ANNEX I

LIST OF NAMES, PHARMACEUTICAL FORM OF THE MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Product invented name	Pharmaceutical form	Animal species	Frequency	Recommended dose	Withdrawal period (meat and milk)
Belgium	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Czech Republic	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC intramam Susp. Ad us. Vet	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Germany	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleissheim	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Estonia	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Greece	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Spain	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
France	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC suspension intramammaire	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Ireland	Intervet Ireland Magna Drive Magna Business Park Citywest Road IE-Dublin 24	Cephaguard DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Italy	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Cyprus	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Latvia	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Lithuania	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days

Member State	Marketing Authorisation Holder	Product invented name	Pharmaceutical form	Animal species	Frequency	Recommended dose	Withdrawal period (meat and milk)
Luxembourg	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Austria	Intervet Gesmbh Siemensstrasse 107 A-1210 Wien	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Poland	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Portugal	Intervet Portugal, Lda. Estrada Nacional 249 PT-2725-397 Mem Martins	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Slovenia	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
Slovakia	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days
United Kingdom	Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan DC	Intramammary ointment	Dairy cows	Single dose	150 mg cefquinome	Meat and offal: 2 days Milk: 49 days

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION OF THE TERMS OF THE MARKETING AUTHORISATION

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION OF THE TERMS OF THE MARKETING AUTHORISATION

1. Introduction and background

Cobactan DC and associated invented names (see Annex I) contains cefquinome, a fourth-generation cephalosporin, indicated for the treatment of subclinical mastitis at drying off and the prevention of new bacterial infections of the udder, during the dry period, in the dairy cows caused by the following sensitive bacteria: *Streptococcus uberis*, *Streptococcus disgalactiae*, *Streptococcus agalactiae*, *Staphylococcus aureus* and coagulase negative staphylococci.

Cobactan DC and associated invented names are approved in several Member States as an intramammary ointment, presented as a pre-filled syringe containing 150 mg of cefquinome (as sulphate).

The Marketing Authorisation Holders (MAHs) submitted a type II variation subject to a mutual recognition procedure in September 2005 (FR/V/148/01/II/02) to reduce the established withdrawal period for milk. The withdrawal period initially established for milk was 49 days after treatment when the dry period was less than 49 days, and 1 day after calving when the dry period was 49 days. The MAHs proposed a reduced withdrawal period of 35 days after treatment.

At the end of the variation procedure the withdrawal period recommended by the Member States involved in the procedure was:

"Milk for human consumption may only be taken after 24 hours post calving with a dry period of more than 49 days. In cows with a dry period of less than 49 days, milk for human consumption may only be taken after 50 days after the last treatment"

The MAHs disagreed with the outcome of the procedure and referred the issue to the EMEA.

The CVMP during its meeting of 19-20 April 2006 initiated a referral procedure under Article 6(13) of Commission Regulation (EC) No 1084/2003 for Cobactan DC containing cefquinome. The scope of the referral was to establish if on the basis of the data available a withdrawal period of 35 days after treatment could be established for milk.

2. Discussion

2.1 Residue depletion in milk

A new residue depletion study in milk was performed with dairy cows with a dry period of 36 days or less and it was submitted to substantiate a reduction of the established withdrawal period for milk requested in the variation procedure. Although the administration of the product to the cows was 28 days before the expected calf delivery, the dry periods varied substantially from 16 to 36 days. The residue depletion study in dairy cows with dry periods of 40 to 58 days on which the withdrawal period was established for the original Marketing Authorisation was also available.

2.2 Derivation of withdrawal periods for milk

Marketing authorisation holders approach

The representative of the MAHs determined the withdrawal period by statistical analysis (Time to safe concentration (TTSC) method) of the milk residue data where time points were expressed as milkings *after treatment* irrespective of the length of the dry period. Also during the dry period two milkings per day were counted although the animals were not milked. The obtained withdrawal period was 69 "milkings" after treatment, i.e. 34.5 days. The MAHs proposed to set the withdrawal period for milk at 35 days after treatment.

In the referral procedure the representative of the MAHs acknowledged that:

- there is a depletion during the dry period,
- there is a more rapid depletion after calving, and
- the withdrawal period in the post-calving milk depends on the length of the dry period.

Two alternatives to express the milk withdrawal period were considered:

1. Withdrawal period after calving

   To express the withdrawal period in milkings post-calving, one has to make several (e.g. 3) categories of dry periods which can be difficult to apply practically. It may also appear illogical in some cases (comparing two withdrawal periods with slightly different dry periods but in different categories). This can be avoided by adding more categories, or even all possible dry period categories. However, this would be impossible to apply in field conditions.

2. Withdrawal period after treatment

   The two phases of depletion in milk (i.e. during the dry period and post-calving) are interlinked and therefore the calculation of the withdrawal period based on the time after treatment can be considered more appropriate because it takes both phases of depletion into consideration. The resulting withdrawal period is valid for all animals, irrespective of the exact length of the dry period.

CVMP considerations

The CVMP Note for Guidance on the determination of the withdrawal periods for milk (EMEA/CVMP/473/98-FINAL) describes how the withdrawal period for milk should be determined for *dry-cow* products. However, the guideline does not explicitly state how the derived withdrawal period should be expressed: as time *after treatment* or as time *after calving*. It is however clear that the dry period should be part of the expression of the withdrawal period. From the text of the guideline it appears most logical to conclude that the withdrawal period should be expressed as time *after calving* for a specified (range of) dry period. Furthermore the guideline on the summary of product characteristics for pharmaceutical veterinary medicinal products included in Volume 6C of the Rules Governing Medicinal Products in the European Union indicates that for dry cow products the withdrawal period for milk is determined by the date of the subsequent calving.

Residue data should be obtained from a sufficient number of animals giving birth within a limited time interval. In the study provided the dry period varied considerably, ranging from 16 to 36 days. The guideline proposes to use the TTSC method on the residue data from animals within a limited span of dry periods, assuming that limited differences in the dry period would have minor influence on the residues.

Due to the fact that (1) there was a wide range of dry periods, and (2) there was a substantial depletion of residues from the quarters of the udders of cows during the dry period, the dry period *does* have a significant influence on the residues at the first milking after calving in this case.

For the reasons mentioned above the approach of the guideline is not valid for the dataset provided in this case. Although individual TTSCs can be calculated, the set of TTSCs does not show a normal or a lognormal distribution. Hence the withdrawal period calculated on the basis of such distributions is largely overestimated in this case.

Using the TTSC method where the TTSCs are expressed as time after treatment is on itself not wrong.

The advantage of the TTSC method is that the shape of the depletion curve is not important. However, because in this case the TTSCs also depend on the dry period (positive trend), the estimation of the distribution is sensitive for the sample of study objects (cows with a certain dry period). The approach of expressing the withdrawal period as time after treatment can only be acceptable if the studied sample from the distribution of dry periods is a fair representation of the true distribution of dry periods in practical circumstances. However, the aim of the study provided was to investigate only

cows with a very short dry period. Therefore the study design was not optimal for this approach. Consequently, the estimated withdrawal period contains some uncertainty caused by the dependency on the length of the dry period. An additional safety span is necessary to account for this uncertainty.

The Committee also considered the study with dry periods between 40 to 59 days. The residues in milk from each cow were below the MRL at the first milking after calving. The Committee concluded that this study should also be considered for the establishment of the withdrawal period. It was not possible to analyse the data from both studies with the available statistical methods. Therefore, the Committee combined the results of both studies by (1) using the withdrawal period of 34.5 days after administration as estimated by the MAH and (2) using the results of the study with longer dry periods to derive a safety span. The safety span of 1.5 days proposed by the representative of the MAHs was accepted. Therefore, the recommended withdrawal period for Cobactan DC is:

- 1 day after calving when dry period is more than 5 weeks;
- 36 days after treatment when dry period is 5 weeks or less.

3. Conclusions

The Committee concluded that the MAHs statistical analysis of the data from the new study was not optimal considering the combination of (1) the dependency of the TTSC's on the length of the dry period, and (2) the selection of cows with very short dry periods in the study. It was therefore considered that a safety span should be included to take into account variation in the data. The initial residue study in dairy cows with dry periods of 40 to 58 days was considered useful to establish the size of that safety span. A safety span of 1.5 days as proposed by the representative of the MAHs was considered acceptable by the CVMP.

Therefore, the Committee, for Medicinal Products for Veterinary Use recommends the variation of the terms of the Marketing Authorisations for Cobactan DC and associated names in order to set a withdrawal period for milk as follows:

- 1 day after calving when dry period is more than 5 weeks;
- 36 days after treatment when dry period is 5 weeks or less.