1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Resflam 300/20 mg/ml Solution for Injection for Cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Oxytetracycline (as Oxytetracycline Dihydrate)	300 mg
Flunixin (as Flunixin Meglumine)	20 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Sodium Formaldehyde Sulphoxylate	4.0 mg
Light Magnesium Oxide	
Glycerol Formal	
Polyethylene Glycol 200	
Sodium Formaldehyde Sulphoxylate	
Monoethanolamine	
Water for Injections	

A clear dark amber solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle.

3.2 Indications for use for each target species

For the treatment of acute respiratory disease caused by oxytetracycline sensitive *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida* where an anti-inflammatory and anti-pyretic effect is required.

3.3 Contraindications

Do not use in animals suffering from cardiac, hepatic or renal disease, where there is a possibility of gastrointestinal ulceration or bleeding. Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Avoid use in dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity.
Do not use in cases of known resistance to tetracyclines.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use in any animals less than 6 weeks of age or in aged animals may involve additional risk due to the antiprostaglandin effects of flunixin on renal function. If such use cannot be avoided, animals may require careful clinical management.

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

Flunixin is toxic to avian scavengers. Do not administer to animals susceptible to enter wild fauna food chain. In case of death or sacrifice of treated animals, ensure that they are not made available to wild fauna.

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

In the case of accidental self-injection, if an allergic reaction occurs, seek medical advice immediately and show the package leaflet or the label to the physician. In case of accidental contact with skin or eyes, rinse with copious amounts of water. If persistent irritation occurs, seek medical advice.
People with known hypersensitivity to tetracycline should avoid contact with the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site reaction[1], Elevated temperature[2], Discoloured teeth[3]

[1] Mild and may persist for up to 30 days. Studies in cattle at the normal dose rate and twice the normal dose rate have shown transient and dose dependent reactions at the injection site leading to increased associated enzymatic activity.
[2] Transient and will be unlikely to occur in animals already suffering from pyrexia.
[3] Use of tetracyclines during teeth and bone development.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

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

The use is not recommended during pregnancy and lactation.

Laboratory studies in laboratory animals have not produced any evidence of teratogenic effects.

3.8 Interaction with other medicinal products and other forms of interaction

Some NSAIDs may be highly bound to plasma proteins and compete with other highly bound drugs which can lead to toxic effects.
Do not administer other NSAIDs concurrently or within 24 hours of each other.
Concurrent use of potentially nephrotoxic drugs should be avoided.
Concurrent use of corticosteroids should be avoided.

3.9 Administration routes and dosage

The product is indicated for deep intramuscular administration to cattle. The recommended dosage is 2 mg/kg flunixin and 30 mg/kg oxytetracycline (equivalent to 1 ml per 10 kg bodyweight).
To ensure correct dosage, bodyweight should be determined as accurately as possible.
This product is recommended for single administration only.
Maximum volume per injection site: 15 ml.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

The product administered to cattle at 4 mg/kg flunixin and 60 mg/kg oxytetracycline (twice the recommended dose) has been shown to be well tolerated. At twice the recommended dose, transient dysentery with or without apathy can occur. These symptoms resolve spontaneously without treatment within 48/72 hours. A transient usually mild reaction at the injection site may be observed following intramuscular administration and may persist beyond the withdrawal period.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance.

Not applicable.

3.12 Withdrawal periods

Meat and offal: 28 days.
Not authorised for use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01A A56

4.2 Pharmacodynamics

Oxytetracycline and flunixin in the combined formulation provide anti-bacterial and anti-inflammatory activities respectively following a single administration.
Oxytetracycline is the 5-OH derivative of tetracycline. The tetracyclines are a family of broad-spectrum bacteriostatic antibiotics which inhibit protein synthesis in susceptible micro-organisms. The tetracyclines, including oxytetracycline are active against many gram-positive and gram-negative bacteria.
After oxytetracycline diffuses through the outer bacterial cell membrane, an active carrier mediated process transports the drugs through the inner cytoplasmic membrane.
Inside the cell, oxytetracycline binds irreversibly to receptors on the 30S sub-unit of the bacterial ribosome where it interferes with the binding of the aminoacyl-transfer RNA to the acceptor site on the

messenger RNA ribosome complex. This effectively prevents the addition of amino acids to the elongating peptide chain, inhibiting protein synthesis.
Flunixin meglumine is a relatively potent non-narcotic, non-steroidal analgesic with anti-inflammatory, anti-endotoxic and anti-pyretic properties.

Flunixin meglumine acts as a reversible inhibitor of cyclo-oxygenase, an important enzyme in the arachidonic acid cascade pathway which is responsible for converting arachidonic acid to cyclic endoperoxides. Consequently, synthesis of eicosanoids, important mediators of the inflammatory process involved in central pyresis, pain perception and tissue inflammation, is inhibited. Through its effects on the arachidonic acid cascade, flunixin also inhibits the production of thromboxane, a potent platelet pro-aggregator and vasoconstrictor which is released during blood clotting. Flunixin exerts its antipyretic effect by inhibiting prostaglandin E_2 synthesis in the hypothalamus. By inhibiting the arachidonic acid cascade pathway, flunixin also produces an anti-endotoxic effect by suppressing eicosanoid formation and therefore preventing their involvement in endotoxin associated disease states.
Acquired resistance to oxytetracycline has been noted. Such resistance is usually plasmid mediated. Cross-resistance to other tetracyclines occurs. Continuous treatment with low doses of oxytetracycline can also result in increased resistance to other antibiotics.

4.3 Pharmacokinetics

Once absorbed, tetracyclines are well distributed throughout the body, with highest concentrations found in liver, spleen, kidney and lung. Tetracyclines are slowly excreted in urine, explaining their long persistence in blood.
Flunixin is characterised by a very high degree of plasma protein binding and hence volumes of distribution are generally low. The unbound fraction is distributed throughout the body fluid, including the CNS. It tends to accumulate in inflamed tissue. Renal excretion contributes extensively to the elimination of flunixin from the body.
After intramuscular administration of the recommended dose of the product to cattle (2 mg flunixin and 30 mg oxytetracycline per kg bodyweight) the following parameters were observed:

Oxytetracycline: C_{max} 11.11 µg/ml; AUC 376.5 µg/ml/hr; T_{max} 5.1 hrs, T½ elimination 36.54 hrs.

Flunixin: C_{max} 2.4 µg/ml; AUC 11.22 µg/ml/hr; T_{max} 1.0 hrs, T½ elimination 4.51 hrs.

Environmental properties

Flunixin is toxic to avian scavengers although foreseen low exposure leads to low risk.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 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.

5.3 Special precautions for storage

Store below 25 °C.
Protect from light.

5.4 Nature and composition of immediate packaging

Immediate packaging: Supplied in 50 ml and 100 ml type I/II, amber glass vials, sealed with bromobutyl rubber bungs and aluminium caps.

Outer packaging and sales presentations:
- Cartons of 1 vial.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Norbrook Laboratories (Ireland) Limited

7. MARKETING AUTHORISATION NUMBER(S)

VPA22664/085/001

8. DATE OF FIRST AUTHORISATION

25/09/2009

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

20/05/2024

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).