ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Moxodex LA 100 mg/ml Solution for Injection for Cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance
Moxidectin 100 mg

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol (E1519)	70 mg
Butyl hydroxytoluene (E321)	NMT 0.6 mg
Sorbitan oleate	
Propylene glycol dicaprylocaprate	

Clear yellow solution for injection, practically free from visible particles.

3. CLINICAL INFORMATION

3.1 Target species

Cattle

3.2 Indications for use for each target species

In cattle weighing from 100 to 500 kg body weight, treatment and prevention of mixed infestations by the following gastro-intestinal nematodes, respiratory nematodes and certain arthropod parasites:

Adult and immature gastro-intestinal nematodes:
. *Haemonchus placei*
. *Haemonchus contortus*
. *Ostertagia ostertagi* (including inhibited larvae)
. *Trichostrongylus axei*
. *Trichostrongylus colubriformis*
. *Nematodirus helvetianus* (adults only)
. *Nematodirus spathiger*
. *Cooperia surnabada*
. *Cooperia oncophora*
. *Cooperia pectinata*
. *Cooperia punctata*
. *Oesophagostomum radiatum*
. *Bunostomum phlebotomum* (adults only)
. *Chabertia ovina* (adults only)
. *Trichuris spp.* (adults only)

Adult and immature respiratory tract nematode
. *Dictyocaulus viviparus*

Warble grubs (migrating larvae)
. *Hypoderma bovis*
. *Hypoderma lineatum*

Lice
. *Linognathus vituli*
. *Haematopinus eurysternus*
. *Solenopotes capillatus*
. *Bovicolabovis* (aid in control)

Mange mites
. *Sarcoptes scabiei*
. *Psoroptes ovis*
. *Chorioptes bovis* (aid in control)

The veterinary medicinal producthas a persistent action and protects cattle for a certain duration against infection or re-infection with the following parasites for the period indicated:

Species	**Protection period (days)**
Dictyocaulus viviparus	120
Ostertagia ostertagi	120
Haemonchus placei	90
Oesophagostomum radiatum	150
Trichostrongylus axei	90
Linognathus vituli	133

The veterinary medicinal product is effective against *Hypoderma* larvae at the time of treatment but its persistent activity against *Hypoderma* has not been evaluated. If the veterinary medicinal product is given before the end of the fly season complimentary treatment with a veterinary medicinal product effective against *Hypoderma* may be required.
Persistent efficacy periods have not been established for parasite species other than those included in the above list. Therefore, re-infection of animals on pasture contaminated by parasites other than these remains possible before the end of the 90 day minimum persistency period demonstrated for specific species.

3.3 Contraindications

Do not use in animals less than 100 kg bodyweight or greater than 500 kg.
Do not inject the veterinary medicinal product by intravascular route. Intravascular injection may result in ataxia, paralysis, convulsions, collapse and death. To prevent any intravascular injection, carefully follow the administration procedure described in item “Administration routes and dosage”.
Do not use in cases of hypersensitivity to the active substance or any of the excipients.

3.4 Special warnings

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 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 subgroups 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.

Underdosing which may due to underestimation of body weight or misadministration of the veterinary medicinal product could result in ineffective use and may favour resistance development.

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.

In the absence of risk of co-infection, a narrow spectrum veterinary medicinal product should be used.

Partial cross-resistance between ivermectin and moxidectin has been reported in nematode parasites. Cases of resistance to moxidectin have been reported in *Cooperia, Ostertagia, Oesophagostomum* and *Trichuris* genera of gastrointestinal nematode parasites of cattle and in *Psoroptes* mites, in the EU and elsewhere.
The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.
Confirmed resistance should be reported to the marketing authorisation holder or to the competent authority.

3.5 Special precautions for use

Special precautions for safe use in the target species:

In order to prevent abscesses, a strict aseptic technique is recommended. The veterinary medicinal product has been formulated specifically for subcutaneous injection in dorsal surface of the ear of cattle and must not be given by any other route of administration or to any other species.
To avoid possible secondary reactions by the death of *Hypoderma* larvae in the spine or the oesophagus of animals, it is recommended to administer a veterinary medicinal product effective against *Hypoderma* larvae after the end of fly activity and before the larvae reach their resting sites. Consult your veterinary surgeon on the correct timing of this treatment.
Immunity to nematodes depends on adequate exposure to infection. Although not normally the case, circumstances could occur in which anthelmintic control measures might increase the vulnerability of cattle to re-infection. Animals may be at risk towards the end of their first grazing season, particularly if the season is long, or in the following year if they move onto heavily contaminated pasture. In such instances, further control measures may be necessary.

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

"Moxidectin or benzyl alcohol may cause hypersensitivity (allergic reactions). People with known hypersensitivity to moxidectin or benzyl alcohol should avoid contact with the veterinary medicinal product.
The veterinary medicinal product may cause skin and eye irritation. Avoid direct contact with skin and eyes. If skin or eye irritation occur, wash with plenty of water.
Wash hands after use.
Do not smoke, drink or eat while handling the veterinary medicinal product.
Take care to avoid self-injection. In case of accidental self-injection, seek medical advice.
Advice to medical practitioners in case of accidental self-injection: Treat symptomatically."

Special precautions for the protection of the environment:

Moxidectin fulfils the criteria for a (very) persistent, bioaccumulative and toxic (PBT) substance; therefore, exposure of the environment to moxidectin must be limited to the extent possible. Treatments should be administered only when necessary and should be based on faecal egg counts or evaluation of the risk of infestation at the animal and/or herd level.
Like other macrocyclic lactones, moxidectin has the potential to adversely affect non-target organisms:

Faeces containing moxidectin excreted onto pasture by treated animals may temporarily reduce the abundance of dung feeding organisms. Following treatment of cattle with the veterinary medicinal product, levels of moxidectin that are potentially toxic to dung fly species may be excreted over a period more than 4 weeks and may decrease dung fly abundance during that period. It has been established in laboratory tests that moxidectin may temporarily affect dung beetle reproduction; however, field studies indicate no long-term effects. Nevertheless, in case of repeated treatments with moxidectin (as with veterinary medicinal products of the same anthelmintic class) it is advisable not to treat animals every time on the same pasture to allow dung fauna populations to recover.

Moxidectin is inherently toxic to aquatic organisms including fish. The veterinary medicinal product should be used only according to the label instructions. Based on the excretion profile of moxidectin when administered as the injectable formulation, treated animals should not have access to watercourses during the 10 days after treatment.

3.6 Adverse events

Cattle

Rare (1 to 10 animals / 10,000 animals treated):	Injection site swelling[1] Depression and ataxia
Undetermined frequency (cannot be estimated from the available data):	Hypersensitivity reaction[2]

[1]Immediate or delayed. These swellings may further develop into abscesses (approx. 1% of cases). The frequency of injection site swellings tends to be higher in the heavier animals. These side effects generally disappear without treatment, within 14 days after administration, some may persist for up to 5 weeks in a number of animals (<5%) and in very rare occasions longer.
[2]In case of hypersensitivity reactions, a symptomatic treatment should be applied.

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 the national competent authority via the national reporting system. See also section “contact details” of the package leaflet for respective contact details.”

3.7 Use during pregnancy, lactation or lay

Pregnancy:
Can be used during pregnancy.

Lactation:
Not applicable. Note 3.12 Withdrawal periods.

3.8 Interaction with other medicinal products and other forms of interaction

The effects of GABA agonists are increased by moxidectin.

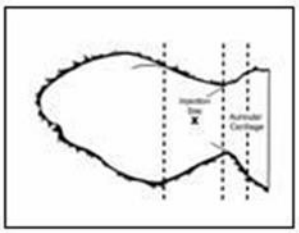
3.9 Administration routes and dosage

For subcutaneous use.
Dosage is 0.5 ml/50 kg bodyweight, equivalent to 1.0 mg moxidectin/kg bodyweight, given by a single subcutaneous injection in the ear using an 18 gauge, 25 – 40 mm hypodermic needle. The 50ml vial stoppers must not be broached more than 20 times and the 250 ml vial should not be broached more than 5 times. Use automatic syringe equipment for the 250 ml vial.

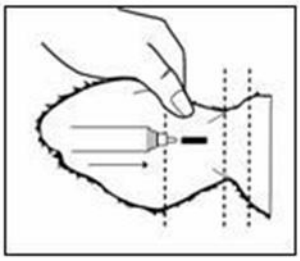
Shake well before use.
To ensure administration of a correct dosage, body weight should be determined as accurately as possible; accuracy of the dosing should be checked.
The injection should be given subcutaneously in the loose tissues on the dorsal surface of the ear, just distal to the distal edge of the auricular cartilage.
The dorsal (outer) surface of the ear should first be cleansed with antiseptic and allowed to briefly air dry. Palpate the edge of the auricular cartilage closest to the head, on the dorsal (hairy) surface of the ear. From this landmark, taking care to avoid blood vessels (artery, vein), the needle should be inserted subcutaneously starting at a point approximately 3 to 3.5 cm distal to this edge (away from the head), and directed towards the base of the ear, and the needle advanced to the hub. At this point, gently aspirate the syringe to confirm that the needle is not in a blood vessel.
Upon injection, the resulting depot should reside just distal to the edge of the auricular cartilage.
Following administration, the needle is withdrawn from the skin as pressure is applied for several seconds with the thumb at the point of insertion.

Due to the long lasting protection against *Dictyocaulus viviparus* and the stomach worms, *Ostertagia ostertagi* and *Haemonchus placei*, a single treatment with the formulation at turn-out helps control parasitic bronchitis (lungworm) and parasitic gastro-enteritis throughout the grazing season by reducing the build-up of infective larvae on pasture associated with these parasites.. Underdosing could result in ineffective use and may favour resistance development.

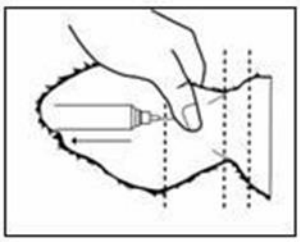
Diagram: Ear injection procedure



- The injection site is approximately 3.5 cm (1.5 inches) distal to the distal edge of the auricular cartilage.



- Use one hand to grasp and steady the ear.
- Inject subcutaneously using an 18 gauge x 1 inch needle.



- Inject contents. Depot should be just distal to the distal edge of the auricular cartilage.
- Apply pressure at the point of insertion as the needle is withdrawn from the skin to help seal the opening.

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

Reactions at the injection site have to be expected more frequently and severe depending on the injected volume. Systemic clinical signs of overdoses are consistent with the mode of action of moxidectin. These clinical signs are manifested as transient salivation, depression, drowsiness and ataxia 24 to 36 hours post-treatment. The systemic clinical signs usually disappear within 36 to 72 hours without treatment. At doses >3 times the recommended dose divided on both ears, the systemic clinical signs included recumbency, muscle tremor, ruminal tympany and dehydration, which were resolved after treatment with fluids. The systemic clinical signs can last for a few days to ten days. There is no specific antidote.

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: 108 days.
Milk: Not permitted for use in lactating animals producing milk for human consumption or industrial purposes or within 80 days of expected parturition.
The withdrawal period is based solely on a single injection at the ear site of injection.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

4.2 Pharmacodynamics

Moxidectin is an endectocide active against a wide range of internal and external parasites and is a second generation macrocyclic lactone of the milbemycin family.
Moxidectin interacts with GABA receptors and glutamate gated chloride channels.
The net effect is to open the chloride channels on the postsynaptic junction to allow the inflow of chloride ions and induce an irreversible resting state. This results in flaccid paralysis and eventual death of parasites exposed to the product.
The exact mechanisms of parasite resistance to moxidectin have not been elucidated. A resistance mechanism involving metabolism by p-glycoproteins and efflux from the cells by ABC transporters has been proposed for ivermectin and a similar mechanism is thought to play a role in moxidectin resistance. However, parasites resistant to ivermectin are known to show some degree but not complete cross-resistance to moxidectin. It has been proposed that the reason for the incomplete cross-resistance is that there are multiple avenues of moxidectin action in target parasites that may include receptors other than the Glutamate-gated chloride channels.

4.3 Pharmacokinetics

Moxidectin is absorbed following subcutaneous injection with maximum blood concentrations being achieved 24 to 48 hours post injection. The product is distributed throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. The depletion half-life in fat is 26 – 32 days.
Moxidectin undergoes limited biotransformation by hydroxylation in the body. The only significant route of excretion is the faeces.

Environmental properties

Moxidectin fulfils the criteria for a (very) persistent, bioaccumulative and toxic (PBT) substance. In particular, in acute and chronic toxicity studies with algae, crustaceans and fish, moxidectin showed toxicity to these organisms, yielding the following endpoints:

Organism		**EC_{50}**	**NOEC**
Algae	*S. capricornutum*	>86.9 µg/l	86.9 µg/l
Crustaceans (Water fleas)	*Daphnia magna* (acute)	0.0302 µg/l	0.011 µg/l
	Daphnia magna (reproduction)	0.0031 µg/l	0.010 µg/l
Fish	*O. mykiss*	0.160 µg/l	Not determined
	L. macrochirus	0.620 µg/l	0.52 µg/l
	P. promelas (early life stages)	Not applicable	0.0032 µg/l
	Cyprinus carpio	0.11 µg/l	Not determined

EC_{50}: the concentration which results in 50% of the test species individuals being adversely affected, i.e. both mortality and sub-lethal effects.
NOEC: the concentration in the study at which no effects are observed.
This implies that when allowing moxidectin to enter water bodies, this may have a severe and lasting impact on aquatic life. To mitigate this risk, all precautions for use and disposal must be adhered to.

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

Do not store above 25 °C.

5.4 Nature and composition of immediate packaging

Nature of the primary container: HDPE vial containing 50 mL and 250 mL of solution for injection sealed with a chlorinated butyl rubber stopper secured with an aluminium seal.

Pack sizes:
Box containing 1 vial of 50 mL size
Box containing 1 vial of 250 mL size
Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.
Do not contaminate watercourses with the product as moxidectin may be dangerous 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

Chanelle Pharmaceuticals Manufacturing Ltd

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).”)