ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE VETERINARY MEDICINAL PRODUCT, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, APPLICANT/ MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	Applicant/ Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration
Austria	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, Suspension zum Eingeben für Ferkel	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Belgium	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, orale suspensie voor biggen	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Bulgaria	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	СЕВАЗУРИЛ 50 мг/мл, суспензия за перорално прилагане при прасета	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Cyprus	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, πόσιμο εναιώρημα για χοιρίδια	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Czech Republic	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, Perorální suspense pro selata	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Denmark	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	Cevazuril 50mg/ml, oral suspension til spædgrise	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Estonia	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE Bristol	CEVAZURIL 50 mg/ml, Suukaudne suspension jaoks põrsad	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.

Member State	Applicant/ Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration
	UK					
France	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, suspension buvable pour porcelets[1]	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Germany	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, Suspension zum Eingeben für Ferkel	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Greece	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, πόσιμο εναιώρημα για χοιρίδια	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Hungary	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, belsőleges szuszpenzió malacoknak	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Ireland	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, oral suspension for piglets	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Italy	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, sospensione orale per suinetti	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Latvia	Ceva Santé Animale Z.I. La Ballastière	CEVAZURIL 50 mg/ml, Suspensija iekšķīgai	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg

[1] Marketing Authorisation granted

Member State	Applicant/ Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration
	33500 Libourne FRANCE	lietošanai dēļ sivēni				toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Lithuania	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, Geriamoji suspensija dėl paršeliai	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Luxembourg	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, suspension buvable pour porcelets[2]	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Malta	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml Suspensjoni orali għal ħnienes	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
The Netherlands	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, orale suspensie voor biggen	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Poland	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, zawiesina doustna dla prosiąt	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Portugal	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, suspensão oral para leitões	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Romania	Ceva Santé Animale Z.I. La Ballastière	CEVAZURIL 50 mg/ml, Suspensie orală pentru	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg

[2] Marketing Authorisation granted

	33500 Libourne FRANCE	purceii				toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Member State	**Applicant/ Marketing Authorisation Holder**	**Invented name**	**Pharmaceutical form**	**Strength**	**Animal species**	**Frequency and route of administration**
Slovakia	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, Perorálna suspenzia pre prasiatka	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
Spain	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, Suspensión Oral para lechones	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.
United Kingdom	Ceva Santé Animale Z.I. La Ballastière 33500 Libourne FRANCE	CEVAZURIL 50 mg/ml, oral suspension for piglets	Oral suspension	50 mg toltrazuril/ml	Piglets	Individual animal treatment. Each piglet to be treated on day 3-5 of life with a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight.

ANNEX II

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CEVAZURIL 50mg/ml oral suspension for piglets

1. Introduction

CEVAZURIL 50 mg/ml oral suspension for piglets is a suspension for oral administration, which contains 50 mg toltrazuril/ml as an active substance. It is indicated for the prevention of clinical signs of coccidiosis in neonatal piglets on farms with a confirmed history of coccidiosis caused by *Isospora sui.* The recommended dose is a single oral dose of 20 mg toltrazuril/kg body weight corresponding to 0.4 ml oral suspension per kg body weight, on day 3-5 of life. The product is a generic of Baycox 5% oral solution.

During the decentralised procedure the disagreement between the Member States was on the adequacy of the data provided for the Phase II Environmental Risk Assessment.

The Applicant initially provided a Phase I evaluation only for the environmental risk assessment of the product concluding that the PEC_{soil} was largely below 100 µg/kg. Some concerned Member States raised potential concerns with the persistence of the main metabolite of toltrazuril, toltrazuril sulphone, and therefore the applicant was required to submit a Phase II.

In response to the questions raised in the decentralised procedure the Applicant referred to the CVMP conclusions reached during the referral procedure under Article 35 of Directive 2001/82/EC regarding veterinary medicinal products containing toltrazuril intended for use in poultry species in relation to environmental risk assessment and argued that:

- The PEC_{soil} was clearly inferior in pigs compared to poultry,
- The rearing and production methods are similar in poultry and pigs,
- The metabolism of toltrazuril was considered as qualitatively similar in poultry and in pigs

Therefore the Applicant considered that the conclusions from the CVMP referral for poultry could be extrapolated to piglets.

This response was accepted by the reference Member State but rejected by some Concerned Member States on the basis that the reference to end point values from published summary of an assessment was not sufficient to substitute environmental risk assessment data. In view of the disagreement the issue was referred to CVMP.

2. Evaluation of the environmental risk assessment

2.1 Assessment of Phase II data provided

The Phase II evaluation performed by the Applicant was based on:

- the conclusions from the referral procedure under Article 35 of Directive 2001/82/EC regarding veterinary medicinal products containing toltrazuril intended for use in poultry species in relation to environmental risk assessment and;
- argumentation for that the predicted environmental concentration (PEC) resulting from the use of the product in pigs is inferior to that, which arises from its use in poultry.

The information provided does not contain details on the design, conduct, analysis and results of the study allowing a full and independent assessment therefore does not allow for a Phase II evaluation according to the legal requirements and relevant guidelines[3] in force.

Furthermore, the scenarios for pig and poultry manure are not necessary comparable as breeding conditions, application and agricultural practises for handling of manure are often very different. It is acknowledged that the main metabolite is probably the same for pigs and poultry for this compound and that the calculations in Phase I of the ERA take 100% of the dose into account (total residue approach) when environmental exposure is calculated. Potential variation in metabolism is therefore of little practical importance in the Phase I calculation of the PEC value.

In summary the CVMP concludes that the information submitted by the Applicant with regard to the Phase II evaluation is insufficient and therefore should a Phase II assessment be required for the evaluation of the product, a marketing authorisation should not be granted.

2.1 Evaluation of Phase I and considerations on the need for a Phase II assessment

In addition to the question whether the provided data was sufficient for a Phase II assessment (see above) the Committee revisited the Phase I submitted with the application in order to reach an opinion on whether the marketing authorisation for the product could be granted or should be refused in accordance with Article 36 of Directive 2001/82/EC.

The Committee considered the Phase I evaluation of the environmental risk assessment from the Applicant for Cevazuril 50 mg/kg for oral use in piglets in order to establish whether the environmental risk assessment of the product could stop at Phase I or whether a Phase II evaluation would be required. This Phase I concludes that the PEC_{soil} for piglets was 12 µg/kg, which is well below the trigger value for a Phase II assessment of 100 µg/kg. Therefore the environmental risk assessment could stop at Phase I, unless there were particular concerns justifying a request for a Phase II evaluation as foreseen in the VICH GL 6.

The VICH GL 6 states that:

> *"Some VMPs that might otherwise stop in Phase I may require additional environmental information to address particular concerns associated with their activity and use. These situations are expected to be the exception rather than the rule and some evidence in support of the concern should be available."*

Some evidence from the public domain indicates that the main metabolite and degradation product in soil of toltrazuril – toltrazuril sulphone – is persistent, phytotoxic and mobile with the potential to leach to groundwater. Therefore, in principle, a Phase II could exceptionally be requested. The CVMP has, however, previously concluded that toltrazuril and toltrazuril sulphone do not pose an unacceptable risk at environmental concentrations exceeding the concentrations predicted as a result of normal use of Cevazuril 50mg/ml oral suspension for piglets. The current evidence is therefore not sufficient to justify a prevalence of particular concern and thereby to request a Phase II evaluation.

The CVMP therefore concluded that the environmental risk assessment of the product can stop at Phase I.

[3] CVMP/VICH GL6: Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I (CVMP/VICH/592/98-FINAL), CVMP/VICH GL38: Environmental impact assessments for veterinary medicinal products (VMPs) - Phase II (CVMP/VICH/790/03-FINAL) and Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005- Rev.1)

GROUNDS FOR RECOMMENDATION OF THE GRANTING OF A MARKETING AUTHORISATION

The CVMP concludes that the information provided by the Applicant does not allow for a Phase II evaluation according to the legal requirements and guidelines in force.

The environmental risk assessment of the product in accordance to the VICH GL 6 (Environmental Impact Assessment for veterinary medicinal products- Phase I, CVMP/VICH/592/98-Final) concluded that the PEC_{soil} for piglets was 12 µg/kg, which is well below the trigger value for a Phase II assessment of 100 µg/kg.

The CVMP considers that on the basis of the current information there is no scientific justification to request a Phase II evaluation and therefore the environmental risk assessment of the product can stop at Phase I.

Having considered the overall data submitted in writing and in the oral explanation the CVMP concluded after consulting with its Environmental Risk Assessment Working Party that the objections raised during the decentralised procedure should not prevent the granting of a Marketing Authorisation.

Therefore, the CVMP recommends the granting of the marketing authorisation for CEVAZURIL 50 mg/ml oral suspension for piglets for which the Summary of Product Characteristics, labeling and package leaflet are set out in Annex III of the CVMP Opinion.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.