SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT
IVERTIN 10 mg/ml Solution for Injection for Cattle and Pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml contains:
Active substance:
Ivermectin.....10.0 mg

Excipients
Propylene glycol (E 1520) .....613.6 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Solution for injection
Clear, colourless solution.

4. CLINICAL PARTICULARS:

4.1 Target species
Cattle and pigs

4.2 Indications for use, specifying target species
Treatment of infections with the following parasites in beef and non-lactating dairy cattle or pigs:

Cattle:

Round gastrointestinal worms
Ostertagia lyrata (Adult, L4)
Haemonchus placei (Adult, L3, L4)
Trichostrongylus axei (Adult,L4)
Trichostrongylus colubriformis (Adult,L4)
Cooperia oncophora (Adult,L4)
Cooperia punctata (Adult,L4)
Cooperia pectinata (Adult, L5)
Oesophagostomum radiatum (Adult,L3, L4)
Nematodirus helvetianus (Adult)
Nematodirus spathiger (Adult)
Bunostomum phlebotomum (Adult, L3, L4)

Adult and inhibited forms of *Ostertagia ostertagi*.

Lungworms
Dictyocaulus viviparus (Adult, L4)

Warble flies (all parasitic stages)
Hypoderma bovis, *H lineatum*

Sucking lice
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange and other acariosis produced by:

Acari
Psoroptes ovis (syn. *P. communis* var. B*ovis*)
*Sarcoptes scabiei (*var. *bovis*)

The product injection helps in the control of the mange mite *Chorioptes bovis* but complete elimination may not occur.

Pigs

Gastrointestinal Roundworms
Ascaris suum
Hyostrongylus rubidus
Oesophagostomum spp.
Strongyloides ransom (adults)

Lungworms
Metastrongylus spp. (adults)

Lice
Haematopinus suis

Mange Mites
Sarcoptes scabiei var. *suis*

4.3 Contraindications
Do not use in cats and dogs as severe adverse reactions may occur.
Do not use in cases of known hypersensitivity to the active substance or to any of the excipients
Do not administer by intramuscular or intravenous route.
See section 4.5

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 body weight, 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.

Resistance to ivermectin has been reported in *Cooperia spp.* and in *Ostertagia ostertagi* in cattle. Resistance has also been reported in *Haemonchus contortus* in cattle outside the EU. Therefore, the use of this product should be based on local (regional, farm) epidemiological information about susceptibility of this 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

Contact with treated and non-treated infected herds must be avoided at least seven days after the treatment.

The product is effective in all hypodermosis stages, however, it is very important to treat on time (at the end of warble fly season). The elimination of *Hypoderma* larvae may cause negative reactions on the host, when they are found in vital areas. Killing *Hypoderma lineatum,* if found in perioesophageal tissue, may cause salivation and tympanism. Killing *Hypoderma bovis*, if found in the vertebral canal, may cause unsteadiness or paralysis. Bovine should be treated before or after those stages of warble flies.

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

In addition, care should be taken to avoid ingestion of spilled product or access to used containers by these other species.

Since ivermectin is highly bound to plasma proteins, special care should be taken in cases of sick animals or in nutritional conditions associated with low plasma protein levels.

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

The product may cause local irritation and/or pain at the site of injection. Direct contact of the product with the skin should be avoided. Take care to avoid self-administration.

Do not smoke or eat while handling the product.

Wash hands after use. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Other precautions

The product is very toxic to aquatic organisms and dung insects. Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment. Long term effects on dung insects caused by continuous or repeated use cannot be excluded. Therefore repeated treatments on a pasture within a season should only be given on the advice of a veterinarian.

4.6 Adverse reactions (frequency and seriousness)

Transient swelling at the injection site is commonly observed following treatment. These reactions can last up to 2 days and disappear without treatment.

Transient pain has been observed in very rare cases.

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 in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

In pigs, the product can be used in breeding sows and boars.

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

4.9 Amounts to be administered and administration route

For single subcutaneous injection.

To ensure administration of a correct dose, body weight 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 overdosing.

Cattle
Ivermectin should be administered at a dose of 200 µg/kg bodyweight (equivalent to 1ml/50 kg bodyweight).
It should be injected subcutaneously in front of or behind shoulder using aseptic technique. The use of a needle 16 gauge x 15 to 20 mm long is suggested. Use sterile equipment.

Equivalent to:

Weight (kg)	Dose (ml)
Up to 50	1
51 – 100	2
101 – 150	3
151 – 200	4
201 – 250	5
251 – 300	6
301 – 350	7
351 – 400	8
401 – 450	9
451 – 500	10
501 – 550	11
551 - 600	12

Duration of the effect:

Ostertagia spp.: at least 7 days has been substantiated
Dictyocaulus viviparus: at least 14 days has been substantiated

Pigs
At the recommended dosage level of 300 µg ivermectin per kg of bodyweight, administer only subcutaneously in the neck in pigs.

Each ml contains 10 mg of ivermectin sufficient to treat 33 kg of bodyweight of pigs.

Use the following dosage table:

Weight (kg)	Dose (ml)
8	0.25
8 – 16	0.5
17 – 33	1.0

34 - 50	1.5
51 – 66	2.0
67 – 99	3.0
100 – 133	4.0
134 – 166	5.0
167 - 200	6.0

Over 200 kg bodyweight, give 1.0 ml per 33 kg bodyweight.

The injection may be given with any standard automatic or single-dose or hypodermic syringe. Use of 1.4 x 15 mm (17 gauge x 1/2 inch) needle is suggested.. Injection of wet or dirty animals is not recommended.
Vial stoppers must not be broached more than 20 times.
In young pigs, especially those weighing under 16kg for which less than 0.5ml of the product is indicated, dosing accuracy is important. The use of a syringe that can accurately deliver increments of 0.1ml is recommended. For piglets weighing less than 16kg give 0.1ml/3kg.

When treating pigs of less than 16kg seek veterinary advice regarding the use of 1ml disposable syringes graduated in increments of 0.1ml.

4.10 Overdose (symptoms, emergency procedures, antidotes)
A single dose of 4.0 mg of ivermectin/kg given subcutaneously (20x recommended dose rate) to bovines caused ataxia and depression.
A dose of 30 mg ivermectin per Kg (100 x the recommended dose of 0.3 mg per kg) injected subcutaneously to pigs caused lethargy, ataxia, bilateral mydriasis, intermittent tremors, labored breathing and lateral recumbency.
If overdose occurs, apply symptomatic treatment.

4. 11 Withdrawal period
Cattle: Meat and offal: 49 days.
Milk: Do not use in lactating dairy cows producing milk for human consumption.
Do not use in non-lactating dairy cows including pregnant heifers within 60 days of calving.
Pigs: Meat and offal 28 days

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Avermectins
ATCVet code: QP54AA01

5.1 Pharmacodynamic properties

Ivermectin is an internal broad-spectrum and external antiparasitic of the avermectin family, which is produced by the fermentation of *Streptomyces avermitilis.*
Ivermectin is a member of the macrocyclic lactones class of endectocides. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels, which occur in invertebrate nerves 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 parasite. Compounds of this class may also interact with other ligand-gated chloride channels such as those gated by 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-gate 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.

Resistances

The resistance mechanism to Ivermectin is not completely determined. Its appearance is associated to modifications in the channels of the chloride ion dependent on glutamate, increasing the number in the binding sites to glutamate and to the increased expression of a membrane P-glycoprotein, which possibly would avoid reaching active concentrations of the ivermectin in the resistant parasite. The resistance to Ivermectin has also been related to a reduction in the cuticle permeability of the nematodes resistant to this drug.

There is cross-resistance with other avermectins and with milbemycins.

5.2. Pharmacokinetic properties
After subcutaneous administration of the recommended dose of ivermectin to cattle (0,2 mg Ivermectin / kg), the following parameters were observed: C_{max} of 44 ng/ml (range: 25.6 – 72.5), t_{max} of 88 h, and AUC of 9702 ng·h/ml. It is also established that Ivermectin is highly bound to plasma proteins (80 %).
Due to its high lipophilic nature, ivermectin is extensively distributed. It tends to accumulate in fat tissue, which acts as a drug reservoir and the highest levels of ivermectin are found in liver and fat.

Ivermectin undergoes little metabolism; most of the dose is excreted unchanged. In cattle, only about 1-2 % is excreted in urine; the remainder is excreted in faeces, approximately 60% is excreted as unaltered drug. The remainder is excreted as metabolites. Non-polar metabolites are found in fat. Ivermectin is also excreted by the mammary gland.

In pigs, after subcutaneous administration of the recommended dose of the product to pig (0,3 mg Ivermectin / kg), a maximum plasmatic concentration of 10 – 20 ng/ml in approximately 2 days is reached.
It is mainly eliminated in faeces and urine. Maximum residues are found in liver and fat, as main product with minor polar metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Propylene glycol (E 1520)
Glycerol formal

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 of the veterinary medicinal product after first opening of the container: 28 days.

6.4 Special precautions for storage
Keep vials in the outer carton.

6.5 Nature and composition of immediate packaging
Polypropylene vials of 50 ml provided with grey rubber stoppers of bromobutyl type I and metallic aluminium capsules with blue FLIP-OFF ring.

Polypropylene vials of 100 ml provided with grey rubber stoppers of bromobutyl type I and metallic aluminium capsules with blue FLIP-OFF ring.

Polypropylene vials of 500 ml provided with grey rubber stoppers of bromobutyl type I and metallic aluminium capsules with blue FLIP-OFF ring..

Bottles of 50 ml, 100 ml, and 500 ml.
Clinical containers of 6, 10 and 12 units of 50 ml, 100 ml, and 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. Do not contaminate surface waters or ditches with the product or used containers.

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS CALIER, S.A.
C/ Barcelonès, 26 (Pla del Ramassà)
LES FRANQUESES DEL VALLÈS, (Barcelona)
SPAIN

8. MARKETING AUTHORISATION NUMBER (S)

Spain: 1474-ESP; Germany: 400781.00.00 ; Austria: Z.Nr.:8-00630 ;
Belgium: AMM: 8505 IE 1 F 12 ; The Netherlands :NL10223 ;
United Kingdom: Vm 20634/4001
Italy:

1 vial of 50 ml:	A.I.C. nº 103691010	10 vials of 50 ml:	A.I.C. nº 103691073
1 vial of 100 ml:	A.I.C. nº 103691022	10 vials of 100 ml:	A.I.C. nº 103691109
1 vial of 500 ml:	A.I.C. nº 103691059	10 vials of 500 ml:	A.I.C. nº 103691198
6 vials of 50 ml:	A.I.C. nº 103691061	12 vials of 50 ml :	A.I.C. nº 103691085
6 vials of 100 ml:	A.I.C. nº 103691097	12 vials of 100 ml:	A.I.C. nº 103691111
6 vials of 500 ml:	A.I.C. nº 103691186	12 vials of 500 ml:	A.I.C. nº 103691200

France:

1 vial of 50 ml: AMM nº 679021 0
6 vials of 50 ml: AMM 679022 7
10 vials of 50 ml: AMM 679023 3
12 vials of 50 ml: AMM 679025 6

1 vial of 100 ml: AMM 679026 2
6 vials of 100 ml: AMM 679027 9
10 vials of 100 ml : AMM 679028 5
12 vials of 100 ml : AMM 679029 1

1 vial of 500 ml : AMM 679039 7
6 vials of 500 ml : AMM 679040 5
10 vials of 500 ml : AMM 679041 1
12 vials of 500 ml : AMM 679042 8

9. DATE OF THE FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

28.10.2002 / 31.08.2009

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE
To be supplied only on veterinary prescription
Administration by a veterinary surgeon or under his/her direct responsibility