ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS, ROUTE OF ADMINISTRATION, ANIMAL SPECIES AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES AND NORWAY

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharmaceutical form	Route of administration	Animal species
Austria	Mérial SAS 29 avenue Tony Garnier F-69007 Lyon France	Eprinex – Lösung zum Auftragen auf die Haut für Rinder	5 mg/ml	Solution	Topical	Cattle
Belgium	Merial Belgium NV/SA Bld Sylvain Dupuislaan 243 B-1070 Bruxelles Belgium	EPRINEX POUR-ON	5 mg/ml	Solution for external use	Topical	Cattle including lactating cows
Denmark	Merial Ltd. P.O. Box 327 Sandringham House Harlow Business Park Harlow UK-Essex CM19 5TG United Kingdom	Eprinex Vet	5 mg/ml	Pour-on solution	Topical	Cattle
Finland	Merial SAS 29 avenue Tony Garnier F-69007 Lyon France	Eprinex pour-on vet	5 mg/ml	Pour-on solution	Topical	Cattle
France	Mérial 29 av Tony Garnier F-69007 Lyon France	EPRINEX pour on pour bovins	5 mg/ml	Cutaneous solution	Topical	Cattle
Germany	Merial GmbH Am Söldnermoos 6 D-85399 Hallbergmoos Germany	Eprinex Pour-on	0.5 g/100 ml	Solution	Topical	Cattle
Ireland	Merial Ltd Limited Sandringham House Harlow Business Park Harlow UK-Essex CM19 5TG United Kingdom	Eprinex Pour-On for beef and dairy cattle	0.5 % w/v	Pour-on solution	Topical	Beef and dairy cattle including lactating dairy cattle
Italy	MERIAL ITALIA spa Milanofiori – Strada 6 Palazzo E/5 I-20090 Assago (MI) Italy	EPRINEX pour-on	5 mg/ml	Solution for external use	Topical	Beef and dairy cattle (including lactating cows)

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharmaceutical form	Route of administration	Animal species
Luxembourg	Merial Belgium NV/SA Bvd Sylvain Dupuislaan 243 B-1070 Bruxelles Belgium	Eprinex Pour-on	5 mg/ml	Solution for external use	Topical	Cattle including lactating cows
The Netherlands	Merial BV Bovenkerkerweg 6-8 1185 XE AMSTELVEEN The Netherlands	Ivomec-Eprinex Pour On voor vlees- en melkvee REGNL 9033	5 mg/ml	Solution	Topical	Cattle
Portugal	Merial Portuguesa Saúde Animal Lda Avenida Maria Lamas Lote 19 B1 A, piso 2 Serra das Minas P-2635-432 Rio de Mouro Portugal	Eprinex Pour-On	5 mg/ml	Pour-on	Topical	Beef and dairy cattle
Spain	Merial Laboratorios S.A. Tarragona 161 E-08014 Barcelona Spain	EPRINEX POUR ON	5 mg/ml	Solution	Topical	Cattle and dairy cows
Sweden	Merial SAS 29 avenue Tony Garnier F-69007 Lyon France	Eprinex Pour-on	5 mg/ml	Pour-on solution	Topical	Lactating and non-lactating cattle
United Kingdom	Merial Ltd Sandringham House Harlow Business Park Harlow UK-Essex CM19 5TG United Kingdom	Eprinex Pour-On for Beef and Dairy Cattle	0.5% w/v	Pour-on solution	Topical	Beef and dairy cattle including lactating dairy cattle
Norway	Merial SAS 29 avenue Tony Garnier F-69007 Lyon France	Eprinex pour-on vet	5 mg/ml	Cutaneous solution	Topical	Cattle (including lactating dairy cows)

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

1. Introduction and Background

Eprinex pour-on products contain eprinomectin, which is a semi-synthetic compound of the avermectin family, intended for the treatment of internal and external parasites in cattle including lactating cows. The product has been authorised in the European Union (all Member States except Greece) and in Norway as a pour on solution for topical use. The withdrawal periods set for edible tissues by the different Member States diverge significantly, from 0 to 21 days. The withdrawal period for milk was consistently set as 0 days.

On 18 June 2003 Germany requested the CVMP to give an opinion under Article 34 of Council Directive 2001/82/EC concerning the divergent decisions taken by the competent national authorities regarding the withdrawal periods for meat and offal when granting the marketing authorisations for Eprinex pour on products.

The CVMP during its meeting of 23 July 2003 decided to start a referral procedure under Article 34 of Council Directive 2001/82/EC for the Eprinex pour-on products containing eprinomectin. The questions identified related to the withdrawal periods and were submitted to the Marketing Authorisation Holders on 28 July 2003. The responses were submitted on 25 November 2003.

The CVMP had previously assessed eprinomectin in respect to the establishment of maximum residue limits (MRLs) in accordance with Council Regulation 2377/90. The CVMP established a toxicological ADI of 5 µg/kg bw (300 µg/person) for eprinomectin, based on the NOEL of 1.0 mg/kg bw/day for mydriasis and focal neuronal degeneration of the nervous system observed in the 53-week toxicity study in beagle dogs and applying a safety factor of 200.

Eprinomectin was included in Annex I of Council Regulation 2377/90 and the following maximum residue limits were established for bovine species:

Muscle: 50 µg/kg
Fat: 250 µg/kg
Liver: 1500 µg/kg
Kidney: 300 µg/kg
Milk: 20 µg/kg

2. Discussion

2.1 Residue depletion studies

For the referral procedure one radiolabelled and three non-radiolabelled residue depletion studies in cattle were submitted. All studies were conducted according to GLP-guidelines and using the formulation as marketed in all relevant Member States and Norway in the correct dosage. In all studies, only perirenal fat was sampled and the residue concentration in dose site fat was not investigated. However, this is not considered as causing difficulties to establish an appropriate withdrawal period.

In the radiolabelled study 14 steers and heifers, aged 8-10 months were administered topically [5-3]H-radiolabelled eprinomectin at a single dose of 0.5 mg/kg bw. Animals were slaughtered at 7, 14, 21 and 28 days after treatment, 3 animals per time point. Tissue samples were taken from muscle, perirenal fat, liver, kidney and dose-site muscle. Marker residue concentrations were determined using a validated HPLC-fluorescence method with a limit of detection of 1 µg/kg and a limit of quantification of 2 µg/kg.

Residues were below the MRL values at all points measured. However, animals were only slaughtered at withdrawal times of 7 days or more, therefore, it could not be excluded that the MRL was not exceeded at earlier time points. Residue concentrations in dose-site muscle showed a large variation, the highest concentration was found in a 28-day sample, the latest time point in the study and residue concentrations were higher than in muscle (by a factor of about 3-4).

In a non-radiolabelled study 17 male castrate and 17 female beef cattle, aged 17 to 20 months, were administered topically eprinomectin at a single dose of 0.5 mg/kg bw. Animals were slaughtered on day 10, 17, 24, 34, 44 and 55 after treatment, 5 animals per time point. Two untreated control animals were slaughtered the day before treatment and 2 others 23 days after treatment. Tissue samples were taken from muscle, perirenal fat, liver, kidney and dose-site muscle. Marker residue concentrations were determined using validated HPLC-fluorescence method with a limit of detection of 1 µg/kg and a limit of quantification of 2 µg/kg.

Residue concentrations were below the MRL values at all points measured. However animals were only slaughtered at withdrawal times of 10 days or more, therefore, it could not be excluded that the MRL was not exceeded at earlier time points.

In a second non-radiolabelled study 14 male castrate and 13 female cattle, aged 12-19 months, were administered topically eprinomectin at a single dose of 0.5 mg/kg bw. Animals were slaughtered at 0.5, 1, 3, 5 and 7 days after treatment, 5 animals per time point. Two untreated control animals were slaughtered two days before treatment. Tissue samples were taken from muscle, perirenal fat, liver, kidney and dose-site muscle. Marker residue concentrations were determined using validated HPLC-fluorescence method with a limit of detection of 1 µg/kg and a limit of quantification of 2 µg/kg.

Tissue residue concentrations were highest after 3 days and declined afterwards and did not exceeded the MRL at any time point.

In the third non-radiolabelled study 12 male non-ruminating calves, aged 11 to 13 weeks, were administered topically eprinomectin at a single dose of 0.5 mg/kg bw. Animals were slaughtered on day 1, 3, 7 and 14 after treatment, 3 animals per time point. One untreated control animal was slaughtered just before treatment and another one after 14 days. Tissue samples were taken from the muscle, perirenal fat, liver, kidney and dose-site muscle. Marker residue concentrations were determined using validated HPLC-fluorescence method with a limit of detection of 1 µg/kg and limit of quantification of 2 µg/kg.

Plasma and residue levels were higher in non-ruminant calves than in adult cattle and it took longer to reach a maximum level; tissue residue concentrations were highest after 7 days. Tissue residue concentrations exceeded the MRL after 1 day (in fat and muscle) and after 7 days (in liver, fat and muscle) but were below the MRL at 14 days post treatment. Residue concentrations in this study showed a large variation.

2.2 Calculation of withdrawal periods

All four studies were considered relevant to be used in the establishment for the determination of the withdrawal period. The withdrawal period was calculated using either the statistical approach or the alternative approach, as appropriate according to the CVMP note for guidance approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95). For 3 studies the data allowed the use of the statistical approach. The withdrawal period calculated was 15 days for 2 of the studies and 3 days for the 3rd one, based on depletion from liver. For the 4th study, the statistical method could not be used due to large variation in the data set. The alternative approach yields a withdrawal period of 14 days plus a safety margin, based on depletion from liver, fat and muscle for the 4th study. This approach yields 7 days plus a safety margin for the 1st study, 10 days plus a safety margin for the 2nd study, and 0.5 days plus a safety margin for the 3rd. Overall, a withdrawal period of 15 days is considered appropriate to ensure depletion of residues below the MRLs.

3. Conclusions and recommendations

Based on the results of the four different residue depletion studies conducted in adult cattle as well in calves, the longest calculated withdrawal period in meat and offal is 15 days (by statistical approach) or 14 days plus a safety margin (by alternative approach). Therefore, the CVMP recommended that all marketing authorisations pour-on solutions containing eprinomectin for topical use in bovine species known as Eprinex or variations of that name as referred to in Annex I a withdrawal period for meat and offal of 15 days is set. The withdrawal period for milk of zero days as established in all the relevant Member States and Norway is unaffected.