Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Curacef duo, 50 mg/ml / 150 mg/ml, Suspension for Injection for Cattle

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Ceftiofur (as hydrochloride)	50.0	mg
Ketoprofen	150.0	mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.
Off - white to pinkish suspension.

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle.

4.2 Indications for use, specifying the target species

For the treatment of bovine respiratory disease (BRD) caused by *Mannheimia haemolytica* and *Pasteurella multocida* susceptible to ceftiofur and the reduction of associated clinical signs of inflammation or pyrexia.

4.3 Contraindications

Do not use in cases of known resistance to other cephalosporins or beta-lactam antibiotics.

Do not use in cases of hypersensitivity to ceftiofur and other b-lactam antibiotics.
Do not use in cases of hypersensitivity to ketoprofen.

Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

Do not administer other non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids concurrently or within 24 hours of each other.

Do not use in animals suffering from cardiac, hepatic or renal disease, where there is the possibility of gastro-intestinal ulceration or bleeding, where there is evidence of a blood dyscrasia.

4.4 Special warnings for each target species

Avoid use in any dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity.

4.5 Special precautions for use

i) Special precautions for use in animals

In case of the occurrence of allergic reaction the treatment should be withdrawn.

The product selects for resistant strains such as bacteria carrying extended spectrum betalactamases (ESBL) and may constitute a risk to human health if these strains disseminate to humans e.g. via food. For this reason, the product should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment.
When inflammation or pyrexia have subsided, the veterinarian should switch to a ceftiofur only-containing product in order to cover 3 to 5 days of continuous antibiotic treatment. Treating for an appropriate length of time is important to limit development of resistance.
Official, national and regional antimicrobial policies should be taken into account when the product is used. Increased use, including use of the product deviating from the instructions given in the SPC, may increase the prevalence of such resistance. Whenever possible, the product should only be used based on susceptibility testing.
The product is intended for treatment of individual animals. Do not use for disease prevention or as a part of herd health programmes. Treatment of groups of animals should be strictly restricted to ongoing disease outbreaks according to the approved conditions of use.

The concomitant use of diuretics or coagulant should be based on a benefit/risk assessment of the responsible veterinarian.

Avoid intra-arterial and intravenous injection.

Use preferably a 14 gauge needle.

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

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and vice versa. Ketoprofen may also cause hypersensitivity.Allergic reactions to these substances may occasionally be serious.

Do not handle this product if you know you are sensitised to active substances or to any of excipients, or if you have been advised not to work with such preparations.

Wash hands after use.

Avoid contact with eyes and skin. In case of contact, wash immediately with water.

If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning.

Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

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

4.6 Adverse reactions (frequency and seriousness)

In field studies, the product has been tested in cattle aged from 1 month old to 12 years without evidencing safety concern.

Mild inflammatory reactions at the injection site, such as tissue oedema, without pain in most cases, were commonly observed in studies.

Hypersensitivity reactions (e.g. skin reactions, anaphylaxia) unrelated to dose and discolouration of the subcutaneous tissue and/or muscle can very rarely be observed.

Gastric or renal intolerance can be observed very rarely in certain individuals, in common with all NSAIDs due to their action of inhibition of prostaglandin synthesis.

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

Even though studies in laboratory animals with ceftiofur or ketoprofen show no evidence of teratogenesis, abortion or influence on reproduction, the reproductive safety of the product has not been specifically investigated in pregnant cows. Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interactions

Some NSAIDs may be highly bound to plasma proteins and compete with other highly bound drugs which can lead to toxic effects.
Do not use in combination with other NSAIDs or with corticosteroids, diuretics, nephrotoxic drugs or anticoagulants.
The bactericidal properties of beta-lactams are neutralised by simultaneous use of bacteriostatic antibiotics (macrolides, sulphonamides and tetracyclines).

4.9 Amounts to be administered and administration route

Intramuscular use.

1 mg ceftiofur/kg/day and 3 mg ketoprofen/kg/day by intramuscular injection, *i.e.* 1 ml/50 kg at each injection. The product should only be used when the disease is associated with clinical signs of inflammation or pyrexia. The product may be administered for 1 to 5 consecutive days depending upon the clinical response on a case by case basis. As the duration for the antibiotic treatment should not be less than 3 to 5 days, when inflammation and pyrexia have subsided, the veterinarian should switch to a ceftiofur only-containing product in order to cover 3 to 5 days of continuous antibiotic treatment. Only few animals are expected to require a fourth or fifth injection with the combined product.

Shake the bottle vigorously for 20 seconds before use to ensure an homogeneous suspension.
Resuspension could be longer after storage at low temperatures.

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

The user should use the most appropriate vial size according to the number of animals to treat.
The 50 ml and 100 ml vials should not be pierced more than 10 times and the 250 ml not more than 18 times. The use of an aspirating needle may be recommended to avoid excessive broaching of the stopper.

Subsequent intramuscular injections must be given at different sites.
Not more than 16 ml should be administered per injection site.

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

No signs of systemic toxicity of the product have been observed at doses up to 5 times the recommended daily dose for 15 consecutive days.

4.11 Withdrawal period(s)

Meat and offal: 8 days
Milk: zero hours

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, ceftiofur, combinations
ATCvet code: QJ01DD99

5.1 Pharmacodynamic properties

Ceftiofur is third generation cephalosporin, which is active against many Gram-positive and Gram-negative bacteria. Ceftiofur, as other beta-lactams, inhibits the bacterial cell wall synthesis, thereby exerting bactericidal properties.
Cell wall synthesis is dependent on enzymes that are called penicillin-binding proteins (PBPs). Bacteria may develop resistance to cephalosporins by four basic mechanisms: 1) altering or acquiring penicillin binding proteins insensitive to an otherwise

effective b -lactam; 2) altering the permeability of the cell to b -lactams; 3) producing b -lactamases that cleave the b -lactam ring of the molecule, or 4) active efflux.
Some beta-lactamases, documented in Gram-negative enteric organisms, may confer elevated MICs to varying degrees to third and fourth generation cephalosporins, as well as penicillins, ampicillin, b -lactam inhibitor combinations, and first and second generation cephalosporins.
Ceftiofur is active against the following microorganisms which are involved in respiratory diseases in cattle: *Pasteurella multocida*, *Mannheimiahaemolytica* (formerly *Pasteurella haemolytica*).

Minimum Inhibitory Concentrations (MICs) have been determined for ceftiofur in European isolates of target bacteria, isolated from diseased animals between 2014 and 2016.

Species (number of isolates)	MIC range (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)
Mannheimia haemolytica(91)	0.002 - 4	0.015	0.06
Pasteurella multocida(155)	0.008 - 0.25	0.015	0.03

MICs of respiratory target pathogens showed mono-modal distribution profiles with good susceptibility towards ceftiofur. Clinical breakpoints (CLSI document VET08 (5) and VET06 (6)) for ceftiofur are established for bovine respiratory disease and *M. haemolytica*, *P. multocida*: susceptible: ≤2 µg/ml; intermediate: 4 µg/ml; resistant: ≥8 µg/ml. According to these breakpoints no clinical resistant strains of respiratory target pathogens were observed.

Ketoprofen is a derivative of phenylpropionic acid, and belongs to the non-steroidal anti-inflammatory group of drugs. The mechanism of action is related to the ability of ketoprofen to interfere with the synthesis of prostaglandins from precursors such as arachidonic acid. Although ketoprofen has no direct effect on endotoxins after they have been produced, it reduces prostaglandin production and hence reduces the many effects of the prostaglandin cascade. Prostaglandins are part of the complex processes involved in the development of endotoxic shock. Like all such substances, its principal pharmacological actions are anti-inflammatory, analgesic and anti-pyretic.

5.2 Pharmacokinetic particulars

After administration, ceftiofur is quickly metabolised to desfuroylceftiofur, the principal active metabolite.

Desfuroylceftiofur has an equivalent anti-microbial activity to ceftiofur against the major target bacteria in animals. The active metabolite is reversibly bound to plasma proteins. Due to transportation with these proteins, the metabolite concentrates at a site of infection, is active and remains active in the presence of necrotic tissue and debris.

Ceftiofur is completely bioavailable following intramuscular administration.

After a single 1 mg/kg dose of ceftiofur (as hydrochloride) given intramuscularly to cattle, maximum ceftiofur and desfuroylceftiofur-related metabolites plasma concentrations of 6.11 ± 1.56 µg/mL (Cmax) are reached within 5 hours (Tmax) after single administration. The apparent terminal elimination half-life (t½) of ceftiofur and desfuroylceftiofur-related metabolites was of 22 hours.
The elimination occurred mainly via the urine (more than 55 %); 31 % of the dose was recovered in the faeces.

Ketoprofen is completely bioavailable following intramuscular administration.

After a single 3 mg/kg dose of ketoprofen given intramuscularly to cattle, maximum ketoprofen plasma concentrations of 5.55 ± 1.58 µg/mL (Cmax) are reached within 4 hours (Tmax) after single administration. The apparent terminal elimination half-life (t½) of ketoprofen was 3.75 hours.

In cattle, ketoprofen is strongly bound to proteins (97%). The elimination occurred mainly via the urine (90 % of the doses), as metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitan oleate
Hydrogenated soya lecithin
Cottonseed oil

6.2 Major incompatibilities

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

6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years for polypropylene vials
Shelf life of the veterinary medicinal product as packaged for sale: 3 years for glass vials
Shelf life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage

Do not freeze.
Keep the glass vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Coloured, type II glass vial with bromobutyl rubber stopper and aluminium cap, packed in a cardboard box
or
Amber coloured, translucent polypropylene (PP) vial containing a stainless steel ball, closed with bromobutyl rubber stopper and aluminium cap, packed in a cardboard box.

Pack sizes:
1 x 50 ml
1 x 100 ml
1 x 250 ml

Not all pack sizes may be marketed.

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

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

7 MARKETING AUTHORISATION HOLDER

Virbac S.A.
1ère avenue
2065 M LID
06516 Carros
France

8 MARKETING AUTHORISATION NUMBER(S)

VPA10988/092/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 August 2014
Date of last renewal: 26 April 2019

10 DATE OF REVISION OF THE TEXT

October 2019