

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

(Italy)

APSASOL AMOXICILLIN TRIHYDRATE 500 mg/g

Powder for use in drinking water for pigs, chickens, ducks and turkeys

(Bulgaria, Croatia, Cyprus, Greece, Hungary, Portugal, Poland, Romania)

APSASOL AMOXICILLIN 500 mg/g

Powder for use in drinking water for pigs, chickens, ducks and turkeys

(Spain)

APSASOL AMOXICILINA 500 mg/g

Powder for use in drinking water for pigs, chickens, ducks and turkeys

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:

Amoxicillin trihydrate 500 mg

(Equivalent to 435.6 mg amoxicillin)

Excipient:

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for use in drinking water.

Almost white fine powder.

4. CLINICAL PARTICULARS

4.1. Target species

Pig, chicken (broiler), duck (broiler) and turkey (for meat production).

4.2. Indications for use, specifying the target species

Chicken (broiler), duck (broiler) and turkey (for meat production): Treatment of pasteurellosis and colibacillosis caused by strains of *Pasteurella* spp. and *Escherichia coli* susceptible - to amoxicillin

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

4.3. Contraindications

Do not use in cases of hypersensitivity to penicillins or other B-lactam antibiotics or to any of the excipients.

Do not use in rabbits, guinea pigs hamsters, gerbils or any other small herbivore. Do not use in horses.

Do not use orally in animals with functional rumen.

4.4. Special warnings for each target species

The uptake of medicated water by animals can be altered as a consequence of illness. In case of insufficient water uptake, animals should be treated parenterally instead.

The use of the product should be combined with good management practices, i.e. good hygiene, proper ventilation, no overstocking

4.5. Special precautions for use

Special precautions for use in animals

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

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

Handle this product with great care to avoid exposure, taking all recommended precautions.

Take the necessary action to prevent the powder from spreading while the product is being added to drinking water.

Avoid inhalation of dust. Wear 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.

Avoid contact with the skin and eyes. Wear gloves, overalls and goggles during preparation and administration of medicated water or liquid feed. In case of contact, rinse with plenty of clean water.

Wash any exposed skin after handling the product or medicated water or feed. Wash hands after use.

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

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.

4.6. Adverse reactions (frequency and seriousness)

In very rare cases the following adverse reactions may appear:

- Hypersensitivity reactions, varying the severity from skin rash to anaphylactic shock.
- Gastrointestinal symptoms(vomiting, diarrhoea).

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 accordingly to the benefit/risk assessment by the responsible veterinarian.

Do not use in birds in lay and within 4 weeks before the start of the laying period.

See section 4.11.

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 antibiotics which inhibit bacterial protein synthesis as they can antagonise the bactericidal effect of penicillins.

Do not administer together with bacteriostatic antibiotics.

4.9. Amounts to be administered and administration route

In drinking water use.

Dosage and treatment regimen

-Pigs: 20 mg of amoxicillin trihydrate/kg of bodyweight every 24 hours (corresponding to 40 mg product/kg bodyweight/day) for 4 days.

-Chicken (broiler): 15 mg of amoxicillin trihydrate/kg of bodyweight every 24 hours (corresponding to 30 mg product/kg bodyweight/day) for 5 days.

-Duck (broiler): 20 mg of amoxicillin trihydrate/kg of bodyweight every 24 hours (corresponding to 40 mg product/kg bodyweight/day) for 3 days.

-Turkey (for meat production): 15 to 20 mg of amoxicillin trihydrate/kg of bodyweight every 24 hours (corresponding to 30-40 mg product/kg bodyweight/day) for 5 days.

The uptake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of amoxicillin has to be adjusted taking into account the daily water consumption.

Based on the dose to be used, and the number and weight of the animals to be treated, the exact daily amount of product can be calculated using the following formula:

$$\text{g of product/ litre of drinking water/day} = \frac{\text{Mean bodyweight (kg) of animals x dose (mg amoxicilin trihydrate/kg bw/day)}}{\text{Mean daily water consumption (litres) x 500}}$$

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.

No other source of drinking water should be available during the medication period. Medicated drinking water should be refreshed every 24 hours.

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,

The required amount of product should be weighed as accurately as possible using suitably calibrated weighing equipment.

4.10. Overdose (symptoms, emergency procedures, antidotes)

Not described. Amoxicillin has a wide margin of safety.

4.11. Withdrawal period(s)

Meat and offal:

Pigs: 6 days

Chicken (broiler): 1 day

Duck (broiler): 9 days

Turkey (for meat production): 5 days

Eggs: Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic Group: Beta-lactam antibacterials, Penicillins with extended spectrum
ATC vet code: QJ01CA04

Pharmacodynamic properties

Amoxicillin is a broad spectrum betalactamic antibiotic belonging to the aminopenicillins group with bactericidal activity.

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 irreversibly 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:
 - *Streptococcus suis*
- Gram-negative:
 - *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 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 produce different types of β -lactamases, which remain in the periplasmic space and which are codified in the chromosome or in the plasmid.

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

Critical concentrations (breakpoints) of sensitivity (S) and resistance (R) in $\mu\text{g/ml}$ (Source: CLSI 2008):

Streptococcus spp ≤ 0.25 (S); ≥ 8 (R)

5.1. Pharmacokinetic properties

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 Broiler:

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 (Cmax) to 0.27 µg/ml (Cmin). Steady state was reached 10 hours after the first administration.”

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid

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: 1 month

Shelf-life after reconstitution according to directions: 24 hours

6.4. Special precautions for storage

Store below 25 °C.

Store in the original container.

6.5. Nature and composition of immediate packaging

Aluminium multi-layer bags with inner layer made of linear low density polyethylene and outer reinforcement polyethylene terephthalate layer. The bags are closed by heat sealing.

Package size:

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 product or waste materials

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

ANDRES PINTALUBA S.A.
Polígono Industrial Agro-Reus
C/ Prudenci Bertrana nº 5
43206 - REUS (Tarragona)
SPAIN

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

ANNEX III
LABELLING AND PACKAGE LEAFLET

COMBINED LABEL AND PACKAGE LEAFLET

1. Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different

Marketing authorisation holder and manufacturer responsible for batch release:

ANDRÉS PINTALUBA, S.A.

C/Prudenci Bertrana nº 5

Polígono Industrial Agro-Reus

43206-Reus

SPAIN

2. Name of the veterinary medicinal product

(Italy)

APSASOL AMOXICILLIN TRIHYDRATE 500 mg/g

Powder for use in drinking water for pigs, chickens, ducks and turkeys

Amoxicillin trihydrate

(Bulgaria, Croatia, Cyprus, Greece, Hungary, Portugal, Poland, Romania)

APSASOL AMOXICILLIN 500 mg/g

Powder for use in drinking water for pigs, chickens, ducks and turkeys

Amoxicillin trihydrate

(Spain)

APSASOL AMOXICILINA 500 mg/g

Powder for use in drinking water for pigs, chickens, ducks and turkeys

Amoxicillin trihydrate

3. Statement of the active substance(s) and other ingredients

Each g contains:

Active substance:

Amoxicillin trihydrate 500 mg

(Equivalent to 435.6 mg amoxicillin)

Excipient, q.s.

Almost white fine powder.

4. Pharmaceutical form

Powder for use in drinking water for pigs, chickens, ducks and turkeys

5. Package size

<Bag of 400 g> <Bag of 1 kg>

Not all pack sizes may be marketed.

6. Indications

Chicken (broiler), duck (broiler) and turkey(for meat production): Treatment of pasteurellosis and colibacillosis caused by strains of *Pasteurella* spp. and *Escherichia coli* susceptible to amoxicillin.
Pig: Treatment of infections caused by strains of *Streptococcus suis* susceptible to amoxicillin.

7. Contraindications

Do not use in cases of hypersensitivity to penicillins or other B-lactam antibiotics or to any of the excipients.

Do not use in rabbits, guinea pigs hamsters,gerbils or any other small herbivore. Do not use in horses. Do not use orally in animals with functional rumen.

8. Adverse reactions

In very rare cases the following adverse reactions may appear:

- Hypersensitivity reactions, varying the severity from skin rash to anaphylactic shock.
- Gastrointestinal symptoms (vomiting, diarrhoea).

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reactions during the course of one treatment)
- 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).

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

Alternatively you can report via your national reporting system.

9. Target species

Pig, chicken (broiler), duck (broiler) and turkey(broiler).

10. Dosage for each species, route(s) and method of administration

In drinking water use.

Dosage and treatment regimen

-Pigs: 20 mg of amoxicillin trihydrate/kg of bodyweight every 24 hours (corresponding to 40 mg product/kg bodyweight/day) for 4 days.

-Chicken (broiler): 15 mg of amoxicillin trihydrate/kg of bodyweight every 24 hours (corresponding to 30 mg product/kg bodyweight/day) for 5 days.

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To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing.

No other source of drinking water should be available during the medication period. Medicated drinking water should be refreshed every 24 hours.

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,

The required amount of product should be weighed as accurately as possible using suitably calibrated weighing equipment.

11. Advice on correct administration

Not applicable.

12. Withdrawal period(s)

Meat and offal:

Pigs: 6 days

Chicken (broiler): 1 day

Duck (broiler): 9 days

Turkey (for meat production) : 5 days

Egg: Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

13. Special storage precautions

Store below 25 °C.

Store in the original container.

14. Special warning(s)

Special warnings for each target species

The uptake of medicated water by animals can be altered as a consequence of illness. In case of insufficient water uptake, animals should be treated parenterally instead.

The use of the product should be combined with good management practices, i.e. good hygiene, proper ventilation, no overstocking

Special precautions for use in animals

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.

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.

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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. Allergic reactions to these substances may occasionally be serious.

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

Handle this product with great care to avoid exposure, taking all recommended precautions.

Take the necessary action to prevent the powder from spreading while the product is being added to drinking water.

Avoid inhalation of dust. Wear 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.

Avoid contact with the skin and eyes. Wear gloves, overalls and goggles during preparation and administration of medicated water or liquid feed. In case of contact, rinse with plenty of clean water.

Wash any exposed skin after handling the product or medicated water or feed. Wash hands after use.

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

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.

Pregnancy and lactation

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 accordingly to the benefit/risk assessment by the responsible veterinarian.

Lay

Do not use in birds in lay and within 4 weeks before the start of the laying period.

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 antibiotics which inhibit bacterial protein synthesis as they can antagonise the bactericidal effect of penicillins.

Do not administer together with bacteriostatic antibiotics.

Overdose (symptoms, emergency procedures, antidotes)

Not described. Amoxicillin has a wide margin of safety.

Incompatibilities

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

15. Special precautions for the disposal of unused product or waste materials, if any

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

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

16. Data on which the package leaflet was last approved

17. Other information

Package sizes:

Bag of 400 g

Bag of 1 kg

Not all pack sizes may be marketed.

18. 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

19. The words “Keep out of the sight and reach of children”
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Keep out of the sight and reach of children.

20. Expiry date

<EXP {month/year}>

Once opened, use by ...

Shelf-life after first opening the container: 1 month

Shelf-life after reconstitution according to directions: 24 hours

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

21. Marketing authorisation number(s)**22. Manufacturer's batch number**

Batch {number}