUTICAL FORM

Oral solution

## 4. PACKAGE SIZE

1 x 250 ml
1 x 1000 ml
6 x 1000 ml

## 5. TARGET SPECIES

Chickens (broilers and future breeders) and turkeys (young turkeys up to 2 kg body weight).

## 6. INDICATIONS

Chickens and turkeys - for treatment of chronic respiratory infections caused by sensitive strains of *Escherichia coli* and *Mycoplasma gallisepticum*.

Turkeys only - for the treatment of infections caused by *Pasteurella multocida*.

Dicural oral solution should be used based on susceptibility testing

## 7. METHOD AND ROUTE OF ADMINISTRATION

For oral administration in drinking water.
Read the package leaflet before use.

## 8. WITHDRAWAL PERIOD

Withdrawal periods - Meat and offal (chickens and turkeys): 24 hours.

Not permitted for use in laying birds producing eggs for human consumption.

## 9. SPECIAL WARNINGS

People with known hypersensitivity to quinolones should avoid any contact with the product.
In order to avoid irritation of skin and/or eyes, use gloves and a face-protecting device when handling this product.

## 10. EXPIRY DATE

EXP {month/year}
Medicated water must be freshly prepared daily.
Shelf life after first opening the container: 1 month.

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Protect from light. Do not freeze.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

*[Not requested on the immediate label]*

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only- to be supplied only on veterinary prescription.

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

*[Not requested on the immediate label]*

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

**Marketing authorisation holder**
Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/97/003/001 – 1 x 250 ml
EU/2/97/003/002 – 1 x 1000 ml
EU/2/97/003/003 – 6 x 1000 ml

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**
**Dicural 15 mg Coated tablets**
**CARTON OF 10 TABLETS / 20 TABLETS / 100 TABLETS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 15 mg coated tablets for dogs

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Difloxacin (as hydrochloride) 15 mg

## 3. PHARMACEUTICAL FORM

Coated tablets

## 4. PACKAGE SIZE

10 tablets
20 tablets
100 tablets

## 5. TARGET SPECIES

Dogs

## 6. INDICATIONS

## 7. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

## 8. WITHDRAWAL PERIOD

[Not applicable.]

## 9. SPECIAL WARNINGS, IF NECESSARY

People with known hypersensitivity to quinolones should avoid any contact with the product.

## 10. EXPIRY DATE

EXP {month/year}

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25-°C. Store in a dry place.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only -to be supplied only on veterinary prescription.

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/97/003/004 – 10 tablets
EU/2/97/003/005 – 20 tablets
EU/2/97/003/006 – 100 tablets

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**
**Dicural 50 mg Coated tablets**
**CARTON OF 10 TABLETS / 20 TABLETS / 100 TABLETS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg coated tablets for dogs

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Difloxacin (as hydrochloride) 50 mg

## 3. PHARMACEUTICAL FORM

Coated tablets

## 4. PACKAGE SIZE

10 tablets
20 tablets
100 tablets

## 5. TARGET SPECIES

Dogs

## 6. INDICATIONS

## 7. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
*[Space shall be provided for the prescribed dose to be indicated on the outer carton]*

## 8. WITHDRAWAL PERIOD

[Not applicable.]

## 9. SPECIAL WARNINGS, IF NECESSARY

People with known hypersensitivity to quinolones should avoid any contact with the product.

## 10. EXPIRY DATE

EXP {month/year}

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25-°C. Store in a dry place.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only -to be supplied only on veterinary prescription.

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/97/003/007 – 10 tablets
EU/2/97/003/008 – 20 tablets
EU/2/97/003/009 – 100 tablets

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**
**Dicural 100 mg Coated tablets**
**CARTON OF 10 TABLETS / 20 TABLETS / 100 TABLETS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 100 mg coated tablets for dogs

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Difloxacin (as hydrochloride) 100 mg

## 3. PHARMACEUTICAL FORM

Coated tablets

## 4. PACKAGE SIZE

10 tablets
20 tablets
100 tablets

## 5. TARGET SPECIES

Dogs

## 6. INDICATIONS

## 7. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
*[Space shall be provided for the prescribed dose to be indicated on the outer carton]*

## 8. WITHDRAWAL PERIOD

[Not applicable.]

## 9. SPECIAL WARNINGS, IF NECESSARY

People with known hypersensitivity to quinolones should avoid any contact with the product.

## 10. EXPIRY DATE

EXP {month/year}

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25-°C. Store in a dry place.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only -to be supplied only on veterinary prescription.

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/97/003/010 – 10 tablets
EU/2/97/003/011 – 20 tablets
EU/2/97/003/012 – 100 tablets

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**
**Dicural 150 mg Coated tablets**
**CARTON OF 10 TABLETS / 20 TABLETS / 100 TABLETS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 150 mg coated tablets for dogs

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Difloxacin (as hydrochloride) 150 mg

## 3. PHARMACEUTICAL FORM

Coated tablets

## 4. PACKAGE SIZE

10 tablets
20 tablets
100 tablets

## 5. TARGET SPECIES

Dogs

## 6. INDICATIONS

## 7. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
*[Space shall be provided for the prescribed dose to be indicated on the outer carton]*

## 8. WITHDRAWAL PERIOD

[Not applicable.]

## 9. SPECIAL WARNINGS, IF NECESSARY

People with known hypersensitivity to quinolones should avoid any contact with the product.

## 10. EXPIRY DATE

EXP {month/year}

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25-°C. Store in a dry place.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only - to be supplied only on veterinary prescription.

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/97/003/013 – 10 tablets
EU/2/97/003/014 – 20 tablets
EU/2/97/003/015 – 100 tablets

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**
**Dicural 15 mg coated tablets**
**Blister label**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 15 mg coated tablets for dogs

Difloxacin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

## 3. EXPIRY DATE

EXP {month/year}

## 4. BATCH NUMBER

Lot {number}

## 5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**
**Dicural 50 mg coated tablets**
**Blister label**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg coated tablets for dogs

Difloxacin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

## 3. EXPIRY DATE

EXP {month/year}

## 4. BATCH NUMBER

Lot {number}

## 5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**
**Dicural 100 mg coated tablets**
**Blister label**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 100 mg coated tablets for dogs

Difloxacin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

## 3. EXPIRY DATE

EXP {month/year}

## 4. BATCH NUMBER

Lot {number}

## 5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**
**Dicural 150 mg coated tablets**
**Blister label**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 150 mg coated tablets for dogs

Difloxacin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

## 3. EXPIRY DATE

EXP {month/year}

## 4. BATCH NUMBER

Lot {number}

## 5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**
**Dicural 50 mg/ml, solution for injection for cattle and dogs**
**CARTON for 50 ml vial**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg/ml solution for injection for cattle and dogs

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

| | |
|---|---|
| Difloxacin (as hydrochloride) | 50 mg/ml |
| Benzyl alcohol | 50 mg/ml |

## 3. PHARMACEUTICAL FORM

Solution for injection

## 4. PACKAGE SIZE

50 ml

## 5. TARGET SPECIES

Cattle (calves and young cattle) and dogs

## 6. INDICATION(S)

Cattle:

- Treatment of Bovine respiratory disease (shipping fever, calf pneumonia) caused by single or mixed infections with *Pasteurella haemolytica*, *Pasteurella multocida*, and/or *Mycoplasma spp*.

Dogs:
Treatment of:

- Acute uncomplicated urinary tract infections caused by *Escherichia coli* or *Staphylococcus spp*
- Superficial pyoderma caused by *Staphylococcus intermedius.*

## 7. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
*[Space shall be provided for the prescribed dose to be indicated on the outer carton]*

## 8. WITHDRAWAL PERIOD

Withdrawal period: **Cattle** - meat and offal 46 days

## 9. SPECIAL WARNING(S), IF NECESSARY

People with a known hypersensitivity to quinolones should avoid any contact with the product.

## 10. EXPIRY DATE

EXP *{month/year}*
Shelf life after first use of the product: 28 days

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the container in the outer carton.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only - to be supplied only on veterinary prescription..

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

EU/2/97/003/016

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE**
**Dicural 50 mg/ml, solution for injection for cattle and dogs**
**50 ml vial label**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg/ml solution for injection for cattle and dogs

## 2. ACTIVE SUBSTANCES

Difloxacin (as hydrochloride) 50 mg/ml

## 3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

50 ml

## 4. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

## 5. WITHDRAWAL PERIOD

Withdrawal period: **Cattle** - meat and offal 46 days

## 6. MANUFACTURER'S BATCH NUMBER

Lot {number}

## 7. EXPIRY DATE

EXP *{month/year}*
Shelf-life after first use of the product: 28 days

## 8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

*[MA Number recommended, but not required on the immediate label]*
EU/2/97/003/016

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND THE IMMEDIATE PACKAGE**
**Dicural 50 mg/ml solution for injection for cattle**
**OUTER CARTON for 100 ml vial / 250 ml vial / VIAL LABEL 100 ml vial / 250 ml vial**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg/ml solution for injection for cattle

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

| | |
|---|---|
| Difloxacin (as hydrochloride) | 50 mg/ml |
| Benzyl alcohol | 50 mg/ml |

## 3. PHARMACEUTICAL FORM

Solution for injection

## 4. PACKAGE SIZE

100 ml
250 ml

## 5. TARGET SPECIES

Cattle (calves and young cattle)

## 6. INDICATION(S)

Treatment of Bovine respiratory disease (shipping fever, calf pneumonia) caused by single or mixed infections with *Pasteurella haemolytica*, *Pasteurella multocida*, and/or *Mycoplasma spp*.

## 7. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
*[Space shall be provided for the prescribed dose to be indicated on the outer carton]*

## 8. WITHDRAWAL PERIOD

Withdrawal period: Meat and offal 46 days

## 9. SPECIAL WARNING(S), IF NECESSARY

People with a known hypersensitivity to quinolones should avoid any contact with the product.

## 10. EXPIRY DATE

EXP *{month/year}*
Shelf-life after first use of the product: 28 days

## 11. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the container in the outer carton.

## 12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

*[Not required on the immediate label]*

Dispose of waste material in accordance with local requirements.

## 13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only. To be supplied only on veterinary prescription..

## 14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

*[Not required on the immediate label]*

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

## 16. MARKETING AUTHORISATION NUMBER(S)

*[Recommended, but not required on the immediate label]*
EU/2/97/003/017 – 100 ml
EU/2/97/003/018 – 250 ml

## 17. MANUFACTURER'S BATCH NUMBER

Lot {number}

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET FOR**
**Dicural 100 mg/ml oral solution for chickens and turkeys**

## 1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

**Marketing authorisation holder**
Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

**Manufacturer for the batch release**
Pfizer Olot, S.L.U.
Ctra. Camprodón, s/n°, Finca La Riba,
Vall de Bianya, 17813 Girona
Spain

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 100 mg/ml oral solution for chickens and turkeys

## 3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENT(S)

Each ml contains:

**Active substance**
Difloxacin (as hydrochloride) 100 mg

**Excipients**

Other excipients, including benzyl alcohol, in an aqueous formulation to 1 ml

## 4. INDICATIONS

In chickens and turkeys: Dicural oral solution is indicated for treatment of chronic respiratory infections caused by sensitive strains of *Escherichia coli* and *Mycoplasma gallisepticum*.

In turkeys: Dicural oral solution is also indicated for the treatment of infections caused by *Pasteurella multocida*.

Dicural oral solution should only be used based on susceptibility testing

## 5. CONTRAINDICATIONS

Since no studies were performed in clinically lame birds, Dicural oral solution should not be used in birds with existing leg-weakness or in birds suffering from osteoporosis.

## 6. ADVERSE REACTIONS

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Chickens (broilers and future breeders)
Turkeys (young turkeys up to 2 kg body weight).

## 8. DOSAGE FOR EACH SPECIES, METHOD AND ROUTE OF ADMINISTRATION

Dicural oral solution must be administrated daily via the drinking water in such a concentration that the dose is 10 mg/kg bodyweight. The administration must be continued for 5 days.

For oral administration in drinking water.

Taking into account the content of difloxacin in the oral solution (10%w/v), the following calculation should be made to determine the volume (ml) to be added for each 1000 litres of water:

$$\frac{\text{number of animals in the house X mean weight of individual animal(kg) X 100}}{\text{total water consumption of the house at the previous day (litres)}}$$

## 9. ADVICE ON CORRECT ADMINISTRATION

The screw cap on the 1 litre bottle can be used as measuring device. If filled to the brim the measuring device provides 50 ml. For the 250 ml bottle a separate measuring device is placed on the screw cap. Measuring lines indicate the volume supplied.

The medicated drinking water should be prepared freshly each day.

No other source of drinking water should be available during the medication period.

No additional chlorine, for example from the use of water chlorinators, or hydrogen peroxide should be added to the drinking water used with this product.

At concentrations in the water of 0.03% (= 300 ml in 1000 litres) or greater, palatability for turkeys may be affected.

## 10. WITHDRAWAL PERIODS

Meat and offal (chicken and turkeys): 24 hours.

Not permitted for use in laying birds producing eggs for human consumption.

## 11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.

Do not store above 25 °C.
Protect from light.

Do not freeze.

Shelf-life after first opening the container: 1 month.
Do not use after the expiry date stated on the label after EXP

## 12. SPECIAL WARNING(S)

Do not use in birds in lay and/or within 4 weeks before the onset of the laying period.>

Heavy reliance on a single class of antibiotics may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antibiotic.

People with known hypersensitivity to quinolones should avoid any contact with the product.
In order to avoid irritation of skin and/or eyes, use gloves and a face-protecting device, when handling this product.

## 13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

## 14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

## 15. OTHER INFORMATION

For animal treatment only. To be supplied only on veterinary prescription.

Dicural oral solution is a yellowish clear aqueous solution and is supplied in plastic white bottles with a screw cap containing 250 or 1000 ml oral solution. Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

België/Belgique/Belgien

Pfizer Animal Health s.a.,

Tél.: +32 (0)2 554 62 11

Република България

Pfizer Luxembourg SARL

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Česká republika

Pfizer Animal Health

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Eesti

Pfizer Animal Health

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Ελλάδα

Pfizer Hellas A.E.

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España

Pfizer S.L.

Tel: +34 91 4909900

Luxembourg

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Tél.: + 32 (0)2 554 62 11

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Pfizer Kft.

Tel: +361 488 3695

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Agrimed Limited

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Pfizer Trading Polska Sp. z.o.o.

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Pfizer

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Pfizer Oy Animal Health,

Puh/Tel: +358 (0)9 4300 40

Sverige

Pfizer Oy Animal Health

Tel: +358 (0)9 4300 40

United Kingdom

Pfizer Ltd

Tel: +44 (0) 1304 616161

**PACKAGE LEAFLET FOR**
**Dicural coated tablets for dogs**

## 1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

**Marketing authorisation holder:**
Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

**Manufacturer for the batch release:**
Pfizer Olot, S.L.U.
Ctra. Camprodón, s/n°, Finca La Riba,
Vall de Bianya, 17813 Girona
Spain

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 15 mg coated tablets for dogs
Dicural 50 mg coated tablets for dogs
Dicural 100 mg coated tablets for dogs
Dicural 150 mg coated tablets for dogs

## 3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each tablet contains:

| | | |
|---|---|---|
| Dicural 15 mg | difloxacin (as hydrochloride) | 15 mg |
| Dicural 50 mg | difloxacin (as hydrochloride) | 50 mg |
| Dicural 100 mg | difloxacin (as hydrochloride) | 100 mg |
| Dicural 150 mg | difloxacin (as hydrochloride) | 150 mg |

## 4. INDICATION(S)

Dicural coated tablets are indicated for the following clinical conditions in dogs:
- Acute uncomplicated urinary tract infections caused by *Escherichia coli* or *Staphylococcus spp.*
- Superficial pyoderma caused by *Staphylococcus intermedius.*

Dicural Coated Tablets should only be used based on susceptibility testing.

## 5. CONTRAINDICATIONS

As for other quinolones, due to possible adverse effects on the articular cartilage of weight bearing joints, difloxacin should not be used during the rapid growth phase, that is, do not use in small-and medium breed dogs up to and including 8 months of age, in large breeds up to 1 year of age and in giant breeds up to 18 months of age.

Do not use in epileptic dogs.

## 6. ADVERSE REACTIONS

Adverse reactions were rare in dogs treated with difloxacin. The observed reactions were inappetence, emesis, diarrhoea, and anal irritation. These adverse reactions were self-limiting within one or two days and did not require additional treatment.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Dogs

## 8. DOSAGE FOR EACH SPECIES, METHOD AND ROUTE(S) OF ADMINISTRATION

The recommended dose of difloxacin is 5 mg/kg bodyweight per day. Dicural coated tablets should be given once a day for at least 5 days. Superficial pyoderma may require treatment for up to a maximum of 21 days. The tablets should be administered for at least 2 days beyond the cessation of clinical signs.

Therapy should be re-evaluated if no improvement is seen within 5 days, or 10 days in the case of superficial pyoderma.

| | **Bodyweight (kg)** | **Dicural 15 mg** | **Dicural 50 mg** | **Dicural 100 mg** | **Dicural 150 mg** |
|---|---|---|---|---|---|
| **Small** | 0 - 3<br>4 - 6 | 1<br>2 | | | |
| **Medium** | 7 - 10<br>11 - 20<br>21 - 30 | (3) | 1<br>2<br>3 | (1) | (1) |
| **Large** | 31 - 40<br>41 - 60 | | | 2<br>3 | (2) |

For oral use.

## 9. ADVICE ON CORRECT ADMINISTRATION

## 10. WITHDRAWAL PERIOD

Not applicable.

## 11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.
Do not store above 25°C. Store in a dry place.
Do not use after the expiry date stated on the carton after EXP.

## 12. SPECIAL WARNING(S)

People with known hypersensitivity to quinolones should avoid any contact with the product.
The use of difloxacin in pregnant or lactating bitches or male stud dogs is not recommended.

Heavy reliance on a single class of antibiotics may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antibiotic.

## 13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

## 14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

## 15. OTHER INFORMATION

For animal treatment only - to be supplied only on veterinary prescription.

Dicural coated tablets consist of a core tablet containing difloxacin hydrochloride and a highly palatable coating. Each strength of the product is available in packs of 10, 20 and 100 tablets. Not all pack sizes may be marketed.

Difloxacin is an aryl-fluoroquinolone with a broad spectrum of antimicrobial activity. Difloxacin can be bactericidal against many Gram-negative micro-organisms and a selection of Gram-positive micro-organisms.

The fluoroquinolones exert their antibacterial effects against both replicating and dormant micro-organisms. Difloxacin acts primarily through inhibition of bacterial DNA gyrase.

The following organisms were tested and found to be susceptible to difloxacin *in vitro*:

*Escherichia coli*
*Klebsiella spp.*
*Pasteurella spp.*
*Pseudomonas spp.*
*Staphylococcus intermedius*

The following organisms were found to be of intermediate susceptibility:

*Proteus spp.*
*Staphylococcus spp.*
*Streptococcus canis (beta)*
*Streptococcus spp.*

Following an oral dose (a plain tablet) in dogs of 5 mg/kg bodyweight, difloxacin reached its average peak plasma concentration of 1.8 µg/ml in approximately 3 hours. Approximately 95 % of the oral dose was absorbed. The elimination half-life averaged 9.3 hours.

Long term daily oral treatment over 180 days at 5 mg/kg bodyweight did not influence difloxacin kinetics, neither by accumulation nor by increased drug metabolism.

For any information about this veterinary medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Pfizer Animal Health s.a.,

Tél.: +32 (0)2 554 62 11

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**PACKAGE LEAFLET FOR:**
**Dicural 50 mg/ml solution for injection for cattle and dogs**

## 1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

**Marketing authorisation holder:**
Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

**Manufacturer for the batch release:**
Pfizer Olot, S.L.U.
Ctra. Camprodón, s/n°, Finca La Riba,
Vall de Bianya, 17813 Girona
Spain

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dicural 50 mg/ml solution for injection for cattle and dogs

## 3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

**Active substance**
Difloxacin (as hydrochloride) 50 mg/ml

**Excipients**
Benzyl alcohol 50 mg/ml

## 4. INDICATION(S)

**Cattle:** Treatment of Bovine respiratory disease (shipping fever, calf pneumonia) caused by single or mixed infections with *Pasteurella haemolytica*, *Pasteurella multocida*, and/or *Mycoplasma spp*.

**Dogs:** treatment of:
- Acute uncomplicated urinary tract infections caused by *Escherichia coli* or *Staphylococcus spp*
- Superficial pyoderma caused by *Staphylococcus intermedius.*

## 5. CONTRAINDICATIONS

**Cattle:** None.

**Dogs:** As for other quinolones, due to possible adverse effects on the articular cartilage of weight bearing joints difloxacin should not be used during the rapid growth phase, that is,. do not use in small and medium-sized breeds of dogs up to and including 8 months of age, in large breeds up to 1 year of age and in giant breeds up to 18 months of age.

Do not use in epileptic dogs.

## 6. ADVERSE REACTIONS

**Cattle:**
In target animal safety studies, subcutaneous administration was generally well tolerated. Transient swelling at the injection site following administration may occur.

**Dogs:**
In target animal safety studies, subcutaneous administration was generally well tolerated. Pruritis and/or local swellings and occasionally a slight pain reaction on injection have been observed. In general the pruritis disappears within a few minutes and the local swelling within a few days.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Cattle (calves and young cattle)\
Dogs

## 8. DOSAGE FOR EACH SPECIES, METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

**Cattle:**
The recommended dose is 2.5 mg difloxacin/kg bodyweight/day for 3 days (that is, 5ml/100 kg bodyweight/day). If there is insufficient improvement after 3 days, the treatment can be continued for another 2 days. For complicated respiratory disease the dose can be doubled to 5 mg/kg bodyweight / day.

**Dogs:**
The recommended dose is 5.0 mg difloxacin/kg body weight in a single injection Treatment should be continued with Dicural coated tablets (read the package leaflet of this product)

## 9. ADVICE ON CORRECT ADMINISTRATION

In **cattle**, the volume administered per injection site should not exceed 7 ml. A new injection site should be used each day.

In **dogs**, the volume administered per injection site should not exceed 5 ml.

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

## 10. WITHDRAWAL PERIOD

**Cattle**: Meat and offal: 46 days

## 11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.

Do not store above 25°-C.
Do not freeze.
Keep the container in the outer carton.
Shelf-life after first use of the product: 28 days.
Do not use after the expiry date stated on the vial after EXP.

## 12. SPECIAL WARNING(S)

Heavy reliance on a single class of antibiotics may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions that have responded poorly, or are expected to respond poorly, to other classes of antibiotic.

Dicural 50 mg/ml solution for injection should only be used based on susceptibility testing.

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
The use of fluoroquinolones in combination with non-steroidal anti-inflammatory drugs (NSAIDs) may cause seizures.
Antagonism may be observed with nitrofurantoin.

People with a known hypersensitivity to quinolones should avoid any contact with the product.

**Overdose**

**Cattle:**
At very high doses adverse effects on the nervous system (ataxia, unsteadiness, twitching, tremors, convulsions, etc.) may occur in cattle. Overdosage may also give rise to oedema and swelling in the knee joints.

**Dogs:**
In dogs the oral administration of difloxacin at up to 5 times the recommended dose rate for 30 days did not result in any adverse reactions.

In another study dogs treated orally with difloxacin at 10 times the recommended dose for 10 days showed occasionally mild adverse reactions such as orange/yellowing discoloration of the faeces, emesis and hypersalivation.

No specific antidotes for difloxacin (or other quinolones) are known, therefore in case of overdosage symptomatic treatment should be given

## 13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

## 14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

## 15. OTHER INFORMATION

For animal treatment only. To be supplied only on veterinary prescription.

Dicural 50 mg/ml, solution for injection for cattle and dogs is available in the following presentations:
Dogs: 50 ml vial.
Cattle: 50, 100 and 250 ml vials.
Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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