Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, applicants / marketing authorisation holders in the Member States

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
Austria	Intervet GmbH Siemensstraße 107 AT-1210 Wien AUSTRIA	Hexadreson 2 mg/ml Injektionslösung für Pferde, Rinder, Schweine, Hunde	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Austria	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml Injektionslösung für Pferde, Rinder, Schweine, Katzen und Hunde	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Belgium	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	RAPIDEXON 2 MG/ML SOLUTION INJECTABLE	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Belgium	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	DEXA-JECT 2 MG/ML oplossing voor injectie voor runderen, paarden, varkens, honden en katten	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Cyprus	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	DEXADRESON INJECTION 2MG/ML	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Czech republic	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Dexadreson, 2 mg/ml Injekční roztok	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Czech republic	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	RAPIDEXON 2 mg/ml injekční roztok	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
Denmark	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Dexadreson Vet	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses
Denmark	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexaject	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Denmark	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Finland	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon vet	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
France	Intervet Rue Olivier De Serres Angers Technopole 49071 Beaucouze Cedex FRANCE	Dexadreson	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, goat, pigs, dogs and cats.
France	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml solution injectable	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
France	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Cortadex 2 mg/ml solution injectable pour bovins, porcins, chiens et chats	Dexamethasone	2 mg/ml	Solution for injection	Cattle, pigs, dogs and cats

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
France	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml solution injectable pour bovins, chevaux, porcins, chiens et chats	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Germany	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleißheim GERMANY	Hexadreson	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Germany	Albrecht GmbH Hauptstr. 6-8 88326 Aulendorf GERMANY	Rapidexon Albrecht 2 mg/ml	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Germany	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Greece	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	DEXADRESON	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Greece	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	RAPIDEXON	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Hungary	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Dexadreson injekció A.U.V.	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
Hungary	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml injekció szarvasmarhák, lovak, sertések, kutyák és macskák részére A.U.V.	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Hungary	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml injekció A.U.V.	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Iceland	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexaject	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Ireland	Intervet Ireland Ltd. Magna Drive, Magna Business Park Citywest Road Dublin 24 IRELAND	Dexadresson 2 mg/ml solution for injection	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Ireland	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml solution for injection	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Ireland	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml solution for injection for cattle, horses, pigs, dogs and cats	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Italy	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Dexadreson	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, goat, pigs, dogs and cats.

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
Latvia	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Dexacortin	Dexamethasone	2 mg/ml	Solution for injection	Cattle, pigs, dogs and cats
Lithuania	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	DEXACORTIN 2 mg/ml solution for injection for cattle, swine, dogs and cats	Dexamethasone	2 mg/ml	Solution for injection	Cattle, pigs, dogs and cats
Lithuania	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	RAPIDEXON 2 mg/ml, solution for injection	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Lithuania	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	DEXA-JECT 2 mg/ml solution for injection for cattle, horse, pigs, dogs and cats	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
The Netherlands	Intervet Nederland B.V. p.o. box 50 5830 AB Boxmeer THE NETHERLANDS	Dexadreson	Dexamethasone	2 mg/ml	Solution for injection	Cattle
The Netherlands	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon	Dexamethasone	2 mg/ml	Solution for injection	Cattle
The Netherlands	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
The Netherlands	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Norway	Intervet AB Box 7121 192 07 Sollentuna SWEDEN	Dexadreson vet.	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Poland	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	DEXACORTIN 2 mg/ml roztwór do wstrzykiwań dla bydła, świń, psów i kotów	Dexamethasone	2 mg/ml	Solution for injection	Cattle, pigs, dogs and cats.
Poland	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	RAPIDEXON 2 mg/ml roztwór do wstrzykiwań	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Poland	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml roztwór do wstrzykiwań dla bydła, koni, świń, psów i kotów	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Portugal	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml, solução injectável	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Portugal	Intervet Portugal – Saúde Animal, Lda Rua Agualva dos Açores n.º 16 2735-557 Agualva-Cacém, PORTUGAL	Dexacortin 2 mg/ml solução injectável para bovinos, suínos, cães e gatos	Dexamethasone	2 mg/ml	Solution for injection	Cattle, pigs, dogs and cats

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
Romania	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	DEXADRESON	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, goat, pigs, dogs and cats
Slovakia	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	Dexadreson 2 mg/ml injekčný roztok	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Slovakia	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml injekčný roztok	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Slovenia	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	RAPIDEXON 2 mg/ml raztopina za injiciranje	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Slovenia	Intervet International B.V. Wim de Körverstraat 35 5831, AN Boxmeer THE NETHERLANDS	DEXACORTIN 2 mg/ml, raztopina za injiciranje za govedo, prašiče, pse in mačke	Dexamethasone	2 mg/ml	Solution for injection	Cattle, pigs, dogs and cats
Spain	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml solución inyectable	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Spain	S.P. Veterinaria, S.A. Ctra. Reus-Vinyols, Km 4,1 43330 Riudoms, Tarragona SPAIN	Dexavex	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species
Spain	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
Sweden	Intervet AB Box 7121 192 07 Sollentuna SWEDEN	Dexadreson vet.	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
United Kingdom	Intervet UK Ltd Walton Manor, Walton Milton Keynes MK7 7AJ UNITED KINGDOM	Dexadreson 2 mg/ml Solution for Injection	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
United Kingdom	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer THE NETHERLANDS	Dexa-ject 2 mg/ml Solution for Injection for Cattle, Horses, Pigs, Dogs and Cats	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats
United Kingdom	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel THE NETHERLANDS	Rapidexon 2 mg/ml Solution for Injection	Dexamethasone	2 mg/ml	Solution for injection	Cattle, horses, pigs, dogs and cats

Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Overall summary of the scientific evaluation of Dexadreson 2 mg/ml and associated names, and generic products thereof *(see Annex I)*

1. Introduction

The veterinary medicinal products Dexadreson 2 mg/ml and its associated names and generic products are solutions for injection which contain 2 mg dexamethasone per ml. Dexamethasone is a long acting synthetic glucocorticoid used as anti-inflammatory, anti-allergic and gluconeogenetic agent for administration to agricultural and domestic animals.

Germany noted that Dexadreson 2 mg/ml and its associated names has different withdrawal periods in cattle (meat and milk) and horses (meat) established by the Member States across the EU/EEA. Consequently Germany considered that it is in the interest of consumer safety to evaluate the adequacy of the meat withdrawal periods in cattle and horses and the milk withdrawal periods in cattle.

Therefore, on 22 August 2012, Germany presented to the Agency a referral notification under Article 35 of Directive 2001/82/EC for Dexadreson 2 mg/ml and associated names, and generic products thereof.

2. Discussion

Cattle

Three residue depletion studies in cattle have been provided, two studies on residue depletion in cattle tissues and one study on residue depletion in milk. All studies were conducted at a single dose of 0.06 mg/kg body weight. According to the current product information for Dexadreson, treatment may be repeated after 24-48 hours. Therefore, none of the studies was conducted at the maximum intended dose as requested in VICH GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods (EMA/CVMP/VICH/463199/2009)[1] and safe withdrawal periods in cattle tissues and milk can only be set for single treatment. In the absence of residue depletion data at the maximum intended dose and further to the concerns expressed above, the marketing authorisation holders agreed to remove the advice on repeat dose treatment after 24-48 hours in cattle from the product information.

Kidney and liver were the tissues where the marker residue persisted longest. One of the studies on residue depletion in cattle tissues was not conducted over a sufficiently long period of time and was therefore not considered suitable to derive a valid withdrawal periods in cattle meat and offal. The other study was considered valid, however, the data set obtained from it did not allow the use of the statistical approach for the determination of withdrawal periods in accordance with the CVMP note for guidance: approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95)[2] as statistical criteria for the linear regression analysis were not fulfilled.

Therefore it was considered appropriate to use the alternative method in order to establish a withdrawal period for cattle tissues. Six days after administration the residue concentrations were

[1] VICH GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods (EMA/CVMP/VICH/463199/2009) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105052.pdf
[2] CVMP note for guidance: approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004428.pdf

below the MRL values in kidney and liver. Due to shortcomings in the design of the study, a maximum safety span of 30% was considered necessary, leading to a withdrawal period of 8 days for the single dose treatment at 0.06 mg dexamethasone per kg body weight.

The residue depletion study in milk was considered acceptable, but the recommended method for the calculation of a milk withdrawal period according to the CVMP note for guidance for the determination of withdrawal periods in milk (EMEA/CVMP/473/98)[3] – the Time to safe concentration (TTSC) method – cannot be used due to the insufficient number of animals included in the study. Therefore a 20% safety span was applied to the observed period of 60 hours, resulting in a withdrawal period of 72 hours, i.e. 3 days, in milk from cows treated at a single dose of 0.06 mg dexamethasone per kg body weight.

Horses

No residue depletion data are available in horses for the single or repeat dose treatment. Withdrawal periods for the minor species horse can be based on comparison of pharmacokinetic data, indicating that depletion of the substance in horses is not slower than in cattle. The same withdrawal period for edible tissues may be applied for cattle and horses for the same dosing regimen, resulting in a withdrawal period for horse meat and offal of 8 days for the single dose treatment of 0.06 mg dexamethasone per kg body weight. The marketing authorisation holders agreed to remove the advice on repeat dose treatment in horses from the product information.

No residue depletion or pharmacokinetic data are available for the much higher dosages recommended for the treatment of shock in horses. No safe withdrawal period for these dosages can be set and the CVMP considered that the shock indication should be withdrawn from the product information of Dexadreson and its generic products, where applicable.

3. Benefit-Risk Assessment

Residue depletion data was made available and supported a cattle meat and offal withdrawal period of 8 days and a cattle milk withdrawal period of 72 hours, as well as a horse meat and offal withdrawal period of 8 days following a single injection at the recommended dose of 0.06 mg dexamethasone per kg body weight.

As there were no residue depletion data with the recommended repeat dose treatment in cattle and horses, the CVMP concluded that the advice on repeat dose treatment in cattle and horses should be removed from the product information. Further to this restriction the CVMP concluded that the single administration of the concerned products does not have an impact on their clinical efficacy.

As there were no data available to support safe withdrawal periods for horse meat and offal following administration of high dosages in case of treatment of shock, the CVMP concluded that the shock indication in horses should be removed from the product information for Dexadreson and its generic products, where applicable.

Assessment of the efficacy of the products for the other approved indications remains unchanged.

Quality, target animals safety, user safety and environmental risk have not been assessed in this referral procedure.

Conclusions on the benefit-risk balance

The benefit-risk balance for the products concerned remains positive subject to amendments in the product information.

[3] CVMP note for guidance for the determination of withdrawal periods in milk (EMEA/CVMP/473/98) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004496.pdf

Grounds for amendment of the summary of product characteristics, labelling and package leaflets

Whereas:

- On the basis of the residue depletion data in cattle and the pharmacokinetic data in horses submitted by the marketing authorisation holders for Dexadreson 2 mg/ml and associated names, and generic products thereof, the CVMP considered that withdrawal periods of 8 days for cattle meat and offal, 72 hours for cattle milk and 8 days for horse meat and offal were safe;
- In the absence of residue depletion or pharmacokinetic data following a repeat treatment in cattle and horses for Dexadreson 2 mg/ml and associated names, and generic products thereof, the CVMP considered that the advice on repeat dose treatment after 24-48 hours in cattle and horses should be removed from the product information;
- In the absence of residue depletion or pharmacokinetic data for the higher dosages recommended for the indication concerning treatment of shock in horses, no safe withdrawal period for these dosages can be set for Dexadreson 2 mg/ml and associated names, and generic products thereof. Therefore the CVMP considered that the indication for treatment of shock in horses should be removed from the product information;
- the CVMP considered that the overall benefit-risk balance is positive for Dexadreson 2 mg/ml and associated names, and generic products thereof subject to amendments in the product information;

the CVMP has recommended variations of the marketing authorisations for Dexadreson 2 mg/ml and associated names, and generic products thereof (see annex I) in order to amend the summaries of product characteristics, labelling and package leaflets in line with recommended changes in the product information as set out in annex III.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

Summary of Product Characteristics

4.2 Indications for use, specifying the target species

……

Delete, where applicable, “in cases of shock in horses”.

……

4.9 Amounts to be administered and administration route

……

Delete, where applicable, all references for repeat treatment in cattle and horses and treatment in cases of shock in horses.

……

4.11 Withdrawal period(s)

……

Cattle:

Meat and offal: 8 days

Milk: 72 hours

Horses:

Meat and offal: 8 days

Not authorised for use in horses producing milk for human consumption.

……

Labelling:

8. WITHDRAWAL PERIOD

……

Cattle:

Meat and offal: 8 days

Milk: 72 hours

Horses:

Meat and offal: 8 days

Not authorised for use in horses producing milk for human consumption.

……

Package leaflet:

4. INDICATIONS

……

Delete, where applicable, “in cases of shock in horses”.

……

8. DOSAGES FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

……

Delete, where applicable, all references for repeat treatment in cattle and horses and treatment in cases of shock in horses.

……

10. WITHDRAWAL PERIOD

……

Cattle:

Meat and offal: 8 days

Milk: 72 hours

Horses:

Meat and offal: 8 days

Not authorised for use in horses producing milk for human consumption.

……