1. NAME OF THE VETERINARY MEDICINAL PRODUCT

EVOCTIN PLUS 10 mg/ml + 100 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
Ivermectin 10 mg
Clorsulon 100 mg

Excipients:

Qualitative composition of excipients and other constituents
Glycerol formal
Propylene glycol

Clear, colourless solution without any visible particles. .

3. CLINICAL INFORMATION

3.1 Target species

Cattle

3.2 Indications for use for each target species

For cattle with, or at risk from mixed infections/infestations by nematodes, ectoparasites and flukes. The veterinary medicinal product is only indicated when use against nematodes, ectoparasites and flukes is indicated at the same time.

Gastrointestinal roundworms:
Ostertagia ostertagi (adults, L3, L4, including the inhibited stage)
Ostertagia lyrata (adults and L4)
Haemonchus placei (adults, L3, L4, including the inhibited stage)
Mecistocirrus digitatus (adults)
Trichostrongylus axei (adults and L4)
Trichostrongylus colubriformis (adults and L4)
Cooperia spp. (adults, L3 and L4)
Cooperia oncophora (adults and L4)
Cooperia punctata (adults and L4)
Cooperia pectinata (adults and L4)
Oesophagostomum radiatum (adults, L3 and L4)
Bunostomum phlebotomum (adults, L3 and L4)
Nematodirus helvetianus (adults)
Nematodirus spathiger (adults)
Strongyloides papillosus (adults)
Toxocara vitulorum (adults, L3 and L4)
Trichuris spp. (adults)

Eye worms:
Thelazia spp. (adults)

Pulmonary roundworms:
Dictyocaulus viviparus (adults and L4)

Microfilariae:
Parafilaria bovicola (adult)

Warbles (all parasitic stage):
Hypoderma bovis,
Hypoderma lineatum
Dermatobia hominis

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Facultative causative agent of skin myases (parasitic stage):
Chrysomya bezziana

Mange Mites (scabies):
Psoroptes bovis
Sarcoptes scabiei var. bovis

Ticks:
Boophilus microplus (maximum effectiveness is achieved on the 4th-5th day after treatment)

Liver flukes:
Fasciola hepatica (adult and developmental stages)
Fasciola gigantica (adult)

Clorsulon in this veterinary medicinal product achieves 70% effectiveness against the immature form of *F. hepatica* (8-week developmental stage).

The veterinary medicinal product may also be used as an aid in the treatment of biting lice (*Damalinia bovis*) and mange mites from the psoroptide family (*Chorioptes bovis)* infestations although treatment may not eliminate them completely.

Persistent effect

In cattle, veterinary medicinal product administered at the recommended dosage controls reinfections with:

- *Dictyocaulus viviparus* larvae for 28 days after treatment
- *Ostertagia ostertagi and Oesophagostomum radiatum* for 21 days after treatment
- *Haemonchus placei, Cooperia punctata, Cooperia oncophora* and *Cooperia surnabada* for 14 days after treatment.

3.3 Contraindications

Do not use intramuscularly or intravenously.
Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use in other animal species. Fatal intolerances to ivermectin have been reported in dogs and turtles.

3.4 Special warnings

Recommendations for responsible use and advice on how to apply targeted treatment as appropriate:

Unnecessary use of antiparasitics or use deviating from the instructions given in the SPC may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary medicinal product should be based on confirmation of the parasitic species and burden, or of the risk of infestation based on its epidemiological features, for each individual animal/herd.

Repeated use for an extended period, particularly when using the same class of substances, increases the risk of resistance development. Within a herd, maintenance of susceptible refugia is essential to reduce that risk. Systematically applied interval-based treatment and treatment of a whole herd should be avoided. Instead, if feasible, only selected individual animals or subgroup should be treated (targeted selective treatment). This should be combined with appropriate husbandry and pasture management measures. Guidance for each specific herd should be sought from the responsible veterinarian.

In the absence of risk of co-infestation with nematodes, arthropods and liver flukes, a narrow spectrum veterinary medicinal product should be used.

Advice on how to assess and handle potential resistance in the animals to be treated:

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method (e.g., Faecal Egg Count Reduction Test (FECRT)).

Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

Resistance to anthelmintic macrocyclic lactones is becoming a problem in *Trichostrongylus* nematodes in cattle in some parts of the world.

Resistance to ivermectin was reported within and outside Europe also for *Cooperia spp*. and *Ostertagia ostertagi* in cattle.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Administration of the veterinary medicinal product to animals with wet or dirty coats is not recommended.

In the treatment of warbles, cattle should be treated either before or after the larval development stages occur to avoid possible adverse effects.
Consult your veterinarian for advice on the correct timing of treatment.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to ivermectin or clorsulon should administer the veterinary medicinal product with caution.

This veterinary medicinal product may cause skin and eye irritation. Avoid contact with skin and eyes. In case of accidental contact with skin or eyes, wash the affected area immediately with plenty of water.

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

Since foetotoxic and teratogenic effects are described in laboratory animals after exposure to glycerol formal, pregnant women or women attempting to conceive should not administer the veterinary medicinal product.

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

Wash hands after use.

Special precautions for the protection of the environment:
The veterinary medicinal product is very toxic to aquatic organisms, and poses a risk to the aquatic compartment, therefore treated animals should not have direct access to ponds, streams or ditches for 14 days after treatment.

The veterinary medicinal product is very toxic to dung fauna and long-term effects on dung insects caused by continuous or repeated use cannot be excluded. Therefore, repeated treatment of animals on a pasture with an ivermectin-containing veterinary medicinal product within a season, should only be given in the absence of alternative treatments or approaches to maintain animal/flock health, as advised by a veterinarian.

3.6 Adverse events

Cattle

Common (1 to 10 animals / 100 animals treated):	Restlessness*
Uncommon (1 to 10 animals / 1,000 animals treated):	Injection site swelling**

*Transient
**Reversible

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 for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy:

Can be used during pregnancy.

3.8 Interaction with other medicinal products and other forms of interaction

No data available.

3.9 Administration routes and dosage

Subcutaneous use.

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

0.2 mg ivermectin and 2 mg clorsulon /kg b.w. (i.e. 1 ml of veterinary medicinal product/50 kg b.w.), subcutaneously into loose skin in front of or behind the shoulder blade.

Underdosing could result in ineffective use and may favour resistance development.

Accuracy of the dosing device should be thoroughly checked.

Divide doses greater than 10 ml between different injection sites and use different sites to those used for other parenteral medications.

A sterile 18-gauge or 21-gauge, needle is recommended.

For 250 ml and 500 ml pack sizes, use of a multiple dose syringe is recommended. To refill the syringe, use of a draw-off needle is recommended to avoid excessive broaching of the stopper.
Do not exceed 30 broachings per stopper.
If the temperature of the medicine drops below 5°C, administration difficulties may occur due to the increased viscosity of the veterinary medicinal product. The temperature of the veterinary medicinal product and the injection device up to approximately 15°C simplifies the administration of the veterinary medicinal product.

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

Trials with a veterinary medicinal product containing ivermectin (10 mg/ml) and clorsulon (100 mg/ml) have shown a wide margin of safety. Administration of 25 ml /50 kg b.w. (25 times the recommended dose) resulted in injection site lesions (including tissue necrosis, edema, fibrosis, and inflammation). No other adverse effects related to overdose were detected.

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

Meat and offal: 66 days

Milk: Not authorised for use in animals producing milk for human consumption. Do not use in pregnant animals which are intended to produce milk for human consumption within 60 days of expected parturition.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QP54AA51

4.2 Pharmacodynamics

Ivermectin
Ivermectin belongs to the group of macrocyclic lactones endectocides, which have a specific mechanism of action. Substances bind selectively to the glutamate-gated chloride ion channels which found 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 parasite. Compounds of this class may also interact with other ligand-gated chloride channels. However, macrocyclic lactones have a lower affinity for mammalian chloride channels and 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 channels and they do not readily cross the blood-brain barrier.

Ivermectin resistant parasites
It has been shown that ivermectin-resistant parasites and other parasites exposed to ivermectin repeatedly exhibit selection on their ABC transport genes (ATP-binding cassette).
Synchronous mutations in the GluCl avr-15, avr-14, and glc-1 genes were required to establish high levels of resistance. If a single gene is mutated, little to no resistance was observed.
A great degree of genetic diversity is a result of the population's massive size, high rate of reproduction, and wide variety of habitats. Therefore, frequent use of macrocyclic lactones contributes in selection of those uncommon individual nematodes with the right allele combinations to reproduce, withstand the standard dosage and create antiparasitic resistance.

Clorsulon
Clorsulon is rapidly absorbed into the circulating blood. Erythrocytes with bound substance as well as plasma are ingested by *Fasciola spp*. Adult *Fasciola spp.* are killed by clorsulon because of inhibition of enzymes in the glycolytic pathway, which is their primary source of energy.

4.3 Pharmacokinetics

Maximum concentration in plasma

After subcutaneous administration of 2 mg clorsulon and 0.2 mg ivermectin per kg body weight, the plasma profile demonstrated slow, steady absorption of ivermectin with peak plasma level averaging 23 ng/ml around day 7 post dose. In contrast, clorsulon appeared rapidly absorbed since the first sampling point, 8 hours post dose, had the highest average residues, approximately 2 µg/ml.

Excretion (duration and route of excretion)

In cattle that received a single dose of tritium-labelled ivermectin (0.2-0.3 mg/kg bw), analyses showed that faeces collected during the first 7 days after application contained almost all of the radioactivity of the dose, only approx. 1-2% was excreted in the urine. Analyses of faeces further demonstrated that approx. 40-50% of the excreted radioactivity is found as an unchanged substance. The remaining 50-60% were present as metabolites or degradation products and almost all of them were more polar than ivermectin.

During the first 7 days, 7 mg/kg clorsulon was administered into the rumen of a 270 kg bull, about 90% of the radiolabelled clorsulon in the administered dose was found in urine (25%) and faeces (65%).

Environmental properties
Ivermectin is very toxic to aquatic organisms and dung fauna and can accumulate in soil and sediment. Like other macrocyclic lactones, ivermectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of ivermectin may take place over a period of several weeks. Faeces containing ivermectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

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: 2 years
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Store below 25 °C.

5.4 Nature and composition of immediate packaging

Brown glass bottles (type II) closed with chlorobutyl rubber stopper (type I) and sealed with an aluminium and flip off polypropylene cap packed into an outer cardboard box.

Package sizes:
Cardboard box with 1 bottle of 100 ml
Cardboard box with 1 bottle of 250 ml
Cardboard box with 1 bottle of 500 ml

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.

The veterinary medicinal product should not enter water courses as ivermectin is very toxic for fish and other aquatic organisms.

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

ADOH B.V.

7. MARKETING AUTHORISATION NUMBER(S)

VPA1717/003/00

8. 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).