[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

IVERTOTAL 10 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Ivermectin……10 mg

Excipients:
Benzyl alcohol (E1519)…….10 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, sheep and pigs.

4.2 Indications for use, specifying the target species

Cattle:

For the treatment of gastrointestinal nematodes, lungworms, eyeworms, warble flies, mites and lice (as shown below) of beef and non-lactating dairy cattle:

Gastrointestinal worms (adults and 4th stage larvae):
- *Ostertagia ostertagi*
- *Ostertagia lyrata*
- *Haemonchus placei*
- *Trichostrongylus colubriformis*
- *Cooperia oncophora* (adults)
- *Cooperia punctata* (adults)
- *Cooperia pectinata* (adults)
- *Bunostomum phlebotomum*
- *Oesophagostomum radiatum*

Lungworms (adult and 4th stage larvae):
- *Dictyocaulus viviparus*

Eyeworms (adult):
- *Thelazia spp*.

Warble flies (parasitic stages):
Hypoderma bovis
H. lineatum

Mites:
Psoroptes ovis
Sarcoptes scabiei var. bovis

Sucking lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

May also be used as an aid in the control of the mange mite *Chorioptes bovis* but complete elimination may not occur.

Treatment with the product at the recommended dose rate prevents re-infection with *Haemonchus placei*, *Cooperia oncophora*, *Cooperia pectinata* and *Trichostrongylus axei* for 7 days after treatment, *Ostertagia ostertagi* and *Oesophagostomum radiatum* for 14 days after treatment and *Dictyocaulus viviparus* for 21 days after treatment.

Sheep

For the treatment of psoroptic mange (sheep scab), gastrointestinal nematodes, lungworms and nasal bots of sheep:

Gastrointestinal roundworms (adults):
Ostertagia circumcincta
Haemonchus contortus
Trichostrongylus axei
T. colubriformis and T. vitrinus
Cooperia curticei
Nematodirus filicollis

Variable activity may be observed against *Cooperia curticei* and *Nematodirus filicollis*.

Lungworms:
Dictyocaulus filaria (adults)

Mange mites:
Psoroptes ovis

Nasal bot:
Oestrus ovis (all larval stages)

Pigs

For the treatment of gastro-intestinal nematodes, lungworms, lice and mange mites of pigs.

Gastro-intestinal worms (adult and fourth stage larvae):

Ascaris suum
Hyostrongylus rubidus
Oesophagostomum spp.
Strongyloides ransomi (adults).

Lungworms:

Metastrongylus spp. (adults)

Lice:

Haematopinus suis

Mange Mites:

Sarcoptes scabiei var. suis

4.3 Contraindications

Do not use in lactating dairy cows and sheep producing milk for human consumption.
Do not use in non-lactating dairy cows, including pregnant dairy heifers or non-lactating dairy sheep within 60 days of calving/lambing.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not administer by the intravenous or intramuscular route.

4.4 Special warnings for each target species

Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:

- Too frequent and repeated use of anthelmintics from the same class, over an extended period of time

- Underdosing, which may be due to underestimation of bodyweight, misadministration of the product, or lack of calibration of the dosing device (if any)

Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Test). Where the results of the test(s) strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used.

Treatment of psoroptic mange (sheep scab) with one injection is not recommended because, although clinical improvement may be seen, elimination of all mites may not occur.
Sheep scab (*Psoroptes ovis*) is an extremely contagious external parasite of sheep. Following treatment of infected sheep great care must be taken to avoid re-infestation as mites may be viable for up to 15 days off the sheep. It is important to ensure all sheep which have been in contact with infected sheep are treated. Contact between treated infected and non-treated, non-infected flocks must be avoided until at least 7 days after the last treatment.

Resistance to ivermectin has been reported in *Ostertagia circumcinta in* lambs and in *Ostertagia ostertagi, Cooperia oncophora* in cattle. Therefore, the use of this product

should be based on local (regional, farm) epidemiological information about susceptibility of these helminth species and recommendations on how to limit further selection for resistance to anthelmintics

4.5 Special precautions for use

Special precautions for use in animals

Avermectins may not be well tolerated in all non-target species. Cases of intolerance with fatal results are reported in dogs – especially Collies, Old English Sheepdogs and related breeds and crosses, and also in turtles/tortoises.

Do not combine treatment with vaccination against lungworms. If vaccinated animals are to be treated, treatment should not be carried out within a period of 28 days before or after vaccination.

The shedding of nematode eggs can continue for some time after treatment.

In Cattle: To avoid secondary reactions due to the death of *Hypoderma* larvae in the oesophagus or in the spine, it is recommended to administer the product at the end of warble fly activity and before the larvae reach their resting sites.

Swab septum before removing each dose.

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

Do not smoke, eat or drink while handling the product.
Wash hands after use.
Take care to avoid self injection: the product may cause local irritation and/or pain at the site of injection.

Other precautions:
Ivermectin is very toxic to aquatic organisms and to coprophilous insects. Treated animals should not have direct access to ponds, streams or ditches for 14 days after treatment. Long-term effects on coprophilous insects caused by continuous or repeated use cannot be excluded. Therefore, repeated treatments on a pasture in the same season should only be administered on the advice of a veterinarian.

4.6 Adverse reactions (frequency and seriousness)

Transitory discomfort has been observed in some animals immediately following subcutaneous administration. In cattle this may include jumping and rolling, but behaviour returns to normal after 15 minutes.
Soft tissue swelling and thickening of the skin at the injection site has been observed in treated animals. Typically these reactions are transient and disappear within one to four weeks.

4.7 Use during pregnancy, lactation or lay

The product can be administered during pregnancy in cows, ewes and sows (for information on use in lactating animals, see sections 4.3 and 4.11).
The fertility of males is not affected by administration of the product.

4.8 Interaction with other medicinal products and other forms of interaction

Do not combine ivermectin treatment with vaccination against lungworms. If vaccinated animals are to be treated, treatment should not be carried out within a period of 28 days before or after vaccination (see section 4.5).

4.9 Amounts to be administered and administration route

For single administration only (except for the treatment of *Psoroptes ovis* infections in sheep)

To ensure administration of a correct dose, bodyweight should be determined as accurately as possible. Accuracy of the dosing device should be checked.

If animals are to be treated collectively rather than individually, they should be grouped according to their bodyweight and dosed accordingly, in order to avoid under- or over-dosing.

Cattle

Dosage:
0.2 mg ivermectin per kg bodyweight, is equivalent to 1.0 ml/50 kg bodyweight

Administration:
Inject subcutaneously in front of, or behind, the shoulder using aseptic technique. A sterile 1.4 x 15 mm needle is recommended.

Sheep

Dosage:
0.2 mg ivermectin per kg bodyweight, is equivalent to 0.5 ml/25 kg bodyweight

Administration:
For the treatment of gastrointestinal roundworms, lungworms and nasal bots inject once subcutaneously in the neck, using aseptic precautions; a sterile 1.4 x 15 mm needle is recommended. For the treatment of *Psoroptes ovis* (sheep scab), two injections with a seven day interval are required to treat clinical signs of scab and to eliminate living mites.

For young lambs weighing less than 20.0 kg give 0.1 ml per 5 kg. In these lambs the use of a syringe which can deliver as little as 0.1 ml is recommended.

Pigs

Dosage:

0.3 mg ivermectin per kg bodyweight, is equivalent to 1.5 ml/50 kg bodyweight

Administration:
The recommended route of administration is by subcutaneous injection into the neck using aseptic technique and a sterile 1.4 x 15 mm needle.

For piglets weighing less than 16 kg give 0.1 ml per 3 kg. In these piglets the use of a syringe which can deliver as little as 0.1 ml is recommended.

When using the 250 or 500 ml pack sizes, use only automatic syringe equipment. To refill the syringe, use of a draw-off needle is recommended to avoid excessive broaching of the stopper. The stopper may be safely punctured up to 30 times.

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

Clinical symptoms of ivermectin toxicity include ataxia and depression. No antidote has been identified. In case of overdose, symptomatic treatment should be given. No signs of toxicity were observed in animals treated at up to 3 times the recommended dose rate.

4.11 Withdrawal period(s)

Cattle:

Meat and offal: 49 days.

Do not use in lactating cows producing milk for human consumption. Do not use in non-lactating dairy cows, including pregnant dairy heifers, within 60 days of calving.

Sheep:

Meat and offal: 42 days.

Do not use in lactating ewes producing milk for human consumption. Do not use in sheep which are intended to produce milk for human consumption within 60 days of lambing.

Pigs:

Meat and offal: 28 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endectocide
ATC vet code: QP54AA01

5.1 Pharmacodynamic properties

Ivermectin is a mixture of two partially modified compounds of abamectin that belongs to the family of avermectins, which are a class of macrocyclic lactones from the group of endectocides. Abamectin is a mixture of two fermentation products of the soil organism *Streptomyces avermitilis*.
Ivermectin is a macrocyclic lactone derivative and acts by inhibiting nerve impulses. It binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the relevant parasites. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels. The macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

5.2 Pharmacokinetic particulars

In each of the target species the pharmacokinetic profile following subcutaneous administration was characterised as follows (pharmacokinetic parameters presented as mean values):

Following administration to cattle, Cmax was 51ng/ml, with a Tmax of 43 h, $T_{1/2}$ of 129 h and an AUC of 7398 ng.h/ml.

Following two subsequent administrations seven days apart to sheep, Cmax was 14 ng/ml, with a Tmax of 202 h, $T_{1/2}$ of 380 h and an AUC of 4686 ng.h/ml.

Following administration to pigs, Cmax was 6.35ng/ml, with a Tmax of 106 h, $T_{1/2}$ of 219 h and an AUC of 1260 ng.h/ml.

Only about 2% of the drug is excreted in urine, faecal excretion being the major route of elimination. Tissue residues of radioactivity following subcutaneous administration of tritium-labelled ivermectin are highest in liver and fat; lowest levels are found in brain.

In cattle, the residual antiparasitic effect of ivermectin is due to its persistence which in turn is due in part to its long intrinsic half life and its relatively high protein binding (90%).

5.3. Environmental properties

Ivermectin has adverse effects on the environment. After treatment, toxic levels of ivermectin are excreted for weeks. Faeces excreted on the grass by treated animals reduces the abundance of coprophagous organisms which could affect the degradation of feces.
Ivermectin is very toxic to aquatic organisms and the coprophagous fauna and can accumulate in soil and sediment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E1519)
Ethanol (96 per cent)
Water for injections
Propylene glycol

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: 28 days

6.4. Special precautions for storage

Store below 30 °C.

6.5 Nature and composition of immediate packaging

250 ml and 500 ml sterile and translucent polypropylene cylindrical vials appropriate for parenteral solutions (European Pharmacopoeia), with grey butyl rubber cap, grey aluminum capsule and Flip-Off seal.

Pack sizes:

- Box with 1 vial of 250 ml
- Box with 1 vial of 500 ml
- Box with 10 vials of 250 ml
- Box with 10 vials of 500 ml

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

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Treated animals should not have access to surface waters for 14 days after treatment to avoid effects on aquatic organisms. Do not contaminate surface waters or ditches with product or used container. Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SP VETERINARIA, S.A.
Ctra. Reus – Vinyols Km 4,1 43330
Riudoms (Tarragona)
SPAIN

8. MARKETING AUTHORISATION NUMBER(S)

ES: 2937 ESP

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12/12/13
Date of last renewal:

10 DATE OF REVISION OF THE TEXT

12/12/13

PROHIBITION OF SALE, SUPPLY AND/OR USE