ANNEX I

LIST OF THE PHARMACEUTICAL FORMS, STRENGTHS, ROUTES OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES OF THE VETERINARY MEDICINAL PRODUCT IN THE MEMBER STATES

ANNEX I

Marketing Authorisation Holder (Name and address):

Reference Member State:

IRELAND

Cross Vetpharm Group Ltd (Bimeda)
Broomhill Road
Tallaght
Dublin 24
Ireland

Concerned Member State:

BELGIUM

Cross Vetpharm Group Ltd (Bimeda)
Broomhill Road
Tallaght
Dublin 24
Ireland

Presentations:

Member State	Invented Name	Strength	Pharmaceutical Form	Target Species	Route of administration	Packaging	Content	Package-size
Ireland	Bovimectin Injection	1 % w/v (10 mg/ml)	Solution for injection	Cattle	Subcutaneous injection	Bottle (Polyethylene)	50 ml	1 bottle
Ireland	Bovimectin Injection	1 % w/v (10 mg/ml)	Solution for injection	Cattle	Subcutaneous injection	Bottle (Polyethylene)	250 ml	1 bottle
Ireland	Bovimectin Injection	1 % w/v (10 mg/ml)	Solution for injection	Cattle	Subcutaneous injection	Bottle (Polyethylene)	500 ml	1 bottle
Belgium	Bovimec B	1 % w/v (10 mg/ml)	Solution for injection	Cattle	Subcutaneous injection	Bottle (Polyethylene)	50 ml	1 bottle
Belgium	Bovimec B	1 % w/v (10 mg/ml)	Solution for injection	Cattle	Subcutaneous injection	Bottle (Polyethylene)	250 ml	1 bottle
Belgium	Bovimec B	1 % w/v (10 mg/ml)	Solution for injection	Cattle	Subcutaneous injection	Bottle (Polyethylene)	500 ml	1 bottle

ANNEX II

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

The basis for the arbitration procedure was the concern raised by Belgium, that plasmatic levels of anthelminthics that have been produced by means of fermentation techniques, such as the macrocyclic lactones (e.g. ivermectin) have no direct correlation with the efficacy of these products *in situ*. The applicant was requested to provide evidence of correlation of plasma concentrations with clinical efficacy against parasites included in the indications on the SPC.

The CVMP considered the written response provided by the Applicant, the joint Rapporteur-Co-Rapporteur's assessment report on the response of the Applicant and the comments from CVMP members, including references to published literature in this field.

Taking into account

- that the application was submitted in accordance with the current guidelines (EMEA/CVMP/016/00 and VICH GL7);
- that bioequivalence with the reference product has been proven;
- that the clinical effect of ivermectin is related to plasma pharmacokinetics;

the CVMP agreed that no dose confirmation study is required to show clinical efficacy..

Therefore, the CVMP has recommended the granting of the Marketing Authorisation(s) for which the Summary of Product Characteristics is set out in Annex III for Bovimectin injection.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS
OF THE REFERENCE MEMBER STATE

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Veterinary Medicinal Product:

Bovimectin Injection, 1%, Solution for injection for Cattle

2. Qualitative and Quantitative Composition in Terms of the Active Substances and Constituents of the Excipients, knowledge of which is essential for proper administration

Active Substance

Ivermectin Ph.Eur. 1.0 % w/v (10 mg/ml)

3. Pharmaceutical Form

Solution for injection

4. Pharmacological Properties, and in so far as this information is useful for Therapeutic Purposes, Pharmacokinetics particulars:

4.1 Pharmacodynamic properties

Ivermectin belongs to the avermectin group. Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind 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 parasite. 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-gates 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.

ATCvet code: QP54AA01

4.2 Pharmacokinetic properties

At a dose level of 0.2 mg ivermectin per kg a mean Cmax of 30.43 ng/ml is reached at a mean Tmax of 131 hours and the mean half-life in plasma is 142.39 hours.
It is also established that ivermectin is distributed mainly in the plasma (80%). This distribution between plasma and blood cells remains relatively constant.
Only about 1-2% is excreted in the urine the remainder is excreted in the faeces, approximately 60% of which is excreted as unaltered drug. The remainder is excreted as metabolites or degradation products. The major metabolite in cattle is 24-hydroxymethyl H2B1a and its fatty acid esters. Almost all of the metabolites of Ivermectin are more polar than the parent compound and no single minor metabolite accounts for more than 4% of total metabolites.

5. Clinical Particulars

5.0 Target Species

Cattle (Beef and non lactating cattle)

Bovimectin Injection for cattle can be given to all ages of animals including young calves.

5.1 Indications For Use:

Bovimectin Injection is indicated for the effective treatment and control of the following harmful parasites of cattle:

Gastro-intestinal roundworms:
Ostertagia spp. (including inhibited *O. ostertagi*) (adult and fourth stage larvae)
Haemonochus placei (adult and fourth stage larvae)
Trichostrongylus spp. (adult and fourth stage larvae)
Cooperia spp. (adult and fourth stage larvae)
Nematodirus spp.(adult)

Lungworms:
Dictyocaulus viviparus. (adult and fourth stage larvae)

Warbles (parasitic stages):
Hypoderma spp.

5.1 Indications For Use:

Mange mites:
Psoroptes bovis
Sarcoptes scabiei var. *bovis.*

Sucking lice:
Linognathus vituli
Haematopinus eurysternus

Persistant activity

Treatment at the recommended dose rate controls re-infection with *Haemonchus placei* and *Cooperia* spp. acquired up to 14 days after treatment, *Ostertagia ostertagi* acquired up to 21 days after treatment and *Dictyocaulus viviparus* acquired up to 28 days after treatment.

To obtain optimal benefit from the persistent activity of Bovimectin Injection for grazing animals it is recommended that calves which are set-stocked in their first grazing season should be treated 3, 8 and 13 weeks after the day of turn-out. This can protect the animals from parasitic gastro-enteritis and lungworm disease throughout the grazing season, provided they are set-stocked, all the calves are included in the program and that no untreated cattle are added to the pasture. Treated calves should always be monitored according to good husbandry practices.

5.2 Contra-indications

Do not use in case of known hypersensitivity to the active ingredient.
Do not administer by the intravenous or intramuscular route.
Bovimectin Injection for Cattle has been formulated specifically for use in this species. 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).

Do not use in cats and dogs.

Do not use in dairy cows, during lactation or the dry period, when milk is intended for human consumption. Do not use in pregnant heifers within 60 days prior to calving.

5.3 Undesirable Effects

Transitory discomfort and a low incidence of soft tissue swelling have been observed at the injection site in some cattle following subcutaneous administration. These reactions have disappeared without treatment within 28 days.

5.4 Special Precautions for Use

Assess bodyweight as accurately as possible before calculating the dosage.

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. Consult your veterinarian on the correct timing of treatment."

5.5 Use During Pregnancy and Lactation:

Bovimectin Injection for cattle can be administered to beef cows at any stage of pregnancy or lactation provided that the milk is not intended for human consumption.

Do not use in dairy cows, during lactation or the dry period, when milk is intended for human consumption. Do not use in pregnant heifers within 60 days prior to calving.

Please refer to point 5.10.

5.6 Interaction with Other Medicaments and other Forms of Interactions:

Bovimectin Injection can be used concurrently without adverse effects with foot and mouth disease vaccine or clostridial vaccine, given at separate injection sites.

5.7 Posology and Method of Administration

Each ml contains 10 mg of ivermectin sufficient to treat 50 kg of bodyweight of cattle. The injection may be given with any standard automatic or single-dose or hypodermic syringe. Use of 17 gauge x ½ inch needle is suggested. Injection of wet or dirty animals is not recommended. If using a single-dose hypodermic syringe, use a separate sterile needle to withdraw Bovimectin Injection from the container.

Bovimectin Injection should be given only by subcutaneous injection at the recommended dosage level of 200 mcg ivermectin per kg bodyweight under the loose skin in front of, or behind, the shoulder in cattle. This is equivalent to 1 ml per 50 kg bodyweight. The volume administered per injection site should not exceed 10ml.

5.8 Overdose

Single doses of 4.0 mg ivermectin per kg (20 x the use level) given subcutaneously resulted in ataxia and depression.

5.9 Special Warnings for each Target Species

Details provided above apply. See also points 5.2, 5.3 and 5.5.

5.10 Withdrawal Periods

Meat: 42 days
Do not use in dairy cows, during lactation or the dry period, when milk is intended for human consumption. Do not use in pregnant heifers within 60 days prior to calving.

5.11 Special Precautions to be taken by the person administering the product to animals

Take care to avoid self-administration: the product may cause local irritation and/or pain at the site of injection.

6. Pharmaceutical Particulars

6.1 Incompatibilities

None known.

6.2 Shelf-life

Shelf-life: 2 years.
Shelf-life after first broaching: 28 days.

6.3 Special Precautions for Storage

None.

6.4 Nature and Contents of Container

Multidose high density polyethylene bottles of 50 ml, 250 ml and 500 ml sealed with bromobutyl seals and plain aluminium overseals, containing a clear, colourless sterile solution.

6.5 Name or Style and Permanent address or Registered Place of Business of the Holder of the Authorisation to place the Product on the Market:

Bimeda,
(a division of Cross Vetpharm Group Limited)
Broomhill Road, Tallaght,
Dublin 24,
Ireland.

6.6 Special Precautions for the disposal of unused product or waste material, if any:

Any unused veterinary product or waste material derived from the product should be disposed of in accordance with local requirements. The product should not enter water courses as this may be dangerous to fish and other aquatic organisms.

7. Additional Information

Marketing Authorisation Number