ANNEX I

NAME, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTES OF ADMINISTRATION, AND MARKETING AUTHORISATION HOLDER

Member State	Marketing Authorisation Holder	Applicant	Product invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose
Austria		Intervet Gesmbh Siemensstrasse 107 A-1210 Wien	Cobactan	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Belgium		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Denmark		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan Vet.	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Germany	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleissheim		Cobactan IV 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Greece		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan IV IM 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Spain		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
France		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan IV IM 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)

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Hungary		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan IV 4.5% A.U.V.	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Ireland		Intervet Ireland Magna Drive, Magna Business Park Citywest Road, IE-Dublin 24	Cephaguard IV IM 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Italy		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan 4.5% IV IM	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Luxembourg		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Netherlands		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Poland		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cobactan 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)
Portugal		Intervet Portugal, Lda. Estrada Nacional 249 PT-2725-397 Mem Martins	Cobactan 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)

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United Kingdom		Intervet International B.V. Wim de Körverstraat 35 NL-5831 AN Boxmeer	Cephaguard IV IM 4.5%	Powder and solvent for solution for injection	45 mg/ml	Horse (adult and foal)	Once or twice daily; Intravenous and intramuscular use	1mg cefquinome/kg bw (1 ml reconstituted solution/45 kg bw)

ANNEX II

SCIENTIFIC CONCLUSIONS

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1. Introduction and background

Cobactan IV 4.5%, presented as a powder and solvent for solution for injection, contains 45 mg/ml cefquinome (as sulphate). The product is indicated to treat respiratory diseases in horses caused by *Streptococcus equi* subsp. *zooepidemicus* and severe bacterial infections with a high risk of septicaemia in foals in which *Escherichia coli* is involved.

The Reference Member State for the Mutual Recognition Procedure regarding Cobactan IV 4.5%, Germany, notified the EMEA on 2 March 2006 that the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMD(v)) failed to reach an agreement regarding the product. Pursuant to Article 33(4) of Directive 2001/82/EC, as amended, the matter has been referred to the CVMP.

The reason for this was that the United Kingdom national competent authority, Veterinary Medicines Directorate (VMD) considered that this medicinal product could present a potential serious risk to public health on the following grounds:

- For the starting material 2,3 cyclohexenopyridine, which also occurs as an impurity in the active substance, cefquinome a positive *in vitro* mutagenicity assay has been reported. Despite the fact that there have also been negative results in two *in vivo* micronucleus assays, the positive *in vitro* results are not negated, as both *in vivo* studies involved the assessment of effects in bone marrow cells. It is considered that a negative result in a second *in vivo* study using a different tissue is required before the concerns about this impurity are allayed.

The CVMP during its meeting of 14-16 March 2006 initiated a referral procedure under Article 33(4) of Directive 2001/82/EC, as amended, for Cobactan IV 4.5% containing cefquinome. The questions identified related to the concerns raised regarding the potential mutagenicity of 2,3-cyclohexenopyridine, the starting material and impurity of cefquinome and were submitted to the Marketing Authorisation Holder on 16 March 2006. The response was submitted to the EMEA on 23 March 2006.

2. Discussion

2.1 Considerations of the safety concerns regarding the starting material 2,3-cyclohexenopyridine

Out of the 11 genotoxicity studies available for 2,3-cyclohexenopyridine, either conducted with cefquinome containing the impurity 2,3-cyclohexenopyridine or with 2,3-cyclohexenopyridine on its own one test (chromosome aberration *in vitro*) resulted in a positive response and only at a high 2,3-cyclohexenopyridine concentration whereas the subsequent mammalian *in vivo* micronucleus test resulted in a negative response.

The CVMP concluded that the clastogenic potential *in vitro* was not demonstrated *in vivo*. As the *in vivo* results are most relevant for human exposure, these results “overrule” the results from the *in vitro* tests. Given (1) the high proliferation rate of bone marrow tissue, (2) the intravenous route of administration, and (3) the high doses employed, it is highly unlikely that a second *in vivo* test in another tissue would give a positive result. In conclusion, the CVMP agrees that it was sufficiently demonstrated that 2,3-cyclohexenopyridine has no clastogenic potential *in vivo*, and that further studies are not warranted.

2.2 Data regarding the specification of cefquinome, in particular in relation the impurity 2,3-cyclohexenopyridine.

The specifications of the active ingredient cefquinome sulphate sterile used in the manufacturing of Cobactan IV 4.5% and the specifications at release and at end of shelf-life for the powder of the finished product Cobactan IV 4.5% were provided. Specifications for cefquinome sulfate report a 2,3- cyclohexenopyridine content of $\leq$1%. The specifications at release and at end of shelf-life reports of contents of 2,3- cyclohexenopyridine of $\leq$1% and $\leq$1.5%, respectively.

2.3 Data concerning the mutagenicity and carcinogenicity of cefquinome and its starter material 2,3-cyclohexenopyridine.

Genotoxicity testing was carried out at the impurity concentration of 1% with cefquinome (8 tests) and in addition 3 tests have been carried out with 2,3-cyclohexenopyridine alone.

One positive result on chromosome aberration was reported. In Chinese hamster lung fibroblasts *in vitro*, 2,3-cyclohexenopyridine induced structural chromosomal aberrations at 600-700 µg/ml in a dose-dependent manner when including metabolic activation in the method. In the direct method, 2,3-cyclohexenopyridine induced slight structural chromosomal aberrations at 350 µg/ml with 24 and 48 h treatments.

The positive finding *in vitro* was further investigated in an *in vivo* micronucleus test. In this study 2,3-cyclohexenopyridine was administered in 0.9% NaCl twice intravenously at an interval of 24 h at doses of 7.5, 25, and 75 mg/kg bw to male and female mice. The highest dose corresponded to the maximum tolerated in a dose range finding assay and also caused clear symptoms of toxicity but no lethality in all animals of the main study. An appropriate positive control was used. The result of the test was negative.

The maximum cefquinome concentrations measured in plasma of treated target animals (e.g. 2 µg/ml after a dose of 1 mg/kg bw) compared with the 2,3-cyclohexenopyridine concentrations expected (e.g. 1% of this impurity in cefquinome leading to 0.02 µg 2,3-cyclohexenopyridine/ml plasma) demonstrates that the concentrations of several hundred µg/ml in the positive *in vitro* test by far exceed the concentrations relevant *in vivo*. Also, the 4 *in vivo* genotoxicity tests performed with cefquinome at low and high concentrations of 2,3-cyclohexenopyridine were negative. Therefore it can be concluded that the effect seen *in vitro* is not of biological relevance.

In vivo results are most relevant for human exposure, as these results “overrule” the results from *in vitro* tests. The clastogenic potential *in vitro* was not demonstrated *in vivo*.

3. Conclusions

The specific findings of a clastogenic potential of 2,3- cyclohexenopyridine in one *in vitro* test at high concentrations was not confirmed to be present at the highest intravenous dose tested (2000 mg/kg bw) in the *in vivo* micronucleus test. Taking into account the intrinsic values and limitations of the tests and that only one out of eleven studies has shown positive results, it is concluded that there are no concerns that 2,3-cyclohexenopyridine may present a potential serious risk to public health. Therefore, the Committee considered that no further mutagenicity study is required for the assessment of the substance.