1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TYLOGRAN, 1000 mg/g, granules for use in drinking water/milk for cattle (calves), pigs, chickens and turkeys (AT, BE, BG, CZ, CY, DE, DK, EE, EL, FI, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SK)

TYLOGRAN, 100%, granules for use in drinking water/milk for cattle (calves), pigs, chickens and turkeys (FR)

TYLOGRAN, 909 mg/g, granules for use in drinking water/milk for cattle (calves), pigs, chickens and turkeys (HR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1.1 g contains:

Active substance:

1 g of tylosin (1000000 IU tylosin, equivalent to 1.1 g of tylosin tartrate)

Almost white to slightly yellow, granular powder.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (calves), pigs, chickens and turkeys.

3.2 Indications for use for each target species

Calves: treatment and metaphylaxis of
- pneumonia caused by *Mycoplasma* spp.

Pigs: treatment and metaphylaxis of
- enzootic pneumonia caused by *Mycoplasma hyopneumoniae* and *Mycoplasma hyorhinis*;
- Porcine Intestinal Adenomatose (PIA or Ileitis) associated with *Lawsonia intracellularis*.

Turkeys: treatment and metaphylaxis of
- infectious sinusitis caused by *Mycoplasma gallisepticum*.

Chickens: treatment and metaphylaxis of
- chronic respiratory diseases (CRD) caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*;
- necrotic enteritis caused by *Clostridium perfringens*.

The presence of the disease in the group/flock must be established before the veterinary medicinal product is used.

3.3 Contraindications

Do not use in cases of hypersensitivity to tylosin or other macrolides.
Do not use in animals with hepatic disorders.
Do not use in horses.

3.4 Special warnings

Severely sick animals that exhibit an altered eating and drinking behaviour should be medicated parenterally.
Do not use in cases of known resistance to tylosin or cross-resistance to other macrolides (MLS-resistance).

3.5 Special precautions for use

Special precautions for safe use in the target species:

Due to likely variability (time, geographical) in susceptibility of bacteria for tylosin, bacteriological sampling and susceptibility testing are recommended.
Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to tylosin and may therefore decrease the effectiveness of treatment with other macrolides due to cross resistance.
Official and local antimicrobial policies should be taken into account when this veterinary medicinal product is used.

Do not leave or dispose of water containing tylosin tartrate where it may be accessible to either animals not under treatment or wildlife.

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

Tylosin may induce irritation.
Macrolides, such as tylosin, may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eye. Hypersensitivity to tylosin may lead to cross reactions to other macrolides and vice versa. Allergic reactions to these substances may occasionally be serious and therefore direct contact should be avoided.
To avoid exposure during preparation of the medicated drinking water, personal protective equipment consisting of overalls, safety glasses, impervious gloves and 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 should be worn.
Wash hands after use.
In the event of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean, running water.
People with known hypersensitivity to tylosin or other macrolides should not handle the veterinary medicinal product.
If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Pigs:

Undetermined frequency (cannot be estimated from the available data):	Diarrhoea[1] Pruritus[1] Erythema[1] Swollen vulva[1] Rectal oedema[1] Rectal prolapse[1]

[1] These reversible signs appeared 48-72 hours after the start of treatment.

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 or label for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay.

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

Laying birds:
Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Antagonism by substances of the lincosamide group occurs.
Do not use in animals vaccinated with tylosin-sensitive vaccines either at the same time or within 1 week previously.

3.9 Administration routes and dosage

In drinking water/milk use.

Calves: *Pneumonia:*
twice daily, 1.1 - 2.2 g of the veterinary medicinal product per 100 kg of body weight,
(20 - 40 mg corresponding to 20 000 – 40 000 IU of tylosin per kg of body weight per day),
for 7 - 14 days.

Pigs: *Enzootic pneumonia*:
2.2 g of the veterinary medicinal product per 100 kg of body weight,
(20 mg corresponding to 20 000 IU of tylosin per kg of body weight per day),
for 10 days.
PIA or Ileitis:
0.55 - 1.1 g of the veterinary medicinal product per 100 kg of body weight,
(5 - 10 mg corresponding to 5 000 – 10 000 IU of tylosin per kg of body weight per day),
for 7 days.

Chickens: *Chronic respiratory diseases (CRD):*
8.25 - 11 g of the veterinary medicinal product per 100 kg of body weight,
(75 - 100 mg corresponding to 75 000 – 100 000 IU of tylosin per kg of body weight per day), for 3 - 5 days.
Necrotic enteritis:
2.2 g of the veterinary medicinal product per 100 kg of body weight,
(20 mg corresponding to 20 000 IU of tylosin per kg of body weight per day), for 3 days.

Turkeys: *Infectious sinusitis:*
8.25 - 11 g of the veterinary medicinal product per 100 kg of body weight,
(75 - 100 mg corresponding to 75 000 – 100 000 IU of tylosin per kg of body weight per day), for 3 - 5 days.

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

For the preparation of the medicated water/milk the body weight of the animals to be treated and their actual daily water/milk consumption should be taken into account. Consumption may vary depending on factors like age, state of health, breed, husbandry system.

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

$$\frac{\text{…… mg veterinary medicinal product per kg body weight per day} \times \text{average body weight (kg) of the animals to be treated}}{\text{average daily water/milk intake (l/animal)}} = \text{...mg veterinary medicinal product per litre of drinking water/milk}$$

The maximum solubility is 1 kg of veterinary medicinal product per 10 litres of water.

Sufficient access to the system of water supply should be available for the animals to be treated to ensure adequate water consumption. No other source of drinking water should be available during the medication period.

Should there be no clear response to treatment within 3 days, the diagnosis should be reconsidered and, if necessary, the treatment approach changed accordingly.
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 which might support development of resistance.

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

There is no evidence of tylosin toxicity in chickens, turkeys, pigs or calves when administered orally at up to three times the recommended dose.

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

Calves (meat and offal):	12 days.
Pigs (meat and offal):	1 day.
Turkeys (meat and offal):	2 days.
Turkeys (eggs):	Zero days.
Chickens (meat and offal):	1 day.
Chickens (eggs):	Zero days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01FA90

4.2 Pharmacodynamics

Tylosin is a macrolide antibiotic isolated from *Streptomyces fradiae*.
The antimicrobial action consist of the inhibition of the protein synthesis in sensitive microorganisms.
The antimicrobial spectrum of tylosin includes Gram-positive bacteria and some Gram-negative bacteria like *Mycoplasma* spp..

Resistance to macrolides is usually plasmid-mediated but modification of ribosomes may occur through chromosomal mutation. Resistance can occur by:
i) decreased entry into bacteria (most common with the Gram-negative bacteria),
ii) synthesis of bacterial enzymes that hydrolyze the drug and,
iii) modification of the ribosome. This latter resistance type may also lead to cross-resistance with other antibiotics that preferentially bind to the bacterial ribosome.

4.3 Pharmacokinetics

Absorption: after oral administration, tylosin reaches maximal plasma concentrations between 1 and 3 hours. Only small/none amounts are found 24 hours after oral administration.
Distribution: after oral administration to pigs, tylosin is found in all tissues between 30 minutes and 2 hours, with the exception of brains and spinal cord. Compared to plasma levels clearly higher tissue concentrations have been observed.
Biotransformation and excretion: it is demonstrated that most of the drug is excreted in the faeces and consist of tylosin (factor A), relomycin (factor D) and dehydrodesmycosin.

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:
- Composite can: 3 years.
- Bucket: 3 years.
- Securitainer: 2 years.

Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after dissolution in drinking water: 24 hours.
Shelf life after dissolution in milk replacer: 3 hours.

5.3 Special precautions for storage

Store below 25ºC. Do not refrigerate or freeze. Protect from frost.
Store in the original container in order to protect from light.
Medicated drinking water should be protected from light.

5.4 Nature and composition of immediate packaging

- Composite can: hardboard can provided with an inner lining of aluminium-paper (polyethylene terephthalate coated) and a seamed tin-plate bottom, closed with a low density polyethylene lid. The can contains 550 g of veterinary medicinal product.
- Bucket: white polypropylene square container provided with a polypropylene lid.

The bucket contains 1 kg, 4 kg or 5 kg of veterinary medicinal product.
- Securitainer: white polypropylene cylindrical container provided with a low density polyethylene lid.

The securitainer contains 100 g, 550 g, 800 g or 1000 g of veterinary medicinal product.

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

Dopharma Research B.V.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

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).