[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

APSASOL HIDOX 500 mg/g
Powder for use in drinking water for chickens, pigs and rabbits.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:
Doxycycline …….. 500 mg
(equivalent to 580 mg of doxycycline hyclate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for use in drinking water
Yellow powder without visible agglomerates neither impurities

4. CLINICAL PARTICULARS

4.1 Target species

Chickens (broilers), pigs (pigs for fattening) and rabbits.

4.2 Indications for use, specifying the target species

Chickens (broilers): Colibacillosis and Chronic Respiratory Disease caused by bacteria sensitive to doxycycline.

Pigs (pigs for fattening): Porcine Respiratory Disease Complex caused by *Pasteurella multocida* and *Mycoplasma hyopneumoniae* sensitive to doxycycline.

Rabbits: treatment and metaphylaxis of infections caused by *Pasteurella multocida* sensitive to doxycycline.
The presence of disease in the herd should be established before metaphylactic treatment.

4.3 Contraindications

Do not use in case of hypersensitivity to tetracyclines and/or to any of the excipients.
Do not use in animals with renal or hepatic disorders.

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 in pigs and rabbits, animals should be treated parenterally instead.

4.5 Special precautions for use

Special precautions for use in animals

Avoid administration in oxidised drinking equipment. The medicated water should be prepared immediately before its use.

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.

Due to variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased animals on farm are highly recommended.

A high resistance rate of *E. coli*, isolated from chickens, against tetracyclines has been documented. Therefore the product should be used for the treatment of infections caused by *E. coli* only after susceptibility testing has been carried out.

As the eradication of the target pathogens may not be achieved, medication should therefore be combined with good animal management practices, e.g. good hygiene, proper ventilation, no overstocking.

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 doxycycline and may decrease the effectiveness of treatment with other tetracyclines due to the potential for cross-resistance.

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

People with known hypersensitivity to tetracyclines should take special care when handling or administering the product or the medicated solution.

During the incorporation of the product into drinking water, avoid the inhalation of dust particles and take the appropriate measures to prevent its spread.

During the handling of the product, skin and eyes contact has to be avoided, to prevent the risk of sensitization and contact dermatitis.

Wear personal protective equipment consisting of overall, dust mask (conforming to European Standard EN149), gloves and safety glasses when handling the veterinary medicinal product.

In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.

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

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

4.6 Adverse reactions (frequency and seriousness)

No adverse reactions have been detected in the studies carried out with de product.
As for all tetracyclines, adverse reactions may occur, such as gastrointestinal disturbances and, with lower frequency, allergic reactions and photosensitisation.
In prolonged treatments digestive alterations may appear due to intestinal dysbiosis.

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

Do not use in breeding animals or in laying hens.

4.8 Interaction with other medicinal products and other forms of interaction

The absorption of doxycycline can be reduced in the presence of high amounts of Ca^{2+}, Fe^{3+}, Mg^{2+} or Al^{3+} in the diet.

Tetracyclines should not be administered with antacids, gels based on aluminum, preparations based on vitamins or minerals, since insoluble complexes are formed, which reduces the absorption of the antibiotic.

Do not use in conjunction with bactericidal antibiotics, such as penicillins or cephalosporins.

Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

To be administered orally via drinking water.

Chickens (broilers): 7.5 – 15 mg of doxycycline/kg bw/day (equivalent to 15 – 30 mg of product/kg bw/day), for 3 – 5 consecutive days.

Pigs (pigs for fattening): 10 mg of doxycycline/kg bw/day (equivalent to 20 mg of product/kg bw/day), for 5 consecutive days.

Rabbits: 60 mg of doxycycline/kg bw/day (equivalent to 120 mg of product/kg bw/day), for 5 consecutive days.

The uptake of medicated water is dependent on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted.

Based on the recommended dose, and the number and weight of the animals to be treated, the exact daily dose should be calculated according to the following formula:

$$\text{mg of product/ litre of drinking water/day} = \frac{\text{mg of product/kg bw/day x Mean bodyweight (kg) of animals x}}{\text{Mean daily water consumption per animal (litres)}}$$

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

Sufficient access to the system of water supply should be available for the animals to be treated to ensure adequate water consumption. During the treatment period animals should not have access to other water sources than the medicated water. Medicated drinking water should be freshly prepared every day. The medicated water must not be prepared or stored in a metal container. 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.

It is recommended to prepare a concentrated pre-solution and to dilute this further to therapeutic concentrations if required. The maximum solubility of the product in water is approximately 200 g/l at room temperature (approx. 20 °C). The maximum solubility can be considerably reduced at low temperature (the maximum solubility is 7.5 g/l at 5 °C).

4.10 Overdose (symptoms, emergency procedures, antidotes)

In pigs, no symptoms of intolerance to the product have been detected in studies conducted with 3 times the therapeutic dose neither after the administration of the veterinary medicinal product for 10 days.

In rabbits, no adverse effects were observed either at the therapeutic dose administered for three times the recommended durations or at three times the therapeutic dose administered during the recommended period.

4.11 Withdrawal periods

Pigs (pigs for fattening): Meat: 2 days

Chickens (broilers):
Meat: 7 days
Eggs: Not for use in birds producing or intended to produce eggs for human consumption.

Rabbits: Meat: 4 days

5. PHARMACOLOGICALPROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Tetracyclines.
ATCvet code: QJ01AA02.

5.1 Pharmacodynamic properties

Doxycycline is an antibacterial agent that acts by interfering with bacterial protein synthesis of susceptible species.

Doxycycline is a semisynthetic tetracycline derivative from oxytetracycline. It acts on the 30S ribosomal subunit of bacteria by reversible binding. This binding blocks the union between tRNA-aminoacyl (transfer RNA) and the complex of mRNA and ribosomes. This avoids the addition of new amino acids to the peptide chain, thus, it inhibits the protein synthesis.

It is active against *Escherichia coli*, *Mycoplasma* spp. and *Pasteurella multocida*.

There are at least two mechanisms of resistance to tetracyclines. The most important mechanism is due to decreased cellular accumulation of the drug. This is due to the establishment of either a pump elimination path or an alteration in the transport system that limits the uptake of tetracycline. The alteration in the transport system is produced by inducible proteins codified in plasmids and transposons. The other mechanism is evidenced by decreased ribosome affinity for the Tetracycline-Mg2+ complex owing to chromosomal mutations.

Cross resistance between tetracyclines has also been described.

Tetracyclines can give rise to a gradual development of bacterial resistances. Some strains of *Pseudomona aeruginosa*, *Proteus*, *Serratia*, *Klebsiella* and *Corynebacterium* seem to be resistant to tetracyclines, like some pathogenic strains of *E. coli*.

5.2 Pharmacokinetic particulars

When doxycycline is administered orally, the bioavailability reaches values greater than 70% in most species.

The food intake could modify the oral bioavailability of doxycycline. In a fasting state the bioavailability is 10-15 % higher than when the animal ingests food.

The doxycycline is widely distributed in the organisms due to its physico-chemical characteristics, because it is highly liposoluble. Doxycycline reaches well-perfused and peripheral tissues. Doxycycline is concentrated in the liver, kidneys, bones and gut. In this last case it is because doxycycline undergoes enterohepatic circulation. Doxycycline reaches higher concentrations in the lungs than in plasma. Therapeutic concentrations have been detected in aqueous humor, myocardium, reproductive tissues, brain and mammary gland. The protein binding ratio at therapeutic plasma concentrations is in the range of 90-92%

40 % of the drug is metabolized and widely excreted by faeces (intestinal and biliary route). The major part is excreted as inactive microbiologically conjugates.

In chickens, after oral administration, doxycycline is quickly absorbed, achieving maximum concentrations (Cmax) around 1.5 h. Bioavailability is 75%. Absorption is decreased in the presence of feed in the gastrointestinal tract, bioavailability is then around 60% and the time to achieve the maximum concentration peak is significantly prolonged, (Tmax) 3.3 h.

In pigs, after a single oral dose of 10 mg of doxycycline/kg, a maximum concentration (Cmax) of 2.9 µg/ml was obtained at about 4.7 h. Bioavailability was 24%.

In rabbits, after the administration of 60 mg of doxycycline/kg bw/day for 5 days, a maximum concentration (Cmax) of 432.49 ng/ml was obtained at about 16.80 h (tmax). Lung doxycycline levels were approximately two times higher than plasmatic concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate (E 386)
Tartaric acid
Sodium saccharin

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: 3 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

This veterinary medicinal product does not require any special storage conditions.
After first opening keep the bag tightly closed in order to protect from light.
Protect the medicated water from direct sunlight.

6.5 Nature and composition of immediate packaging

Aluminum multi-layer bags with inner layer made of linear low density polyethylene (LDPE) and outer reinforcement polyethylene terephthalate (PET) layer. The bags are closed by heat sealing.

Pack sizes:
Bag of 200 g
Bag of 300 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 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

ANDRÉS PINTALUBA S.A.
POLÍGONO INDUSTRIAL AGRO-REUS
C/ PRUDENCI BERTRANA Nº 5
43206 - REUS (TARRAGONA)
SPAIN

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Conditions of sale: Under veterinary prescription.
Conditions of use: Administration under control or supervision of a veterinary surgeon.

ANNEX III

LABELLING AND PACKAGE LEAFLET

COMBINED LABEL 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
ESPAÑA

2. Name of the veterinary medicinal product

APSASOL HIDOX 500 mg/g
Powder for use in drinking water for chickens, pigs and rabbits.
Doxycycline hyclate

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

Each gram contains:

Active substance:
Doxycycline …….. 500 mg
(equivalent to 580 mg of doxycycline hyclate)

Yellow powder without visible agglomerates neither impurities

4. Pharmaceutical form

Powder for use in drinking water.

5. Package size

200 g
300 g
1 kg

6. Indication(s)

Chickens (broilers): Colibacillosis and Chronic Respiratory Disease caused by bacteria sensitive to doxycycline.

Pigs (pigs for fattening): Porcine Respiratory Disease Complex caused by *Pasteurella multocida* and *Mycoplasma hyopneumoniae* sensitive to doxycycline.

Rabbits: treatment and metaphylaxis of infections caused by *Pasteurella multocida* sensitive to doxycycline.

The presence of disease in the herd should be established before metaphylactic treatment.

7. Contraindications

Do not use in case of hypersensitivity to tetracyclines and/or to any of the excipients.
Do not use in animals with renal or hepatic disorders.

8. Adverse reactions

No adverse reactions have been detected in the studies carried out with de product.
As for all tetracyclines, adverse reactions may occur, such as gastrointestinal disturbances and, with lower frequency, allergic reactions and photosensitisation
In prolonged treatments digestive alterations may appear due to intestinal dysbiosis.

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).

If you notice any side effects, even those not already listed 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

Chickens (broilers), pigs (pigs for fattening) and rabbits.

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

To be administered orally via drinking water.

Chickens (broilers): 7.5 – 15 mg of doxycycline/kg bw/day (equivalent to 15 – 30 mg of product/kg bw/day), for 3 – 5 consecutive days.

Pigs (pigs for fattening): 10 mg of doxycycline/kg bw/day (equivalent to 20 mg of product/kg bw/day), for 5 consecutive days.

Rabbits: 60 mg of doxycycline/kg bw/day (equivalent to 120 mg of product/kg bw/day), for 5 consecutive days.

11. Advice on correct administration

The uptake of medicated water is dependent on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted.

Based on the recommended dose, and the number and weight of the animals to be treated, the exact daily dose should be calculated according to the following formula:

$$\text{mg of product/ litre of drinking water/day} = \frac{\text{mg of product/kg bw/day} \times \text{Mean bodyweight (kg) of animals}}{\text{Mean daily water consumption per animal (litres)}}$$

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

Sufficient access to the system of water supply should be available for the animals to be treated to ensure adequate water consumption. During the treatment period animals should not have access to other water sources than the medicated water. Medicated drinking water should be freshly prepared every day. The medicated water must not be prepared or stored in a metal container. 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.

It is recommended to prepare a concentrated pre-solution and to dilute this further to therapeutic concentrations if required. The maximum solubility of the product in water is approximately 200 g/l at room temperature (approx. 20 °C). The maximum solubility can be considerably reduced at low temperature (the maximum solubility is 7.5 g/l at 5 °C).

12. Withdrawal period(s)

Pigs (pigs for fattening): Meat: 2 days

Poultry (chickens):
Meat: 7 days
Eggs: Not for use in birds producing or intended to produce eggs for human consumption.

Rabbits: Meat: 4 days

13. Special storage precautions

This veterinary medicinal product does not require any special storage conditions.
After first opening keep the bag tightly closed in order to protect from light.
Protect the medicated water from direct sunlight.

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 in pigs and rabbits, animals should be treated parenterally instead.

Special precautions for use in animals:

Avoid administration in oxidised drinking equipment. The medicated water should be prepared immediately before its use.

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.
Due to variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased animals on farm are highly recommended.

A high resistance rate of *E. coli*, isolated from chickens, against tetracyclines has been documented. Therefore the product should be used for the treatment of infections caused by *E. coli* only after susceptibility testing has been carried out.

As the eradication of the target pathogens may not be achieved, medication should therefore be combined with good animal management practices, e.g. good hygiene, proper ventilation, no overstocking.

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 leaflet may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with other tetracyclines due to the potential for cross-resistance.

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

People with known hypersensitivity to tetracyclines should take special care when handling or administering the product or the medicated solution.

During the incorporation of the product into drinking water, avoid the inhalation of dust particles and take the appropriate measures to prevent its spread.

During the handling of the product, skin and eyes contact has to be avoided, to prevent the risk of sensitization and contact dermatitis.

Wear personal protective equipment consisting of overall, dust mask (conforming to European Standard EN149), gloves and safety glasses when handling the veterinary medicinal product.

In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.

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

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

Pregnancy and lactation

Do not use in breeding animals.

Lay

Do not use in laying hens.

Interaction with other medicinal products and other forms of interaction:

The absorption of doxycycline can be reduced in the presence of high amounts of Ca^{2+}, Fe^{3+}, Mg^{2+} or Al^{3+} in the diet.

Tetracyclines should not be administered with antacids, gels based on aluminum, preparations based on vitamins or minerals, since insoluble complexes are formed, which reduces the absorption of the antibiotic.

Do not use in conjunction with bactericidal antibiotics, such as penicillins or cephalosporins.

Doxycycline increases the action of anticoagulants.

Overdose (symptoms, emergency procedures, antidotes):

In pigs, no symptoms of intolerance to the product have been detected in studies conducted with 3 times the therapeutic dose neither after the administration of the veterinary medicinal product for 10 days.

In rabbits, no adverse effects were observed either at the therapeutic dose administered for three times the recommended durations or at three times the therapeutic dose administered during the recommended period.

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 or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

16. Date on which the label was last approved

17. Other information

Package sizes:
Bag of 200 g
Bag of 300 g
Bag of 1 kg

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

Magyarország
TOLNAGRO Kft.
Rákóczi u. 142-146.
7100 Szekszárd
Tel.: +36 74 528 528
nyaraimiklos@tolnagro.hu

Ελλάδα
ELANCO HELLAS SACI
335, Messogion Avenue
152 31 Chalandri Athens
Τηλ: + 30 231 0 289118
vgiannakis@elanco.gr

Hrvatska
MOUNT-TRADE d.o.o.
Industrijska 13
Garešnica 43280
Tel: +385 (0)43 485 914
k.mislav@gmail.com

Polska
PRIMA Andrzej Tuszyński
ul. Stanisława Webera 4
PL – 41 800 Zabrze
Tel.: + (32) 271 39 73
a.tuszynski@wp.pl

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.
Administration under control or supervision of a veterinary surgeon.

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

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 immediate packaging: 1 month.

Shelf life after reconstitution according to directions: 24 hours.

21. Marketing authorisation number(s)

22. Manufacturer's batch number

Batch {number}