1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Composil 150 mg/ml suspension for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Amoxicillin	150 mg
(equivalent to amoxicillin trihydrate	172 mg)

Excipients:

Qualitative composition of excipients and other constituents
Silica colloidal anhydrous
Sorbitan oleate
Propylene glycol dicaprylocaprate

A white to off-white uniform suspension.

3. CLINICAL INFORMATION

3.1 Target species

Cattle and pigs.

3.2 Indications for use for each target species

In cattle: Treatment of respiratory infections caused by *Mannheimia haemolytica* and *Pasteurella multocida*.

In pigs: Treatment of respiratory infections caused by *Pasteurella multocida*.

3.3 Contraindications

Do not use in cases of hypersensitivity to penicillins, cephalosporins or to any of the excipients.
Do not use in cases of severe renal dysfunction with anuria and oliguria.
Do not use in case of infection with beta-lactamase-producing bacteria.
Do not use in rabbits, hares, hamsters, guinea pigs or other small herbivores.
Do not use in Equidae, because amoxicillin – like all aminopenicillins – may adversely affect the bacterial flora of the caecum.

3.4 Special warnings

This veterinary medicinal product is not effective against beta-lactamase producing organisms. Cross-resistance has been shown between amoxicillin and other penicillins, in particular aminopenicillins. Use of the veterinary medicinal product/amoxicillin should be carefully considered when antimicrobial susceptibility testing has shown resistance to penicillins because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

Narrow spectrum antibiotic therapy with a lower risk of antimicrobial resistance selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

The feeding of waste milk containing residues of amoxicillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Penicillins and cephalosporins may cause an allergic reaction following accidental injection, inhalation, ingestion, or absorption via the skin, which may be life threatening. Hypersensitivity to penicillins may lead to cross sensitivity to cephalosporins and vice versa. Avoid direct contact of the veterinary medicinal product with the skin or the mucosae.
Avoid oral ingestion, including hand-to-mouth-contact.
Do not smoke, eat or drink during use of the veterinary medicinal product.
Handle the veterinary medicinal product with great care to avoid exposure.
Wear gloves and wash hands after use of the veterinary medicinal product.
In case of contact with the skin or eyes, wash immediately with water.
If you develop symptoms following exposure, such as a skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips and eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle, pigs:

Rare (1 to 10 animals / 10,000 animals treated):	Injection site irritation[1]
Undetermined frequency (cannot be estimated from the available data):	Allergic reaction[2] (e.g. urticaria, anaphylactic shock)

[1]Of low intensity, recedes spontaneously and quickly. Frequency may be decreased by reducing the volume of injection per injection site (see section 3.9).
[2] Varying in severity. In case of allergic reaction treatment should be discontinued and a symptomatic treatment should be initiated.

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 its local representative 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

The tolerance of the veterinary medicinal product in cattle and pigs during pregnancy and lactation has not been investigated.

Pregnancy and lactation:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects of amoxicillin.
Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

As there is evidence of *in vitro* antagonism between beta-lactam antibiotics and the following bacteriostatic antibiotics (erythromycin and other macrolides, tetracyclines, sulfonamides), concomitant use is generally not recommended.

3.9 Administration routes and dosage

Intramuscular use.

Dosage: 15 mg amoxicillin per kg bodyweight; corresponding to 1 ml of the veterinary medicinal product per 10 kg BW.
Administration should be repeated after 48 hours.
To ensure a correct dosage, body weight should be determined as accurately as possible.

Do not administer more than 20 ml of the veterinary medicinal product per injection site in cattle.
Do not administer more than 6 ml of the veterinary medicinal product per injection site in pigs.

Shake the vial vigorously for 30 seconds to achieve full resuspension before use.

Do not broach the vial more than 10 times: if necessary, use automatic syringes.

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

No adverse effects were observed at a dose corresponding to 5 times the therapeutic dose, with the exception, in a limited number of animals, of a slight local reaction at the injection site, transient, reversible without treatment and without consequences for the animal.

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

Cattle:
Meat and offal: 18 days.
Milk: 72 hours.
Pigs:
Meat and offal: 16 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01CA04

4.2 Pharmacodynamics

Amoxicillin is a broad-spectrum antibiotic of the amino-penicillin family with close structural relationship to ampicillin.
Amoxicillin exerts its bactericidal, time-dependent effect by inhibiting the biochemical process of bacterial wall synthesis, through a selective and irreversible blockade of several enzymes, in particular transpeptidases, endopeptidases and carboxypeptidases. In susceptible bacteria, impairment of cell wall synthesis, particularly during multiplication, leads to lysis of the bacteria.

Amoxicillin is active against the following microorganisms which are involved in respiratory diseases in cattle: *Mannheimia haemolytica* and *Pasteurella multocida*. Amoxicillin is also active against *Pasteurella multocida* that is involved in respiratory diseases in pigs.
Bacteria which normally present resistance to amoxicillin are Staphylococcus species producing penicillinase, Enterobacteria such as *Klebsiella* spp, *Enterobacter* spp, *Proteus* spp and *E. coli*.

There are three main mechanisms of resistance to beta-lactams antibiotics: beta-lactamase production, production of penicillin binding proteins (PBP) and decreased penetration of the outer membrane.

Bacterial resistance towards amoxicillin is primarily mediated through ß-lactamases which inactivate the antimicrobial by hydrolysis of the ß-lactam ring.
These beta-lactamases are extracellular in Gram-positive bacteria (*Staphylococcus aureus*) whereas they are located in the periplasmic space in Gram-negative bacteria.
Gram-positive bacteria can produce beta-lactamases in large quantities. These enzymes are codified in plasmids, which can be transferred to other bacteria.
Acquired resistances are frequent for Gram-negative bacteria such as *E. coli* which produce different types of β-lactamases that remain in the periplasmic space.
Complete cross resistance exists between amoxicillin and other penicillins, in particular other aminopenicillins.
The use of extended spectrum beta-lactam drugs (e.g. aminopenicillins) might lead to the selection of multi-resistant bacterial phenotypes (e.g. those producing extended spectrum beta-lactamases (ESBLs)).

4.3 Pharmacokinetics

In cattle Cmax (4.04µg/ml) is reached 2.04 hours after intramuscular administration. In pigs Cmax (6.49µg/ml) is reached 2.17 hours after intramuscular administration.

Amoxicillin is mainly distributed to the extra-cellular compartment. Its distribution into tissues is facilitated by its low degree of plasma protein binding (17%). Concentrations in pulmonary, pleural and bronchial tissues are similar to plasma concentrations. Amoxicillin diffuses into pleural and synovial fluid and into lymphatic tissue.
Amoxicillin is biotransformed in the liver by hydrolysis of the ß-lactam ring leading to inactive penicilloic acid (20%).
Amoxicillin is mainly excreted in active form via the kidneys, and secondarily by the biliary route and through milk.

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 when stored in glass vials.

Shelf-life of the veterinary medicinal product as packaged for sale: 18 months when stored in HDPE vials.
Shelf-life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

Do not store above 25°C

5.4 Nature and composition of immediate packaging

100 ml Type II clear glass vial closed with a nitrile rubber stopper and an aluminium over seal. 100 ml and 250 ml high density polyethylene vial sealed with a nitrile rubber stopper and aluminium over seal.

Pack sizes:
- 100 ml vial in a cardboard box.
- 12 x 100 ml vials in a cardboard/polystyrene box.
- 250 ml vial
- 6 x 250 ml vials in a cardboard/polystyrene box.

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

Univet Ltd.

7. MARKETING AUTHORISATION NUMBER(S)

VPA10990/055/001

8. DATE OF FIRST AUTHORISATION

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

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).