ANNEX I

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

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharma-ceutical form	Animal species	Frequency	Recommended dose	Withdrawal period (meat and milk)
Austria	Pfizer Corp. Austria Seidengasse 33-35 1071 Wien	Dectomax 1% Injektions-lösung für Rinder und Schafe	10 mg /ml	Solution for injection	Cattle and sheep No treatment of animals producing milk for human consumption	Single dose	200 µg/kg bw	Meat: Cattle: 42 days Sheep: 40 days
Belgium	Pfizer Animal Health S.A. Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgique	Dectomax	10 mg/ml	Solution for injection	Cattle and sheep	Single dose	200 µg/kg bw	Meat: Cattle: 42 days Sheep: 35 days Milk: Cattle: 60 days Sheep: 70 days
Denmark	Pfizer Aps Lautrupvang 8 DK 2750 Ballerup	Dectomax Vet DK MT NO 15721	10 mg/ml	Solution for injection	Cattle Not to be used in cattle producing milk for human consumption.	Single dose	200 µg/kg bw	Meat: 45 days Milk: Not to be used later than 60 days prior to expected calving.
Finland	Pfizer Oy, Animal Health Tietokuja 4 00330 Helsinki Finland	Dectomax Vet	10 mg/ml	Solution for injection	Cattle, Reindeer, Pigs Not permitted for use in animals producing milk for human consumption during lactation	Single dose	Cattle and reindeer: 200 µg / kg bw Swine: 300 µg / kg bw	Meat: Cattle and reindeer: 42 days Swine: 49 days Milk: Withdrawal period for milk 60 days for heifers, reindeer and animals during the dry period
France	Pfizer 23/25 Ave du docteur Lannelongue 75014 Paris France	Dectomax	10 mg/ml	Solution for injection	Cattle and sheep Not for use in dairy cows during lactating or drying off and not for use in dairy ewes	Single dose	Cattle: 200 µg/kg bw (sc only) Sheep: 200 µg/kg bw (sc or im)	Meat: Cattle: 42 days Sheep: 35 days (im), 56 days (sc)
Germany	Pfizer GmbH Pfizerstrasse 1 76139 Karlsruhe Germany	Dectomax	10 mg/ml	Solution for injection	Cattle and sheep Not permitted for use in lactating animals producing milk for human consumption	Single dose	200 µg/kg bw	Meat: Cattle, sheep: 60 days

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharma-ceutical form	Animal species	Frequency	Recommended dose	Withdrawal period (meat and milk)
Greece	Pfizer Hellas Alketou 5 11633 Pagrati – Athina Greece	Dectomax	10 mg/ml	Solution for injection	Sheep Cattle Not for use in dairy cows. Pigs	Single dose	Sheep: 200 µg/kg bw (sc, im) Cattle: 200 µg/kg bw (sc) Pigs: 300 µg/kg bw (im)	Meat: Sheep: 35 days Cattle: 42 days Pigs: 49 days Milk: Sheep: Do not use in dairy sheep, including pregnant ewes within 50 days of lambing Cattle: Do not use in non lactating dairy cows including pregnant dairy heifers within 60 days of calving
Ireland	Pfizer Ltd. Walton Oaks, Dorking Road Tadworth, Surrey KT20 7NT England	Dectomax 1% Injectable solution	10 mg/ml	Solution for injection	Cattle and sheep	Single dose	Cattle: 200 µg/kg bw Sheep: 300 µg/kg bw	Meat Cattle: 63 days Sheep: 63 days
Italy	Pfizer Italia SRL Via Valbondione 113 00188 Roma	Dectomax 1% (doramectin)	10 mg/ml	Solution for injection	Cattle, sheep and pigs Use not permitted in animals producing milk for human use	Single dose	Cattle and sheep: 200 µg/kg bw Pigs: 300 µg/kg bw	Meat: Cattle: 42 days Sheep: 35 days Pigs: 37 days
Luxembourg	Pfizer Animal Health Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgique	Dectomax	10 mg/ml	Injection	Cattle and sheep Not for use in cattle producing milk for human consumption. Not for use in sheep producing milk for human consumption	Single dose	Cattle: 200 µg/kg bw (sc) Sheep: 300 µg/kg bw (sc or im)	Meat: Cattle: 42 days Sheep: 35 days Milk: Cattle: Do not use in dry dairy cows including pregnant heifers within 60 days before calving. Sheep: Not for use in the last 70 days before lambing

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharma-ceutical form	Animal species	Frequency	Recommended dose	Withdrawal period (meat and milk)
The Netherlands	Pfizer Animal Health B.V. PO Box 37 2900 AA CAPELLE AAN DEN IJSSEL The Netherlands	Dectomax (REG NL 9844) Prontax (REG NL 9884)	10 mg/ml	Solution for injection	Non-lactating cattle and sheep, pigs	Single dose. Sheep; repeated if signs of *P.ovis* infection do not disappear in 14 days	Cattle and sheep: 200 µg/kg bw Pigs: 300 µg / kg bw	Meat: Cattle: 75 days Sheep: 70 days Pigs: 77 days Milk: Cattle and sheep: product not allowed for milking sheep.
Portugal	Laboratórios Pfizer, Lda Lagoas Park Edifício 10 2740-244 Porte Salvo Portugal	Dectomax solution injectable	10 mg/ml	Solution for injection	Cattle, sheep and pigs	Single dose	Cattle and sheep: 200 µg / kg bw Pigs: 300 µg / kg bw	Meat: Cattle: 42 days. Sheep: 35 days. Pigs: 56 days Milk: Cattle: Forbidden in lactating cows, not to be administered 60 days before calving. Sheep: Forbidden in lactating sheep, not to be administered 70 days before lambing
Spain	Pfizer Avda.De Europa, 20b Parque Empresarial La Moraleja 28108 ALCOBENDAS	Dectomax solution injectable	10 mg/ml	Solution for injection	Cattle and sheep	Single dose	200 µg/kg bw	Meat Cattle: 42 days Sheep: 60 days
Sweden	Pfizer AB Box 501 183 25 Täby Sweden	Dectomax vet	10 mg/ml	Solution for injection	Cattle, sheep, (reindeer)	Not specified in the SPC	Catt1e (and reindeer): 200 µg/kg bw (sc) Sheep: 200 µg/kg bw (sc or im)	Meat: Cattle: 49 days Sheep: 45 days (im); 60 days (sc) Reindeer: 42 days Milk: Cattle: forbidden in lactating cows, not to be administered less than 60 days before calving Sheep: forbidden in lactating sheep, not to be administered less than 70 days before lambing

Member State	Marketing Authorisation Holder	Product trade name	Strength	Pharma-ceutical form	Animal species	Frequency	Recommended dose	Withdrawal period (meat and milk)
United Kingdom	Pfizer Ltd Pfizer Ltd, Sandwich, Kent, CT13 9NJ, UK	Dectomax Injectable Solution for Cattle and Sheep	10mg/ml	Solution for injection	Sheep and cattle Not permitted for use in lactating ewes or cows used to produce milk for human consumption	Single dose	Sheep: 300 µg/kg bw Cattle: 200 µg/kg bw	Meat: Cattle: 70 days Sheep: 56 days Milk: Cattle:Do not use in dry dairy cows including pregnant heifers within 60 days before calving
Iceland	Pfizer A/S Vestre Gade 18 2650 Hvidovre Denmark	Dextomax	1 %	Solution for injection	Cattle esp. bullocks, Not for use in lactating cows producing milk for human consumption, even in the resting period Sheep: Not for use in dairy ewes producing milk for human consumption. Not for use in pregnant ewes Pigs	Single dose	Cattle: 200 µg/kg bw (sc) Sheep: 200 µg/kg bw (sc, im) Pigs: 300 µg/kg bw Small pigs < 16 kg: < 4 kg: 0,1 ml 5-7 kg: 0,2 ml 8-10 kg: 0,3 ml 11-13 kg: 0,4 ml 14-16 kg: 0,5 ml	Meat: Cattle: 45 days. Sheep: 35 days Milk: Cattle: Not to be used for pregnant cows 60 days before giving birth. Sheep: Not to be used in dairy ewes, for at least 70 days before giving birth, if the milk is going to be used for human consumption
Norway	Pfizer As, Norway Orion Pharma As Animal Health P.O. Box 52 0508 Oslo, Norway	Dectomax	10 mg/ml	Solution for injection	Cattle, sheep, pigs, reindeer Not for use in lactating cattle, ewes or reindeer used to produce milk for human consumption	Not specified in the SPC	Cattle and reindeer: 200 µg/kg bw Sheep: 200 µg/kg bw (sc, im), (Nematodirus 300 µg/kg bw (sc, im)) Pigs: 300 µg/kg bw	Meat: Cattle and reindeer: 42 days Sheep: 45 days (im), 60 days (sc) - Nematodirus battus 55 days (im), 70 days (sc) Pigs: Meat: 49 days Milk: Cattle: Not for use in the last 60 days before calving. Sheep: Not for use in the last 70 days before lambing.

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

1. Introduction and Background

Dectomax injectable solution contains doramectin, which is a semi-synthetic compound of the avermectin family, intended for the treatment of internal and external parasites in cattle, sheep, pigs and reindeer, excluding lactating animals producing milk for human consumption. The product has been authorised in the EU Member States and EEA/EFTA States listed in Annex I as an injectable solution for intramuscular and/or subcutaneous administration. The withdrawal periods set for edible tissues of ovine species by the different Member States diverge significantly, from 35 to 70 days.

On 27 January 2004 the United Kingdom requested the CVMP to give an opinion under Article 34 of Council Directive 2001/82/EC concerning the divergent decisions taken by the concerned competent national authorities regarding the withdrawal periods for meat and offal when granting the marketing authorisations for Dectomax injectable products for use in ovine species.

The CVMP during its meeting of 10-12 February 2004 initiated a referral procedure under Article 34 of Council Directive 2001/82/EC for Dectomax injectable solution products containing doramectin. The questions identified related to the withdrawal periods and were submitted to the Marketing Authorisation Holders on 16 February 2004. The responses were submitted on 17 June 2004.

On 7 September 2004, the CVMP adopted an opinion recommending that the withdrawal period for injectable solutions containing doramectin for intramuscular use in ovine species should be 70 days for meat and offal. With respect to the subcutaneous use in ovine species, the Committee recommended that no withdrawal period could be set and references to this route of administration should be removed from the product literature.

On 17 September 2004, an intention to appeal against the opinion was submitted to the EMEA by the representative of the Marketing Authorisation Holders. The grounds for the appeal were submitted to the EMEA on 8 November 2004.

The CVMP had previously assessed doramectin in respect to the establishment of maximum residue limits (MRLs) in accordance with Council Regulation 2377/90. The CVMP established a toxicological ADI of 0.5 µg/kg bw (30 µg/person) for doramectin, based on the NOEL of 0.1 mg/kg bw/day for mydriasis observed in a 3-month toxicity study in beagle dogs and applying a safety factor of 200.

Doramectin was included in Annex I of Council Regulation (EEC) No 2377/90 and the following maximum residue limits were established for ovine species:

Muscle: 20 µg/kg	Fat: 100 µg/kg
Liver: 50 µg/kg	Kidney: 30 µg/kg

2. Discussion

2.1 Residue depletion studies

For the referral procedure, the representative of the Marketing Authorisation Holder presented three studies.

In first study, thirty-two sheep (group 2) received an intramuscular injection of doramectin at a dose of 300 µg/kg bw on 2 occasions, 7 days apart. Four sheep (group 3) were given a single intramuscular injection of doramectin at a dose of 300 µg/kg bw on study day 0. The remaining 4 sheep (group 1) served as untreated controls. Group 2 animals were sacrificed (2 males and 2 females at each time point) at 7, 14, 21, 28, 35, 42, 49 and 56 days after the second treatment. Group 3 animals were sacrificed at day 35 after treatment. At sacrifice the liver, kidneys, the injection site, samples of fat and skeletal muscle were taken from each animal. The concentration of doramectin in the various tissues was determined in duplicate tissue samples (injection site quadruplicate) using a validated HPLC procedure (limit of detection 0.5 µg/kg, limit of quantification 2.5 µg/kg (5 µg/kg in fat).

In the group 2 animals given two doses, the injection sites contained the highest residues followed by liver and fat. In the injection sites, the doramectin concentrations were 709 to 5731 µg/kg at 7 days, 326 to 4144 µg/kg at 14 days, 96.3 to 1381 µg/kg at 21 days, 40.1 to 754 µg/kg at 28 days, 4.88 to 119 µg/kg at 35 days, 24.4 to 185 µg/kg at 42 days, less than 2.5 to 94.3 at 49 days and less than 2.5 to 31.5 µg/kg at 56 days.

In the group 3 animals that received a single dose, mean residues were all below 10 µg/kg in liver (2.56 to 7.72 µg/kg), kidney (less than 2.5 to 2.58 µg/kg), fat (less than 2.5 to 17.4 µg/kg) and skeletal muscle (less than 2.5 to 4.89) after 35 days. Injection site residues ranged from 67.3 to 144 µg/kg at this single time-point. Comparison of the data from groups 2 and 3 indicated that administration of the second dose did not affect the depletion profile in edible tissue at withdrawal times around 35 days.

In the second study twenty sheep were injected subcutaneously with ^{3}H –radiolabelled doramectin at a dose level of 300 µg/kg. A further 2 animals served as untreated controls. Groups of 4 sheep (2 male, 2 female) were sacrificed at 14, 35, 42, 49 and 56 days after treatment. At sacrifice the liver, kidneys, the injection site, fat and skeletal muscle were taken. The tissue samples were homogenised and the concentration of doramectin in a single sub-sample was determined using a validated HPLC analytical method (limit of detection 0.5 µg/kg, limit of quantification 2.5 µg/kg).

Highest concentrations of doramectin in liver, kidney, muscle and fat were found at 14 days (mean values were: liver, 38.8 $\pm$ 14.5 µg/kg; kidney, 12.3 $\pm$ 7.4 µg/kg; skeletal muscle, 9.8 $\pm$ 4.6 µg/kg and fat, 62.2 $\pm$ 25.6 µg/kg). At all other time-points doramectin concentrations in liver, kidney and skeletal muscle were at or below the limit of quantification. In fat, residues were below 8 µg/kg at all remaining time-points. Concentrations of doramectin in injection site tissue were very variable and the mean value remained above the MRL at all sacrifice times (629 $\pm$ 829 µg/kg at 14 days, 108 $\pm$ 101 µg/kg at 35 days, 25.5 $\pm$ 42.4 µg/kg at 42 days, 103 $\pm$ 101 µg/kg at 49 days and 112 $\pm$ 106 µg/kg at 56 days).

The third study was a re-analysis of injection site tissue from the second study due to the high variability of the results obtained. Following extensive re-homogenisation of the remaining injection site tissue (38-204 g) four 2.5 g sub-samples were analysed per animal for doramectin determination. Despite the extensive re-homogenisation and increased number of sub-samples the results remained highly variable with mean values exceeding the MRL at all time-points (1866.8 $\pm$ 1725.9 µg/kg at 14 days, 267 $\pm$ 283.1 µg/kg at 35 days, 81.8 $\pm$ 60.1 µg/kg at 42 days, 261.4 $\pm$ 302.6 µg/kg at 49 days and 82.8 $\pm$ 66.4 µg/kg at 56 days).

2.2 Calculation of withdrawal periods

Withdrawal periods were based on statistical calculations of injection site residues relative to the muscle MRL as recommended in the CVMP working paper on injection site residues (III/5933//94-EN). This approach offers the highest degree of consumer protection

For the first study, statistical calculation of the withdrawal period for injection site tissue following intramuscular injection in accordance with EMEA/CVMP/036/95-FINAL gives a period of 70 days (rounded to whole weeks).

Neither the second nor third studies are suitable for the determination of a withdrawal period following subcutaneous administration. A withdrawal period of 182 days was calculated, but in the opinion of the CVMP this approach is not sustainable as there are no actual time point slaughter studies to confirm this prediction and extrapolation from the concentration of residues found in the samples at the injection site to predict an adequate withdrawal period is difficult. A simplified approach to the residues at the injection site is not possible as residues were above the MRL of 20 µg/kg in most of the samples taken at the last period in which the animals were slaughtered (56 days).

3. Conclusions and recommendations

The CVMP working paper on injection site residues (III/5933/94-EN) recommends that the injection site and its residues be treated as “normal” muscle where one of the target tissues is muscle. The withdrawal period should be based on residue depletion to below the MRL at the injection site. Only

where muscle is not a target tissue and hence there is no MRL for muscle should an ADI approach be considered.

The Committee, having considered the matter as set out in the appended Referral Assessment Report, recommends that the withdrawal period for injectable solutions containing doramectin for intramuscular use in ovine species should be 70 days for meat and offal. Although, a lower dose of 200 μg/kg bw is also indicated in a number of Member States as well as the higher dose of 300 μg/kg bw, no residues data was provided for this lower dose. Therefore, the recommendation of a 70-day withdrawal period applies to both doses.

With respect to doramectin administered subcutaneously the studies reviewed did not provide reliable data from which a valid calculation could be made. On the basis of the data that were available, no withdrawal period could be set for the subcutaneous injection of doramectin and references to administration by this route should be removed from the product literature.