ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE VETERINARY MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTE(S) OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Invented name	Marketing Authorisation Holder, Company Name and Address	Animal species	Pharmaceutical form	Strength	Indications
Austria	Baycox 25 mg/ml Lösung zum Eingeben für Hühner und Puten	Bayer Austria Ges.m.b.H Herbststraße 6-10 1160 Wien Austria	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Belgium	Baycox 2,5 % orale oplossing	Bayer SA-NV Health Care Animal Health Louizalaan 143 Avenue Louise 1050 Brussel Belgium	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Bulgaria	Baycox 2,5 % solution	Bayer HealthCare AG 51368 Leverkusen Germany	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Bulgaria	Cevazuril oral solution	Ceva Sante Animale La Balastriere 33501 Libourne Cedex France	Broilers, breeders, pullets and turkeys	Oral solution	25 mg/ml	Prevention and treatment of coccidiosis
Cyprus	Baycox 2,5 % oral solution	Bayer HealthCare AG 51368 Leverkusen Germany	Broilers and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Czech Republic	Baycox 2.5 % sol. ad us. vet.	Bayer s.r.o. Litvinovska 609/3 190 21 Praha 9 Czech Republic	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
France	Baycox 2,5 %	BAYER SANTE 13 rue Jean Jaures 92807 PUTEAUX France	Chickens: broilers, pullets and breeders	Oral solution	25 mg/ml	Prevention and treatment of coccidiosis

Member State	Invented name	Marketing Authorisation Holder, Company Name and Address	Animal species	Pharmaceutical form	Strength	Indications
France	CEVAZURIL	Ceva Sante Animale La Balastriere 33501 Libourne Cedex France	Chickens: broilers, pullets and breeders	Oral solution	25 mg/ml	Prevention and treatment of coccidiosis
Germany	Baycox 2.5 %	Bayer Vital GmbH 51368 Leverkusen Germany	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Greece	Baycox 2,5 % oral solution	Bayer HealthCare AG 51368 Leverkusen Germany	Broilers and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Hungary	Baycox 2.5 % solution A.U.V.	Bayer Hungaria Kft.Co. LTD. Alkotás u.50 1123 Budapest Hungary	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Ireland	Baycox 2.5 % Solution	Bayer Ltd Animal Health Division The Atrium Blackthorn Road Dublin 18 Ireland	Chickens	Oral solution	25 mg/ml	Treatment and control of coccidiosis
Italy	Baycox soluzione 2.5%	Bayer S.p.A. Viale Certosa, 130 20156 Milano Italia	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Italy	Cevazuril[1]	CEVA VETEM S.p.A. Via Colleoni, 15 Agrate Brianza Italia	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis

[1] The marketing authorisation is suspended on 12 June 2007

Member State	Invented name	Marketing Authorisation Holder, Company Name and Address	Animal species	Pharmaceutical form	Strength	Indications
Poland	Baycox 2,5 %	Bayer HealthCare AG 51368 Leverkusen Germany	Broilers, breeders, turkeys and pigeons	Oral solution	25 mg/ml	Chickens and turkeys: treatment of coccidiosis Pigeons: Treatment and prevention of coccidiosis
Portugal	Baycox 2,5 % oral solution	Bayer Portugal S.A Rua Da Quinta do Pinheiro, N.º 5 2794-003 Carnaxide Portugal	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Romania	Cevazuril	Ceva Sante Animale La Balastriere 33501 Libourne Cedex France	Broilers, breeders, pullets and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Slovakia	Baycox 2.5 % sol. a.u.v.	Bayer s.r.o. Litvinovska 609/3 190 21 Praha 9 Czech Republic	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
Slovenia	Baycox 2,5 % w/v oral solution	Bayer d.o.o., Bravničarjeva 13, 1000 Ljubljana Slovenia	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis

Member State	Invented name	Marketing Authorisation Holder, Company Name and Address	Animal species	Pharmaceutical form	Strength	Indications
The Netherlands	Baycox 2.5 %	Bayer BV HealthCare Animal Health Postbus 80 3640 AB Mijdrecht Energieweg 1 3641 RT MIJDRECHT The Netherlands	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
The Netherlands	Baycox oplossing 2.5%	Bayer BV HealthCare Animal Health Postbus 80 3640 AB Mijdrecht Energieweg 1 3641 RT MIJDRECHT The Netherlands	Chickens and turkeys	Oral solution	25 mg/ml	Treatment of coccidiosis
United Kingdom	Baycox 2.5 % Oral Solution	Bayer Plc Animal Health Division Bayer House Strawberry Hill Newbury Berkshire RG14 1JA United Kingdom	Broilers and broiler breeders	Oral solution	25 mg/ml	Treatment of coccidiosis

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

SCIENTIFIC CONCLUSIONS

1. Introduction and background

Toltrazuril is administered orally in the drinking water for the treatment of coccidiosis. In practice this means that in intensive systems all the birds in one house will be treated even though not all are exhibiting signs of disease. In some Member States (Bulgaria, France and Romania) indications include the prevention of coccidiosis. In Ireland indications include the control of coccidiosis. The dose and duration of treatment in all Member States for chickens and turkeys is 7 mg/kg bodyweight per day for two consecutive days. However, in some Member States (Czech Republic, Hungary, Italy, The Netherlands, Portugal and the United Kingdom) administration can be repeated after five days in the face of severe challenge. In Poland the product is authorised in pigeons for treatment and prevention of coccidiosis at a dose of 20 mg/kg bodyweight per day for three consecutive days.

1.1 Concerns raised by Germany

Germany considered that the authorisation of Baycox 2.5 % solution may present a potential serious risk to the environment on the following grounds:

Non-acceptable risk to higher plants

There is evidence of a non-acceptable risk for plants when manure obtained from Baycox 2.5 % treated poultry are applied to agricultural land.

Contamination of groundwater with organohalogens, list I of the European Directive 80/68/EEC

Toltrazuril sulfone (Ponazuril) the major metabolite of toltrazuril, may reach groundwater after spreading of Baycox 2.5 % contaminated poultry manure on agricultural land ($PEC_{groundwater}$ >0.1 µg/l). Toltrazuril and its major metabolite toltrazuril sulfone are organohalogens, included in list I of the European Groundwater Directive 80/68/EEC. List I substances must be prevented from entering to groundwater.

Questions to the CVMP:

1) Is it a serious risk for the environment if one trophic level of the terrestrial ecosystem, i.e. plants, is affected by the use of Baycox 2.5 %? If so, which are the appropriate risk mitigation measures to reduce the risk to the environment to an acceptable level?

2) Is it acceptable that the active ingredient of Baycox 2.5 %, toltrazuril, may enter groundwater after application to target animals although the active substance is listed in the EU Groundwater Directive 80/68/EEC?

1.2 Information made available to the CVMP

Responses to the CVMP list of questions containing the three points considered by the CVMP (as listed in the opinion) were received from Bayer HealthCare AH (Baycox) and Ceva Santé Animale (Cevazuril). The data submitted by the Marketing Authorisation Holders was only for chickens and turkeys.

2. Critical evaluation

The products under consideration contain the active substance toltrazuril and are indicated for use in poultry for the treatment of coccidiosis. The group of products was referred to CVMP as it was considered that there was the potential for unacceptable risks to terrestrial plants and to groundwater.

In both chickens and turkeys, toltrazuril is administered orally in the drinking water at a dose of 7 mg/kg bodyweight per day for two consecutive days. In some Member States this administration can be repeated after five days in the face of severe challenge. The information provided stressed the importance of the product for use in cases where coccidiostats and vaccination had failed, given the limited availability of other treatments (amprolium, sulphonamides) and the need to rotate these treatments in order to avoid/postpone the development of resistance. It was also indicated that in practice repeat treatment with the product is never used as it is unnecessary.

In chickens the product is used in broilers and pullets destined to become laying birds. Broilers are treated after 14 days of age and usually no earlier than 18-19 days due to the epidemiology of the disease. Because of the length of the withdrawal period, in some countries broilers are treated rarely. In pullets the product can be used after two weeks of age and before the animals come into lay. The use of the product in both types of chicken is infrequent as coccidiosis is mainly controlled by good hygiene and coccidiostats or vaccines. In turkeys the product is used in animals of 5-6 weeks of age.

In summary the pattern of use is of a product which is not routinely used in either chickens or turkeys, but is used in the face of an outbreak of coccidiosis.

The main use is in pullets with broilers being treated rarely. It is highly unlikely that in normal use more than one or two cycles of broilers would be treated in any one year. In the estimation of exposure the information provided indicates that it is not necessary to calculate a plateau concentration for toltrazuril sulfone as this will not be attained in practice.

Information provided on the way chicken litter is processed and handled in practice indicates that houses are cleaned after the crop of birds has been removed. Litter from the house may be spread onto land as organic manure, but it is very rarely spread onto grassland because of the possibility of the ammonia ‘burning’ the grass and the possibility that grazing animals will pick up disease organisms from the litter. Manure from chicken farms is also collected for transport and sale, in which case manure from treated birds is likely to be mixed with litter from untreated birds. Broiler chicken litter is also taken for incineration to produce power (about 40 % in The Netherlands). This information further reduces the chances of litter from treated birds being repeatedly spread onto the same land year after year.

2.1 Risk to terrestrial plants

After administration of toltrazuril to the target animal the dose is excreted as a mixture of parent compound and a major metabolite toltrazuril sulfone. In the soil toltrazuril is rapidly degraded (DT_{50} 7.5 days) to toltrazuril sulfone.

Toltrazuril sulfone has been shown to be very persistent in soil (DT_{50} 472 days), however it should be noted that there is a high degree of variability in the data (range 87-3285 days) which creates some uncertainty when estimating plateau values. Toltrazuril sulfone is slightly mobile in soil (mean K_{oc} 616.5). It has been shown to be toxic to terrestrial plants with greater effects on plant growth compared with plant emergence. The PNEC for growth effects on terrestrial plants is 45 µg/kg determined from the NOEC of 0.45 mg/kg for *P. trivialis* and an assessment factor of 10. In this evaluation a considerable number of plant species have been tested and it has been possible to use a sensitivity distribution to calculate an HC_5 of 150 µg/kg (the HC_5 is the hazardous concentration below which 95 % of plant species will not be affected).

When toltrazuril products for poultry are used as intended, the properties of toltrazuril sulfone suggest that there may be a potential for adverse effects being manifest in terrestrial plants when manure from treated birds is spread onto land and a potential for the compound to leach into groundwater at concentrations which may present an unacceptable risk for the environment.

The exposure of soil to toltrazuril sulfone has been determined using acceptable equations. The input parameters were those agreed in the CVMP guideline (Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005)) with the exception of bodyweight, which for broilers and turkeys was age specific, and nitrogen production per place per year, which for broilers (0.34 kg N/place/year) and turkeys (1.23 kg N/place/year) was higher than the value in the guideline as it was agreed that birds with coccidiosis would have a lower feed conversion efficiency and excrete more nitrogen than healthy birds. This approach is justified and accepted by the CVMP.

In order to assess the risk for plants the $PEC_{soil\ initial}$ for both grassland and arable land was compared with the PNEC for plants of 45 µg/kg. Only for broilers treated for 9 cycles per year and only when litter is spread on grassland could there be an unacceptable risk for plants (Risk Quotient (RQ) value >1). For broiler breeders, pullets and turkeys the RQ was <1 in all cases.

Target group	**Cycles per year**	**$PEC_{soil\ initial}$ (µg/kg)**		**RQ value**		**Application rate (g/ha)**
		Grass	Arable	Grass	Arable	
Broilers 21d (0.95 kg)	9	86	22	1.9	0.5	64.5
Broilers 28d (1.3 kg)		117	29	2.6	0.7	87.8
Broiler breeders	1	8.4	2.1	0.2	0.05	6.3
Pullets	2.6	30	7.5	0.7	0.17	22.5
Turkeys 6 weeks (2.75 kg)	2.7	21	5.3	0.5	0.13	15.8

However, as can be seen from the PEC values in the above table there is not an unacceptable risk for 95 % of plant species when the PECs are compared with the HC_5 value of 150 µg/kg. Comparison of the data for plants with the $PEC_{soil\ initial}$ value is considered to be justified on the basis of the information provided on the use of the product. It is highly unlikely that litter from a house of treated birds will be repeatedly spread onto the same area of land year after year for the following reasons:

- treatment is limited to treatment of outbreaks of coccidiosis;
- litter is likely to be diluted, because much of it is collected and sold for use off the farm.
- in many broiler production facilities there are only 6-7 cycles per year

It should also be noted that if, for example, broiler litter was spread onto land once every three years the $PEC_{soil\text{-}initial}$ value would increase by 25 % (maximum 146 µg/kg) meaning RQ values remain below 1 compared with the HC_5.

It was therefore concluded that the marketing authorisations can be maintained without special warnings in point 5.3 (Environmental properties) of the SPC provided the product is used as indicated by the Marketing Authorisation Holders in their responses to questions by the Committee, i.e. a dose of 7 mg/kg bw on two consecutive days for the treatment of coccidiosis in chickens and turkeys. However, there are changes required to the SPCs of some of the authorised products to bring them in line with the indications and dosing regimens used in the environmental risk assessment.

2.2 Risk to groundwater

Concerning the potential entry of toltrazuril sulfone into groundwater the following points extracted from the Groundwater Directive 80/68/EEC are considered pertinent:

- the purpose of the Directive is to prevent the pollution of groundwater by substances belonging to the families and groups of substances in lists I or II,
- "indirect discharge" means the introduction into groundwater of substances in lists I or II after percolation through the ground or subsoil (this is the route of exposure to toltrazuril sulfone),
- pollution of groundwater is considered any entry of a substance into groundwater which will endanger human health or water supplies, harm living resources and the aquatic ecosystem or interfere with other legitimate uses of water,
- Member States shall take the necessary steps to prevent the introduction into groundwater of substances in list I,
- the Directive does not apply to discharges which are found by the competent authority of the Member State concerned to contain substances in lists I or II in a quantity and concentration so small as to obviate any present or future danger of deterioration in the quality of the receiving groundwater.

Following the introduction of the Water Framework Directive (2000/60/EC) the Groundwater Directive (80/68/EEC) will be repealed by 2013. It will be replaced by Directive (2006/118/EC) which will come into force before 2013. In essence the provisions of Directive 80/68/EEC are now covered by the Water Framework Directive and the new Groundwater Directive and are essentially unchanged.

The most important element in relation to the environmental risk assessment of Directive 2001/82/EC is that the risk for the environment should be identified and mitigated (if necessary and possible), and the marketing authorisation should be based on a benefit/risk evaluation (including environmental risks).

The trigger value of 0.1 µg/l that is used in some assessment frameworks as a surrogate zero for pollutants in groundwater is not mentioned in the Groundwater Directive (80/68/EEC) and is specific for pesticides and biocides in the replacement Groundwater Directive.

According to the ground water directive any decision to prevent substances from entering the groundwater is to be based on an exposure based risk assessment.

Based on the highest application rate of toltrazuril sulfone to soil of 87.8 g/ha the $PEC_{groundwater}$ has been calculated using the FOCUS PEARL (v3.3) model. All parameters in the model were in line with those considered acceptable in the CVMP guideline (Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005)). The model used a sensitive scenario for groundwater and assumed a worst case scenario of annual application of litter from treated birds to the soil. The $PEC_{groundwater}$ for this sensitive scenario was 1.1 µg/l. Toltrazuril sulfone has a low toxicity to aquatic organisms with the lowest relevant PNEC being 24 µg/l (Daphnia). Comparison of the PEC and PNEC indicates that the risk to any biota in groundwater is acceptable.

Groundwater is also used as a source of drinking water. To assess the risk to human health consideration was given to the consumer safety evaluation with regards to residues of toltrazuril in food products of animal origin. The ADI established for toltrazuril is 2 µg/kg bodyweight, i.e. 120 µg/person. Based on a consumption of 2 l of drinking water per person per day the concentration of toltrazuril sulfone potentially present in groundwater would use up 1.8 % of the ADI. This proportion is compatible with the theoretical maximum daily intake of toltrazuril sulfone in other foodstuffs, as calculated when establishing MRLs for toltrazuril.

It is concluded from the above evaluation that the marketing authorisations can be maintained without special warnings in point 5.3 (Environmental properties) of the SPC provided the product is used as indicated by the Marketing Authorisation Holders in their responses to questions by the Committee, i.e. a dose of 7 mg/kg bw on two consecutive days for the treatment of coccidiosis in chickens and turkeys. However, as no data were provided for use in other avian species apart from chickens and turkeys, or for the administration of repeated treatment or for preventive treatment, all the calculations were based on use of the products for a single course of treatment in chickens and turkeys. It should be noted that a second course of treatment is not considered necessary as reported by Marketing Authorisation Holders. The indication for prevention and control of coccidiosis and mention of repeated treatment should be removed from those SPCs which currently include it. The dose recommended for pigeons (20 mg/kg for 3 days) is about 4 times higher than the dose recommended for chickens and turkeys (7 mg/kg bw for 2 consecutive days). As no data generated from use in pigeons was provided for the environmental risk assessment it was not possible to conclude on the risk for the environment taking into account the higher dose for pigeons.

3. Conclusions and recommendations

The CVMP having considered the data provided and the scientific discussion within the Committee concluded that after administration of products containing toltrazuril to the target animal the dose is excreted as a mixture of parent compound and a major metabolite toltrazuril sulfone. In the soil toltrazuril is rapidly degraded (DT_{50} 7.5 days) to toltrazuril sulfone. For these reasons the focus of the risk assessment is on toltrazuril sulfone.

For the exposure assessment the equations according to the CVMP guideline (Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005)) were used with modified parameters to reflect the actual use of toltrazuril.

The assessment of the risk presented by toltrazuril sulfone to terrestrial plants and to groundwater demonstrated that the use of products containing toltrazuril is acceptable and the marketing authorisations can be maintained without special warnings in point 5.3 (Environmental properties) of the SPC provided the product is used as indicated by the Marketing Authorisation Holders in their responses to questions by the Committee, i.e. a dose of 7 mg/kg bw on two consecutive days for the treatment of coccidiosis in chickens and turkeys. However, it was noted that the indications, species and posology in the SPCs of some of the authorised products were different and these therefore need to be amended to bring them in line with the indications and dosing regimens used in the environmental risk assessment.

Therefore the Committee recommends maintaining the Marketing Authorisations for all veterinary medicinal products as referred to in Annex I and to vary the Marketing Authorisations in order to harmonise the indications and dosing regimens as described in the paragraph above. This procedure will involve removing the following recommendations and indications for which no data were provided:

- repeat treatment can be administered after 5 days if infection is severe;
- prevention and control of coccidiosis;
- use in pigeons.

ANNEX III

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS

Amendments to be included in the relevant sections of the SPC:

4. CLINICAL PARTICULARS

Delete, where applicable, prevention and control of coccidiosis.

Delete, where applicable, repeated treatment.

Delete, where applicable, pigeons.