1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Rhemox 500 mg/g powder for use in drinking water for pigs, chicken broilers, duck broilers and turkeys for meat production
Rhemox 500 mg/g powder for use in drinking water for pigs, chickens, ducks and turkeys
Rhemox 435.6 mg/g powder for use in drinking water for pigs, chicken broilers, duck broilers and turkeys for meat production

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:
Amoxicillin trihydrate 500 mg
(Equivalent to 435.6 mg Amoxicillin)

"Only for France:"
Amoxicillin (as trihydrate) 435.6 mg
(Equivalent to 500 mg of Amoxicillin trihydrate)

Excipient:
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for use in drinking water.
Fine and homogeneous white to cream white powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs
Chicken (broiler), duck (duck broiler) and turkey (turkey for meat production).

4.2 Indications for use, specifying the target species

Pigs: Treatment of infections caused by strains of *Streptococcus suis* susceptible to amoxicillin.

Chicken broilers, duck broilers and turkeys for meat production: Treatment of pasteurellosis and colibacillosis caused by strains of *Pasteurella* spp. and *Escherichia coli* susceptible to amoxicillin.

4.3 Contraindications

Do not use in cases of hypersensitivity to penicillins, to other beta-lactams or to any of the excipients.
Do not use orally in rabbits, guinea pigs, hamsters or other small herbivores, given that amoxicillin, as for all aminopenicillins, has deleterious effects on caecal bacteria.
Do not use in horse given that amoxicillin, as all aminopenicillins, has an important effect on caecal bacteria.
Do not use orally in animals with functional rumen.
Do not use in animals with renal disease, including anuria and oliguria.

4.4 Special warnings for each target species

The use of the product should be combined with good management practices, i.e. good hygiene, proper ventilation, no overstocking.
The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water, animals should be treated parenterally.

4.5 Special precautions for use

Special precautions for use in animals
Not effective against beta-lactamase producing organisms.
Use of the product should be based on susceptibility testing of the bacteria isolated from the animals. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
Official, national and regional 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 amoxicillin and may decrease the effectiveness of treatment with other penicillins, due to the potential for crossresistance.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Penicillins and cephalosporins may cause hypersensitivity reactions (allergy) following injection, inhalation, ingestion or contact with the skin. Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious. This product might be irritant to skin, eyes and mucous membranes.

Do not handle the product if you are allergic to penicillins and/or cephalosporins or if you have

been advised not to work with such preparations.

Handle the product with great care to avoid inhaling the dust and contact with the skin, eyes and mucous membranes, during preparation and administration of medicated water, taking special precautions.

Personal protective equipment consisting of either a disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143, gloves, overalls and approved goggles should be worn when handling the veterinary medicinal product or medicated water.

Do not smoke, eat or drink while handling the product.
Wash hands after use.
In case of contact with the skin, eyes and mucous membranes, rinse with plenty of clean water.

If symptoms appear following exposure, such as a skin rash, seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases the following adverse reactions may appear:
Hypersensitivity reactions, which may occasionally be serious, may occur, the severity varying from skin rash to anaphylactic shock.
Gastrointestinal symptoms (vomiting, diarrhoea).
Secondary infections from non-sensitive microorganisms after prolonged use.

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

Laboratory studies in rats and mice have not produced any evidence of teratogenic, foetotoxic, maternotoxic effects.
The safety of the veterinary medicinal product has not been established during pregnancy or lactation in sows. Use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use simultaneously with neomycin since it blocks the absorption of oral penicillins.
Do not use together with bacteriostatic antibiotics, such as tetracyclines, macrolides, sulphonamides, as they can antagonise the bactericidal effect of penicillins.

4.9 Amounts to be administered and administration route

For administration in drinking water. Clear and colourless liquid when in solution.
Medicated drinking water should be refreshed or replaced every 24 hours.
The uptake of medicated water depends on the clinical condition of the animals, the environment, the age and the kind of feed provided. In order to obtain the correct dosage, the concentration of active substance has to be adjusted accordingly.

Dosage and treatment regimen

Pigs: 20 mg of amoxicillin trihydrate – equivalent to 17.4 mg of amoxicillin/kg of body weight every 24 hours (corresponding to 40 mg product/kg bodyweight/day) for 4 days.
Broilers: 15 mg of amoxicillin trihydrate – equivalent to 13.1 mg of amoxicillin/kg of body weight every 24 hours (corresponding to 30 mg product/kg bodyweight/day) for 5 days.
Duck broilers: 20 mg of amoxicillin trihydrate – equivalent to 17.4 mg of amoxicillin/kg of body weight every 24 hours (corresponding to 40 mg product/kg bodyweight/day) for 3 days.
Turkeys for meat production: 15 to 20 mg of amoxicillin trihydrate – equivalent to 13.1 to 17.4 mg of amoxicillin/kg of body weight every 24 hours (corresponding to 30-40 mg product/kg bodyweight/day) for 5 days.

Use the following formula in order to calculate the quantity of the product (mg) that should be incorporated in the drinking water tank:

$$\frac{\text{Dose (mg product per kg body weight per day)} \times \text{mean body weight (kg) of animals to be treated}}{\text{mean daily water consumption (litre) per animal per day}} = \text{___ mg product per litre drinking water}$$

The product must first be diluted in a small quantity of water in order to obtain a stock solution which is either further diluted in the drinking water tank or introduced via a water proportioner pump. When using a proportioner, adjust the pump between 2 to 5% and adapt the volume of preparation accordingly. The maximum solubility of the product is 20 g/l.

The use of suitably calibrated weighing equipment for the administration of the calculated amount of the product is recommended.
To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.

Prepare the solution with fresh tap water immediately before use.
Water uptake should be monitored at frequent intervals during medication.
In order to ensure consumption of the medicated water, animals should not have access to other water supplies whilst being treated.
After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

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

No other adverse reactions are known than those mentioned in section 4.6.
In case of overdose, the treatment should be symptomatic. No specific antidote is available.

4.11 Withdrawal period

Meat and offal: Pigs: 6 days.
Chickens: 1 day.
Turkeys: 5 days.
Ducks: 9 days.
Not authorised for use in birds producing eggs for human consumption and within 4 weeks before onset of the laying period.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Beta-Lactam Antibacterials, Penicillins with extended spectrum
ATCvet code: QJ01CA04

5.1 Pharmacodynamic properties

Amoxicillin is a broad spectrum β-lactam antibiotic belonging to the aminopenicillins group. It has bactericidal activity and acts against Gram-positive and Gram-negative microorganisms.

Mechanism of action
The antibacterial mechanism of action of amoxicillin consists of the inhibition of the biochemical processes of bacterial cell wall synthesis by selectively and irreversible blocking different enzymes involved in such processes, largely transpeptidase, endopeptidase and carboxypeptidase. The inadequate synthesis of the bacterial wall in susceptible species produces an osmotic imbalance which particularly affects growing bacteria (when bacterial wall synthesis processes are especially important), finally leading to lysis of the bacterial cell.

Spectrum of action
The species considered to be sensitive to amoxicillin include:
- Gram-positive bacteria.

Streptococci (*Streptococcus suis*)

- Gram-negative bacteria:
Pasteurella spp.
Escherichia coli

However, the bacteria which generally present resistance to amoxicillin are:
- Penicillinase-producing staphylococci.
- Some enterobacteria such as *Klebsiella spp., Enterobacter spp., Proteus spp.* and other gram-negative bacteria such as *Pseudomonas aeruginosa*.

The principal mechanism of bacterial resistance to amoxicillin is the production of β-lactamases, enzymes which inactivate the antibacterial product by hydrolysis of the β-lactam ring, thus obtaining penicillanic acid, a stable but inactive compound. Bacterial β-lactamases can be acquired via plasmids or can be constitutive (chromosomal).

These β-lactamases are exocellular in Gram-positive bacteria (*Staphylococcus aureus*) and found in the periplasmic space in Gram-negative bacteria.

Gram-positive bacteria are capable of producing and secreting large quantities of β-lactamases. These enzymes are encoded in plasmids which can be transferred by phages to other bacteria.

Gram-negative bacteria such as *E. coli* produce different types of β-lactamases which remain in the periplasmic space. They are encoded in both the chromosome and the plasmids.

The mechanism of resistance to penicillin by *S. suis* involves modifications in Penicillin-Binding Proteins (PBPs) in the form of overproduction and/ or a decreased affinity for penicillin. Penicillin resistance in *S. suis* is chromosomally encoded.

Antimicrobial resistance in *P. multocida* has been related to small, nonconjugative plasmids encoding beta-lactamases conferring resistance to ampicillin.

There is complete cross-resistance between amoxicillin and other penicillins, in particular, other aminopenicillins (ampicillin).

5.2 Pharmacokinetic particulars

General

Absorption of oral amoxicillin is independent from food intake and peak plasma concentrations are reached rapidly in most animal species, from 1 to 2 hours after the product's administration.

Amoxicillin binds sparingly to plasma proteins and rapidly spreads to the body fluids and tissues. Amoxicillin is widely distributed in the extracellular compartment. Its distribution to the tissues is facilitated by its low binding rate to plasma proteins.

The metabolism of amoxicillin is limited to hydrolysis of the β-lactam ring, leading to the release of inactive penicillanic acid (20%). Biotransformation takes place in the liver.

Most amoxicillin is eliminated through the kidneys in active form. It is also excreted in small quantities in milk and bile.

CHICKEN BROILERS

Oral bioavailability is about 67%. Maximum plasma concentration is reached in around one

hour. It is well and quickly distributed in the organism, with low binding to plasma proteins (17-20%).

PIGS:
After the administration of the product at the recommended dose in drinking water, plasma concentrations ranged from 0.53 μg/ml (C_{max}) to 0.27 μg/ml (C_{min}). Steady state was reached 10 hours after the first administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hexametaphosphate
Sodium dihydrogen phosphate anhydrous
Sodium carbonate
Silica, colloidal anhydrous

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.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dilution or reconstitution according to directions: 16 hours.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5. Nature and composition of immediate packaging

Bags of a complex film comprising an outer layer of polyester, an intermediate layer of aluminium and an inner layer of transparent polyethylene.

Package sizes:
Bag of 400 g
Bag of 1 kg

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Industrial Veterinaria, S.A.
Esmeralda, 19
08950 Esplugues de Llobregat
(Barcelona) Spain

8. MARKETING AUTHORISATION NUMBER

VPA10509/006/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/10/2015

10. DATE OF REVISION OF THE TEXT

12/04/2023

PROHIBITION OF SALE, SUPPLY AND/OR USE
Veterinary medicinal product subject to prescription
Administration by a veterinary surgeon or under their direct responsibility