

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Baytril Direct 100 mg/ml Injektionslösung für Rinder und Schweine [AT]
Baytril Inject – Soluzione iniettabile 100mg/ml per bovini e suini [IT]
Baytril XM 100 mg/mL Solution injectable pour bovins et pores [FR]
Baytril Inject 100 mg/ml Injektionslösung für Rinder und Schweine [DE]
Baytril Max 100 mg/ml Solution for Injection for Cattle and Pigs[IE, UK]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:

Enrofloxacin 100 mg

Excipients:

n-Butanol 30 mg

Benzyl alcohol (E 1519) 20 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, yellow solution

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, Pig

4.2 Indications for use, specifying the target species

Cattle:

For the treatment of respiratory tract infections caused by enrofloxacin-sensitive *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida* and *Mycoplasma* spp.

For the treatment of mastitis caused by enrofloxacin-sensitive *E. coli*.

Pig:

For the treatment of bacterial bronchopneumonia caused by enrofloxacin-sensitive *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and complicated by *Haemophilus parasuis* as a secondary pathogen in pigs.

4.3 Contraindications

Do not use for prophylaxis.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients. Do not use in known cases of resistance to other (fluoro)quinolones due to the potential for cross-resistance.

Do not use in animals with central nervous system-associated seizure disorders. Do not use in the presence of existing disorders of cartilage development or musculoskeletal damage around functionally significant or weight-bearing joints.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

For repeated injection or for injection volumes exceeding 15 ml (cattle) or 7.5 ml (pigs, calves) in divided doses, a new site must be chosen for each injection.

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.

Enrofloxacin is eliminated renally. As with all fluoroquinolones, delayed excretion can therefore be expected in the presence of existing renal damage.

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

Direct contact with the skin should be avoided due to sensitisation, contact dermatitis and possible hypersensitivity reactions.

People with known hypersensitivity to (fluoro)quinolones should avoid contact with the product.

Wash hands after use.

In the event of accidental splash into the eye, rinse with large amounts of clean water. If irritation occurs, seek medical advice.

Do not eat, drink or smoke while handling the product.

Take care to avoid accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.

4.6 Adverse reactions (frequency and seriousness)

In rare cases, transitory inflammatory reactions (swelling, redness) can occur at the injection site.

These regress within a few days without further therapeutic measures.

In rare cases, intravenous treatment can cause shock reactions in cattle, probably as a result of circulatory disturbances.

Gastrointestinal disturbances may occur in isolated cases during treatment of calves.

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

May be used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Antagonist effects due to concurrent administration of macrolides and tetracyclines may occur. Enrofloxacin may interfere with the metabolism of theophylline, decreasing theophylline clearance resulting in increased plasma levels of theophylline.

4.9 Amounts to be administered and administration route

Cattle:

The dosage for respiratory disease is 7.5 mg enrofloxacin per kg body weight (BW) for a single treatment by subcutaneous administration (s.c.).

This is equivalent to

7.5 ml of the product per 100 kg BW and day
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Do not administer more than 15 ml (cattle) or 7.5 ml (calf) per injection site (s.c.). In case of serious or chronic respiratory disease a second injection may be required after 48 hours.

The dosage for the treatment of colimastitis is 5 mg enrofloxacin per kg body weight (BW) by intravenous administration (i.v.).

This is equivalent to

5 ml of the product per 100 kg BW and day
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The treatment of colimastitis should be exclusively by intravenous application on 2 to 3 consecutive days.

Pig:

The dosage for respiratory tract infections is 7.5 mg enrofloxacin per kg body weight for a single treatment by intramuscular administration (i.m.).

This is equivalent to

0.75 ml of the product per 10 kg BW and day
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Do not administer more than 7.5 ml per injection site (i.m.). In cases of serious or chronic respiratory disease a second injection may be required after 48 hours.

Method of administration:

Repeated injections should be made at different injection sites.

Cattle:

For subcutaneous injection (respiratory disease) or for intravenous injection (colimastitis).

Pig:

For intramuscular injection into the neck muscles behind the ear.

To ensure administration of the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The stopper may be safely punctured up to 20 times.

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

In cattle a dose of 25 mg/kg bodyweight administered by the subcutaneous route for 15 consecutive days is tolerated without any clinical symptoms. Higher doses in cattle and doses of around 25 mg/kg and above in pigs may cause lethargy, lameness, ataxia, slight salivation and muscle tremors.

Do not exceed the recommended dose. In accidental overdose there is no antidote and treatment should be symptomatic.

4.11 Withdrawal period(s)

Cattle:

Meat and offal:

s.c.: 14 days

i.v.: 7 days

Milk:

s.c.: 120 hours

i.v.: 72 hours

Pig:

Meat and offal: 12 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, Fluoroquinolones,
ATCvet code: QJ01MA90

5.1 Pharmacodynamic properties

Enrofloxacin has a spectrum of activity which includes enrofloxacin-sensitive *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma* spp., and *E. coli* in cattle as well as *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis* in pigs.

Enrofloxacin belongs to the fluoroquinolone group of antibiotics. The substance has bactericidal activity which is mediated by binding to subunit A of DNA gyrase and the resulting selective inhibition of this enzyme.

DNA gyrase is a topoisomerase. These enzymes are involved in the replication, transcription and recombination of bacterial DNA. Fluoroquinolones also influence bacteria in the stationary phase by altering cell wall permeability.

Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

The inhibitory and bactericidal concentrations of enrofloxacin are very close, being either identical or differing by no more than 1-2 dilution steps.

MIC-Data

Cattle:

Species	Country	Year of Isolation	Number of strains	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Resistance (%)
<i>Mannheimia haemolytica</i>	EU ⁽¹⁾	2009-12	149	0.03	0.25	0.7
<i>Pasteurella</i>	EU ⁽¹⁾	2009-12	134	0.015	0.03	3.0

<i>multocida</i>						
<i>Histophilus somni</i>	EU ⁽¹⁾	2009-12	66	0.03	0.06	0.0
<i>Escherichia coli</i> (mastitis)	EU ⁽²⁾	2009-12	207	0.03	0.06	n.a. ⁽⁵⁾
<i>Mycoplasma bovis</i>	EU ⁽³⁾	2010-12	156	0.25	4	n.a. ⁽⁵⁾
	F ⁽⁴⁾	2010-12	143	0.5	0.5	n.a. ⁽⁵⁾

EU: Europe; F: France; ⁽¹⁾ VET MICROBIOL 194, 2016, 11-22; ⁽²⁾ INT J ANTIMICROB AGENTS 46, 2015, 13-20; ⁽³⁾ VET MICROBIOL 204, 2017, 188-193; ⁽⁴⁾ PLoS One, 2014; 9(2): e87672; ⁽⁵⁾ n.a.: not applicable.

Pig:

Species	Country	Year of Isolation	Number of strains	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Resistance (%)
<i>Actinobacillus pleuropneumoniae</i>	EU ⁽¹⁾	2009-12	158	0.03	0.06	1.3
<i>Pasteurella multocida</i>	EU ⁽¹⁾	2009-12	152	0.015	0.03	0.0
<i>Haemophilus parasuis</i>	EU ⁽¹⁾	2009-12	68	0.008	0.06	n.a. ⁽²⁾

EU: Europe; ⁽¹⁾ VET MICROBIOL 194, 2016, 11-22; ⁽²⁾ n.a.: not applicable.

Enrofloxacin resistance breakpoints [R] are available for *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* isolated from cattle ($R \geq 2$ µg/ml, CLSI document VET01S 3rd Edition) and for *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* isolated from pigs ($R \geq 1$ µg/ml, CLSI document VET01S 3rd Edition).

5.2 Pharmacokinetic particulars

Following subcutaneous administration of the product in cattle or intramuscular administration in pigs, the active substance, enrofloxacin, is absorbed very rapidly and almost completely (high bioavailability).

Cattle:

After subcutaneous administration at a dose rate of 7.5 mg enrofloxacin per kg body weight to non-lactating cattle peak plasma concentrations of 0.82 mg/L are reached within 5 hours. The overall drug exposure in plasma is 9.1 mg*hr/L. Enrofloxacin is eliminated from the body at a half-life of 6.4 hr. Approximately 50% of enrofloxacin is metabolised to the active substance ciprofloxacin. Ciprofloxacin is eliminated from the body at a half-life of 6.8 hr.

After intravenous injection at a dose rate of 5.0 mg enrofloxacin per kg body weight to lactating cows, peak plasma concentrations of approx. 23 mg/L are reached immediately. The overall drug exposure in plasma is 4.4 mg*hr/L. Enrofloxacin is eliminated from the body at a half-life of 0.9 hr. Approximately 50% of parent compound is metabolised to ciprofloxacin with peak plasma concentrations of 1.2 mg/L reached at 0.2 hr. Mean elimination half-life of ciprofloxacin is 2.1 hr.

In milk the metabolite ciprofloxacin mainly accounts for antibacterial activity (approx. 90%). Ciprofloxacin reaches peak milk concentrations of 4 mg/L within 2 hr after intravenous dosing. Total exposure in milk over 24 hours is approx. 21 mg*hr/L. Ciprofloxacin is eliminated from milk at a half-life of 2.4 hr. Peak concentrations of 1.2 mg enrofloxacin per litre are reached in milk within 0.5 hours with an total enrofloxacin exposure in milk of approx. 2.2 mg*hr/L. Enrofloxacin is eliminated from milk at 0.9 hr.

Pig:

After intramuscular administration of 7.5 mg/kg body weight to pigs a mean peak serum concentration of 1.46 mg/L was achieved within 4 hours. The overall drug exposure over 24 hours was 20.9 mg*hr/L. The drug was eliminated from the central compartment at a terminal half-life of 13.1 hr. With peak concentrations less than 0.06 mg/L mean serum concentrations of ciprofloxacin were very low.

Enrofloxacin has a high volume of distribution. The concentrations in the tissues and organs mostly significantly exceed serum levels. Organs in which high concentrations can be expected include the lungs, liver, kidneys, gut and muscle tissue.

Enrofloxacin is eliminated renally.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E 1519)

Arginine

n-Butanol

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: 3 years

Shelf life after first opening of the immediate packaging: 28 days

6.4. Special precautions for storage

Protect from frost.

6.5 Nature and composition of immediate packaging

Cardboard box with one brown glass bottle (Type I) containing 100 ml with chlorobutyl rubber stopper secured by an aluminium crimp cap.

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

{Name Address Country}

<{Tel}>

<{Fax}>

<{E-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:<{DD/MM/YYYY}

Date of last renewal: {DD/MM/YYYY}...

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be supplied only on veterinary prescription.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND THE IMMEDIATE PACKAGE

Card box and package leaflet for brown glass bottle (Type 1)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Baytril Direct 100 mg/ml Injektionslösung für Rinder und Schweine [AT]
Baytril Inject – Soluzione iniettabile 100mg/ml per bovini e suini [IT]
Baytril XM 100 mg/mL Solution injectable pour bovins et porcs [FR]
Baytril Inject 100 mg/ml Injektionslösung für Rinder und Schweine [DE]
Baytril Max 100 mg/ml Solution for Injection for Cattle and Pigs [IE, UK]

Enrofloxacin

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains:

Active substance:

Enrofloxacin 100 mg

Excipients:

n-Butanol 30 mg

Benzyl alcohol (E 1519) 20 mg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml

5. TARGET SPECIES

Cattle, Pig

6. INDICATION(S)

Read the package leaflet before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD (S)

Withdrawal periods:

Cattle:

Meat and offal:

s.c.: 14 days

i.v.: 7 days

Milk:

s.c.: 120 hours

i.v.: 72 hours

Pig:

Meat and offal: i.m. 12 days

9. SPECIAL WARNING(S), IF NECESSARY

Accidental injection is dangerous - Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/ year}

Shelf-life after first opening the immediate packaging: 28 days.

Once broached use within...

11. SPECIAL STORAGE CONDITIONS

Protect from frost.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS 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, IF APPLICABLE

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

14. THE WORDS “KEEP OUT OF THE SIGHT AND AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name Address}

<{Tel}>

<{Fax}>

<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

B. PACKAGE LEAFLET

Do not use in cases of hypersensitivity to the active substance or to any of the excipients. Do not use in known cases of resistance to other (fluoro)quinolones due to the potential for cross-resistance.

Do not use in animals with central nervous system-associated seizure disorders. Do not use in the presence of existing disorders of cartilage development or musculoskeletal damage around functionally significant or weight-bearing joints.

6. ADVERSE REACTIONS

In rare cases, transitory inflammatory reactions (swelling, redness) can occur at the injection site. These regress within a few days without further therapeutic measures. In rare cases, intravenous treatment can cause shock reactions in cattle, probably as a result of circulatory disturbances. Gastrointestinal disturbances may occur in isolated cases during treatment of calves.

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

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)

7. TARGET SPECIES

Cattle, Pig

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

Cattle:

The dosage for respiratory disease is 7.5 mg enrofloxacin per kg body weight (BW) for a single treatment by subcutaneous administration (s.c.).

This is equivalent to

7.5 ml of the product per 100 kg BW and day
--

Do not administer more than 15 ml (cattle) or 7.5 ml (calf) per injection site (s.c.).

In case of serious or chronic respiratory disease a second injection may be required after 48 hours.

The dosage for the treatment of colimastitis is 5 mg enrofloxacin per kg body weight (BW) by intravenous administration (i.v.).

This is equivalent to

5 ml of the product per 100 kg BW and day
--

The treatment of colimastitis should be exclusively by intravenous application on 2 to 3 consecutive days.

Pig:

The dosage for respiratory tract infections is 7.5 mg enrofloxacin per kg body weight for a single treatment by intramuscular administration (i.m.).

This is equivalent to

0.75 ml of the product per 10 kg BW and day
--

Do not administer more than 7.5 ml per injection site (i.m.). In cases of serious or chronic respiratory disease a second injection may be required after 48 hours.

Method of administration:

Repeated injections should be made at different injection sites.

Cattle:

For subcutaneous injection (respiratory disease) or for intravenous injection (colimastitis).

Pig:

For intramuscular injection into the neck muscles behind the ear.

To ensure administration of the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The stopper may be safely punctured up to 20 times.

9. ADVICE ON CORRECT ADMINISTRATION

To ensure administration of the correct dosage, body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

Cattle:

Meat and offal:

s.c.: 14 days
i.v.: 7 days

Milk:

s.c.: 120 hours
i.v.: 72 hours

Pig:

Meat and offal: 12 days

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Protect from frost.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton and label after {EXP}. The expiry date refers to the last day of that month.

Shelf-life after first opening the container: 28 days.

12. SPECIAL WARNING(S)

Special precautions for use in animals:

For repeated injection or for injection volumes exceeding 15 ml (cattle) or 7.5 ml (pigs, calves) in divided doses, a new site must be chosen for each injection.

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.

Enrofloxacin is eliminated renally. As with all fluoroquinolones, delayed excretion can therefore be expected in the presence of existing renal damage.

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

Direct contact with the skin should be avoided due to sensitisation, contact dermatitis and possible hypersensitivity reactions.

People with known hypersensitivity to (fluoro)quinolones should avoid contact with the product.

Wash hands after use.

In the event of accidental splash into the eye, rinse with large amounts of clean water. If irritation occurs, seek medical advice.

Do not eat, drink or smoke while handling the product.

Take care to avoid accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.

Pregnancy and lactation:

May be used during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:

Antagonist effects due to concurrent administration of macrolides and tetracyclines may occur.

Enrofloxacin may interfere with the metabolism of theophylline, decreasing theophylline clearance resulting in increased plasma levels of theophylline.

Overdose (symptoms, emergency procedures, antidotes):

In cattle a dose of 25 mg/kg bodyweight administered by the subcutaneous route for 15 consecutive days is tolerated without any clinical symptoms. Higher doses in cattle and doses of around 25 mg/kg and above in pigs may cause lethargy, lameness, ataxia, slight salivation and muscle tremors.

Do not exceed the recommended dose. In accidental overdose there is no antidote and treatment should be symptomatic.

Incompatibilities:

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

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

Medicines should not be disposed of via wastewater. Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Package size: 100 ml

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