Annex I

List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, withdrawal periods, applicant, marketing authorisation holder in the member states

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strengths	Animal species	Recommended dose, frequency and route of administration	Withdrawal period (meat and milk)
Ireland	Norbrook Laboratories Limited Station Works, Newry, Co. Down BT35 6JP Northern Ireland	Noroclav Lactating Cow Intramammary Suspension	Intramammary suspension	Amoxicillin 200 mg Clavulanic acid 50 mg Prednisolone 10 mg	Lactating cattle	Intramammary administration to lactating cattle at a dose rate of 3 syringes per affected quarter administered singly at 12 hour intervals	Not established
United Kingdom	Norbrook Laboratories Limited Station Works, Newry, Co. Down BT35 6JP Northern Ireland	Combimox Lactating Cow Intramammary Suspension	Intramammary suspension	Amoxicillin 200 mg Clavulanic acid 50 mg Prednisolone 10 mg	Lactating cattle	Intramammary administration to lactating cattle at a dose rate of 3 syringes per affected quarter administered singly at 12 hour intervals	Meat: 7 days Milk: 60 hours

Annex II

Scientific conclusions and grounds for refusal of the granting of the marketing authorisation(s)

Overall summary of the scientific evaluation of Combimox Lactating Cow Intramammary Suspension

1. Introduction

Combimox Lactating Cow Intramammary Suspension (hereinafter referred to as Combimox) is an intramammary suspension containing amoxicillin (as amoxicillin trihydrate), clavulanic acid (as potassium clavulanate) and prednisolone. Amoxicillin is a semi-synthetic aminopenicillin with broad-spectrum bactericidal activity. Clavulanic acid, a naturally-occurring substance is a beta-lactamase inhibitor and chemical synergist for amoxicillin. Prednisolone is an anti-inflammatory corticosteroid. Combimox is presented in unit-dose syringes as an oily suspension to be administered via the intramammary route. Combimox is intended for the treatment of mastitis in lactating cows caused by the major pathogens commonly occurring from the bovine udder (*Staphylococci*, *Streptococci* and *Escherichia coli*).

Combimox was authorised in the United Kingdom on 9 May 2003 under Article 13(1) of Directive 2001/82/EC. At the time of initial authorisation, the difficulties of attempting to demonstrate bioequivalence of intramammary preparations were less well known and the general principles applied by the applicant in conducting their package of pharmacokinetic studies were accepted.

The application was submitted to the Concerned Member State, Ireland, under the mutual recognition procedure. During the procedure, there was disagreement between the Reference Member State and Concerned Member State on the applicability of demonstrating systemic bioequivalence for a locally-applied, locally-acting product, as well as an additional concern on the adequacy of the proposed withdrawal period. Ireland considered that the authorisation of Combimox may present a potential serious risk to human and animal health since the safety and efficacy of the product had not been sufficiently demonstrated. Consequently the matter was referred to the CVMP

The CVMP was asked to give its opinion on the concerns raised by Ireland and to conclude on the benefit/risk balance for Combimox.

2. Assessment of the data submitted

For applications made under Article 13(1) of Directive 2001/82/EC the applicant is not required to submit results of pharmacological, toxicological and clinical trials. In support of Combimox, studies were submitted to compare milk and plasma pharmacokinetics between the generic and reference products. A tolerance study was presented to evaluate the safety of the product in lactating cows. A user risk assessment and a Phase I environmental risk assessment were also provided.

Three comparative pharmacokinetic studies were carried out with Combimox and the reference product, all with a two-period cross-over design.

- A comparative plasma study was carried out to measure plasma concentrations of amoxicillin, clavulanate and prednisolone following intramammary infusion.
- A comparative milk study was carried out to measure milk concentrations of amoxicillin and clavulanic acid. This study also served to provide data on the residues of amoxicillin and clavulanic measured in the (udder) quarter milk samples obtained at regular timepoints after infusion of Combimox and the reference product.
- A comparative milk study was carried out to measure milk concentrations of prednisolone following intramammary infusion. This study also served to provide data on the residues of this active substance.

The plasma data showed that, overall, the confidence intervals were within the acceptance limits for amoxicillin and prednisolone. No conclusions could be reached for clavulanic acid since levels were mostly below the limit of quantification.

The results of the milk studies demonstrated that the concentrations of the active substances were similar to those of the reference product following the intramammary infusion of Combimox, although it was noted that there was considerable inter-quarter and inter-animal variability in each of the pharmacokinetic parameters measured.

There was discussion by the CVMP on applying the same pharmacokinetic parameters from classical plasma bioequivalence studies to comparative data in milk. The main principle behind bioequivalence is to compare the rate and extent of exposure so sampling cannot be made from the same compartment as administration and excretion. Thus the current bioequivalence guidelines were not intended to apply to intramammary products as it is unclear to what extent a certain kinetic profile in milk correlates to behaviour at the site of action.

When preparing the approach used to investigate similarity in terms of efficacy for Combimox, the applicant had not pursued conducting comparative clinical studies since it was expected that clinical trials would not be sensitive enough to pick up differences between Combimox and the reference product. Furthermore, the applicant contended that milk was not excluded from the CVMP guideline for the conduct of bioequivalence studies (reference in section 5.1 to "other biological fluid"). Consequently the applicant argued that *in vivo* comparative pharmacokinetic data in milk and plasma was an appropriate approach for the investigation of bioequivalence for an intramammary product. The CVMP was unable to conclude positively on this approach.

The applicant further claimed that the formulation of Combimox was sufficiently similar to the reference product to allow a waiver from the need to present *in vivo* data. When asked to further substantiate this claim, the applicant provided comparative data on the physico-chemical characteristics of the product, including viscosity, particle size and dissolution in milk, between Combimox and the reference product. It was concluded that, although Combimox was shown to be similar to the reference product with respect to formulation, particle size and viscosity, this could only be seen as supportive in this case and could not substitute clinical studies to demonstrate efficacy. The dissolution data in particular were inconclusive due to limitations of the study design.

Regarding residues, the data from the comparative milk studies showed that, at the timepoint corresponding to the proposed withdrawal period of 60 hours, all quarter milk samples had concentrations of amoxicillin above the MRL for milk (4 µg/kg) and a proportion of the milk samples contained clavulanic acid at or above the MRL for milk of 200 µg/kg. At the last sampling timepoint (108 hours), half of the quarter milk samples had amoxicillin concentrations above the MRL. All quarter milk samples from 84 hours onwards had clavulanic acid concentrations below the milk MRL. For prednisolone, the data showed that the levels were well below the milk MRL of 6 µg/kg from 24 hours onwards.

As a result of this data showing that the MRL was exceeded at timepoints beyond the withdrawal period, the applicant proposed a new withdrawal period of 120 hours, based on statistical extrapolation of their comparative data in milk. It was concluded that the data set and statistical analyses used to extrapolate the proposed withdrawal period to 120 hours were flawed and did not provide an adequate basis upon which to derive a withdrawal period.

An additional issue reviewed by the CVMP was a change in the formulation of Combimox during development to increase the stability of the product, which was identified as potentially affecting the release of the active substances from the product into the tissue. The applicant presented comparative viscosity data between the 'old' and 'new' formulations of Combimox.

Grounds for refusal of the granting of the marketing authorisation and suspension of the existing marketing authorisation

The CVMP considered that:

- the data submitted in support of this application failed to show that bioequivalence had been demonstrated by appropriate bioavailability studies between the test and reference products;
- the efficacy of Combimox was not confirmed;
- the proposed withdrawal period for Combimox was insufficiently substantiated;
- it is not possible, on the basis of the data submitted in support of this application, to establish a positive benefit-risk balance for this product.

Therefore the CVMP concluded that the particulars submitted in support of the application do not comply with Article 13 of Directive 2001/82/EC and recommended the refusal of granting the Marketing Authorisation in the Concerned Member State and the suspension of the existing Marketing Authorisation in the Reference Member State. The conditions for lifting the suspension are outlined in Annex III.

Annex III

Grounds for the lifting of the suspension of the Marketing Authorisation

Prior to the lifting of the suspension of the marketing authorisation, the national competent authority of the Reference Member State shall ensure that the following conditions are fulfilled by the marketing authorisation holder:

1. Appropriate clinical data should be provided to confirm the efficacy of Combimox Lactating Cow Intramammary Suspension. A design of non-inferiority to the reference product should be considered, with particular attention to assay sensitivity (e.g. a three-arm study with placebo). The dose-limiting pathogen is penicillinase-producing *Staphylococcus aureus*.
2. A residue depletion study in milk should be performed in accordance with the 'Note for guidance for the determination of withdrawal periods for milk' (EMEA/CVMP/473/98-FINAL)