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Committee for Medicinal Products for Veterinary Use

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for DRAXXIN (EMEA/V/C/000077/II/0034)

International non-proprietary name: Tulathromycin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 19 December 2014 an application for a type II variation for DRAXXIN.

1.2. Scope of the variation

To change the withdrawal periods for cattle and pigs affecting all registered DRAXXIN presentations (EU/2/03/041/001-008), following the revision of MRLs for tulathromycin.

Current	**Proposed**
SPC (section 4.11 Withdrawal period(s)); Annex III. A – Labelling (Section 8. Withdrawal period (section 5. for small immediate packaging)); Annex III. B - Package leaflet (Section 10. Withdrawal period)	SPC (section 4.11 Withdrawal period(s)); Annex III. A – Labelling (Section 8. Withdrawal period (section 5. for small immediate packaging)); Annex III. B - Package leaflet (Section 10. Withdrawal period)
DRAXXIN 100 mg/ml solution for injection for cattle and pigs	DRAXXIN 100 mg/ml solution for injection for cattle and pigs
Cattle (meat and offal): 49 days.	Cattle (meat and offal): 22 days.
Pigs (meat and offal): 33 days.	Pigs (meat and offal): 13 days.
DRAXXIN 25 mg/ml solution for injection for pigs	DRAXXIN 25 mg/ml solution for injection for pigs
Meat and offal: 33 days.	Meat and offal: 13 days.

2. Scientific discussion

2.1. Assessment

On 10 July 2014, the CVMP adopted an opinion recommending final maximum residue limits (MRLs) for tulathromycin in bovine and porcine species further to an application for the modification of MRLs and a recommendation of provisional MRLs. The recommendation for provisional MRLs was adopted by the European Commission on 19 December 2014 and the recommendation for final MRLs was adopted on 10 March 2015. Table 1 of the Annex to Commission Regulation (EU) No. 37/2010 was amended to include the following entry for tulathromycin in bovine and porcine species:

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Tulathromycin	(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one expressed as tulathromycin equivalents	Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Anti-infectious agents/ Antibiotics
		Porcine	800 µg/kg 300 µg/kg 4000 µg/kg 8000 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney		

An injection site residue reference value (ISRRV) of 6000 µg/kg, applicable to both cattle and pigs has been established and must be taken into account when establishing appropriate withdrawal times.

Based on the revised MRLs and data from the cattle and pig residue studies, the applicant presented re-calculations of withdrawal periods for porcine and bovine tissues.

Pigs

Withdrawal periods were calculated for liver, kidney, non-injection site muscle and skin and fat based on their respective MRLs and for injection site tissues using the ADI approach as well as using the ISRRV.

Table 1: Calculated withdrawal periods for porcine tissues following a revised ADI of 3000 µg/person and based on revised MRLs for liver, kidney, skin and fat and muscle (a) without considering the injection site and (b) using the ADI approach to consider the injection site

(a)

NOEL (µg/kg)	5000	Safety factor (SF) = 100			95:95 Stats
ADI (µg/kg)	50	(NOEL/SF)			
ADI (µg/day)	3000	NOEL/SF x 60 kg BW			
Tissue	**MRL (µg/kg)**	**Marker/Total ratio**	**Consumption factor (kg/day)**	**Intake (µg)**	**WDP (days)**
Liver	4000	0.94	0.1	425.53	2
Kidney	8000	0.83	0.05	481.93	1
Muscle	800	0.86	0.3	279.07	7
Skin/fat	300	0.28	0.05	53.57	12
Injection site	-----	0.89	0.3	-----	-----
		Total intake (µg)		1240.10	
		% of ADI		41.34%	

(b)

NOEL (µg/kg)	5000	Safety factor (SF) = 100			95:95 Stats
ADI (µg/kg)	50	(NOEL/SF)			
ADI (µg/day)	3000	NOEL/SF x 60 kg BW			
Tissue	**MRL (µg/kg)**	**Marker/Total ratio**	**Consumption factor (kg/day)**	**Intake (µg)**	**WDP (days)**
Liver	4000	0.94	0.1	425.53	2
Kidney	8000	0.83	0.05	481.93	1
Muscle	-----	0.86	0.3	-----	-----
Skin/fat	300	0.28	0.05	53.57	13
Injection site	6000 (ISRRV)	0.89	0.3	2022.5	9*
		Total intake (µg)		2983.50	
		% of ADI		99.45%**	

* ADI approach
** Calculation based on an ISRRV of 6000 µg/kg accounting for muscle tissue and a ratio of marker to total residue of 0.89, would result in consumer intake of 2983.50 µg representing approximately 99.45% of the ADI.

The statistical results support a withdrawal period of 2 days for liver, a withdrawal period of 1 day for kidney and a withdrawal period of 7 days in muscle.

In skin and fat, although residue concentrations were almost unchanged between days 25 and 36, analysis based on all data points is appropriate as values are above the limit of detection (LOD) and as linearity assumption was not seriously violated. The statistical results support a withdrawal period of 13 days based on all data points.

Injection sites

A withdrawal period for injection sites was calculated based on total residue concentrations derived from the residue study in pigs. Analysis was conducted by taking the marker residue data from liver, kidney, skin and fat and injection site, applying appropriate correction factors, performing a summation of all tissues to get total tulathromycin residue equivalents followed by a statistical analysis relative to the revised ADI of 3000 µg/person (i.e. using the ADI approach described in the CVMP Note for guidance: approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95 FINAL)).

In accordance with the original CVMP assessment and use of the ADI approach, the total residue depletion study is considered most appropriate for this analysis as injection site tissue was collected per EMA guidelines. The marker residue study collected injection site samples according to the standards for subcutaneous injection instead of the required intramuscular injection.

The statistical results support a withdrawal period of 9 days.

To further verify that the injection site is not the withdrawal period determining tissue, the ISRRV value of 6000 µg/kg was applied to injection site residue data to determine the withdrawal time necessary for injection site residues not to violate this limit (using the data from the total residue depletion study) in line with the approach described in the CVMP draft reflection paper on injection-site residues: considerations for risk assessment and residue surveillance (EMA/CVMP/520190/2007-Rev.1). The resulting withdrawal period was calculated to be 12 days.

In addition, calculation of the withdrawal period based on the ADI approach leads to similar results (a withdrawal period of 9 days) as the calculation based on the ADI approach and using data from the total residue study. However, sampling of injection site muscle was inadequate in the marker residue study, leading probably to an underestimate of residue concentrations.

The marker residue study as well as the total residue studies have several shortcomings based on current requirements. For the marker residue study sampling of injection site tissues was considered to be inadequate, as the whole area of the needle track and of drug release was not fully included in the

injection site samples. The total residue study included only four animals per slaughter day and only four time points. In both studies, no surrounding injection site samples were taken. Nevertheless, the three different kinds of analysis of injection site residues (both studies using the ADI approach, and one study using the ISRRV approach) consistently show that withdrawal periods are below the withdrawal time for skin and fat and that the injection site would not be the withdrawal period determining tissue.

In summary, skin and fat is considered the withdrawal period determining tissue and an overall withdrawal period of 13 days is considered appropriate to ensure consumer safety for use of DRAXXIN 100 mg/ml. The same withdrawal period is considered acceptable for DRAXXIN 25 mg/ml.

Cattle:

The theoretical maximum daily intake (TMDI) from bovine tissues (liver, kidney, fat and injection site) is 2929.77 µg, representing 97.77% of the ADI for edible tissues. Withdrawal periods were calculated for liver, kidney, non-injection site muscle and fat based on their respective MRLs and for injection site tissues based on the ADI and ISRRV approaches.

Table 2: Calculated withdrawal periods for bovine tissues following a revised ADI of 3000 µg/person and based on revised MRLs for liver, kidney, skin and fat and muscle (a) without considering the injection site and (b) using the ADI approach to consider the injection site

(a)

NOEL (µg/kg)	5000	Safety factor (SF) = 100			95:95 Stats
ADI (µg/kg)	50	(NOEL/SF)			
ADI (µg/day)	3000	NOEL/SF x 60 kg BW			
Tissue	**MRL (µg/kg)**	**Marker/Total ratio**	**Consumption factor (kg/day)**	**Intake (µg)**	**WDP (days)**
Liver	4500	0.61	0.1	737.71	22
Kidney	3000	0.78	0.05	192.31	19
Muscle	300	0.79	0.3	113.92	17
Skin/fat	200	0.46	0.05	21.74	19
Injection site	-----	0.91	0.3	-----	-----
		Total intake (µg)		1065.66	
		% of ADI		35.52%	

(b)

NOEL (µg/kg)	5000	Safety factor (SF) = 100			95:95 Stats
ADI (µg/kg)	50	(NOEL/SF)			
ADI (µg/day)	3000	NOEL/SF x 60 kg BW			
Tissue	**MRL (µg/kg)**	**Marker/Total ratio**	**Consumption factor (kg/day)**	**Intake (µg)**	**WDP (days)**
Liver	4500	0.61	0.1	737.71	22
Kidney	3000	0.78	0.05	192.31	19
Muscle	-----	0.79	0.3	-----	-----
Skin/fat	200	0.46	0.05	21.74	19
Injection site	6000 (ISRRV)	0.91	0.3	1978.0	21*
		Total intake (µg)		2929.77	
		% of ADI		97.66%	

* ADI approach
** Calculation based on an ISRRV of 6000 µg/kg accounting for muscle tissue and a ratio of marker to total residue of 0.89, would result in consumer intake of 2929.77 µg representing approximately 97.66% of the ADI.

The statistical results support a withdrawal period of 22 days for liver, 19 days for kidney, 17 days for muscle and 19 days for fat.

Injection sites

A withdrawal period for injection sites was calculated based on marker residue data from liver, kidney, fat and injection site, applying appropriate correction factors, performing a summation of all tissues to get

total tulathromycin residue equivalents followed by a statistical analysis relative to the ADI of 3000 µg/person (i.e. using the ADI approach described in the CVMP Note for guidance: approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95 FINAL)).

The statistical results support a withdrawal period of 19 days using the ADI approach.

To further verify whether the withdrawal period for injection sites would not be the overall withdrawal period another calculation based on data from the marker residue study using the ISRRV of 6000 µg/kg and marker concentrations at injection sites was conducted, resulting in a withdrawal period of 21 days.

In cases where an ISRRV has been set, this is considered the most relevant benchmark against which to determine withdrawal periods at injection sites.

Overall, the longest withdrawal period has been derived from the liver tissue data (22 days). Therefore, liver is the withdrawal period determining tissue, leading to an overall withdrawal period of 22 days in tissues from cattle treated with DRAXXIN 100 mg/ml. The same withdrawal period is considered acceptable for DRAXXIN 25 mg/ml.

2.2. Summary and conclusions

Updated calculations based on the residue depletion studies already present in the original assessment report taking into account the revised MRLs and ADI were conducted. For pigs, additionally to the pivotal marker residue study, data from the total residue study were considered relevant for the assessment of injection site residues, as in the pivotal residue depletion study the area of the needle track and of drug release was not fully included in the injection site samples and sampling of injection site tissues was considered inadequate. In cattle, data from the marker residue study were considered most relevant for use in withdrawal period determination.

In pigs, skin and fat is the withdrawal period determining tissue. Calculation based on data from the marker residue study results in a withdrawal period of 13 days.

In cattle, the longest withdrawal period was derived from liver tissues, resulting in an overall withdrawal period of 22 days.

In both species, injection site residues do not determine the withdrawal periods.

3. Benefit-risk assessment

3.1. Benefit assessment

No changes in the benefit assessment result from this variation application.

3.2. Risk assessment

The consumer safety assessment has been updated to reflect the revised MRLs and ADI. The revised withdrawal periods of 13 days for pigs and 22 days for cattle are considered adequate to prevent consumer intake of residues.

3.3. Evaluation of the benefit-risk balance

No change to the impact on the environment is envisaged.

The benefit-risk balance remains positive based on the revised withdrawal periods, as they reflect revised MRL and ADI values and ensure these are not violated.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

The withdrawal period proposed for porcine tissues (13 days) is considered acceptable.

The withdrawal period proposed for bovine tissues (22 days) is considered acceptable.

4.1. Changes to the community marketing authorisation

Changes are required in the Annexes to the Community marketing authorisation.

Annexes I, II, IIIA and B.