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Committee for Medicinal Products for Veterinary Use (CVMP)

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Opinion of the Committee for Medicinal Products for Veterinary Use regarding a request pursuant to Article 30(3) of Regulation (EC) No 726/2004

In relation to the potential risk for the consumer resulting from the use of lidocaine in food producing species

Basis for opinion

On 21 December 2012, The Netherlands presented to the European Medicines Agency ('the Agency') a request for an opinion from the Committee for Medicinal Products for Veterinary Use, on a scientific matter concerning the potential risk for the consumer resulting from the use of lidocaine in food producing species, in accordance with Article 30(3) of Regulation (EC) No 726/2004.

Lidocaine was assessed by the CVMP for the purpose of establishing maximum residue limits (MRLs) in 1999. The evaluation concluded that numerical MRL values were not required for the protection of the consumer and therefore the substance is included in Table 1 of the Annex of Commission Regulation (EU) No 37/2010 with a "no MRL required" classification but with the use restricted to horses and for local/regional anaesthesia only.

Lidocaine can therefore only be used in *equidae* or exceptionally in other species in line with the provisions of Article 11 of Directive 2001/82/EC (under the so-called "cascade"). It is reported that products containing lidocaine are in fact widely used in major food producing species such as cattle and pigs under the cascade due to the lack of authorised anaesthetics in those animal species.

The CVMP previously concluded that MRLs could not be established in food producing species other than horses because the metabolism in these species was unknown. A particular concern was a metabolite of lidocaine, 2,6-xylylidine, but data on the occurrence of this metabolite was not available for most food producing species. 2,6-Xylylidine was shown to have genotoxic characteristics *in vivo* (see CVMP MRL Summary Report) ¹.

Recent research indicates that 2,6-xylylidine is the main metabolite produced by primary hepatocytes and liver microsomes from pigs and cattle when exposed to lidocaine *in vitro* (Thuesen and Friis,

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500014745.pdf



2012)². The presence of 2,6-xylylidine in the urine of pigs and cattle was confirmed after intravenous administration of lidocaine (personal communication C. Friis, 2012).

The Dutch authorities considered that the data available indicate a reason for concern with regard to consumer safety and that in order to decide if any actions are necessary at EU level, e.g., related to the marketing authorisations and/or the MRL status of lidocaine, a common understanding of the scientific conclusions on the hazards and consumer risks resulting from the use of lidocaine in food producing species was required.

In the scientific opinion, the Committee was requested to address the following questions:

1. Can the CVMP confirm that 2,6-xylylidine is a genotoxic carcinogen? From the information available, it appears that 2,6-xylylidine is carcinogenic (carcinomas at multiple sites), however, genotoxicity studies suggest that not 2,6-xylylidine but actually a further metabolite is responsible for the genotoxic action, as the results of *in vitro* studies were positive with metabolic activation only.
2. It appears that humans can metabolise lidocaine into 2,6-xylylidine. Therefore, even if 2,6-xylylidine is not formed in the food producing species (as in horses), the exposure to the parent substance lidocaine via food of animal origin may eventually cause consumer exposure to 2,6-xylylidine. Does the CVMP consider that there is a consumer risk for genotoxic and/or carcinogenic effects following exposure to the parent substance lidocaine?
3. What is the consumer risk of exposure to lidocaine-related residues in food resulting from the use of lidocaine in horses, pigs and cattle? Please note that withdrawal periods in horses would be 0 days and the use in other species 28 days for slaughter and 7 days for milk (according to the current rules of the cascade).
4. Does the CVMP consider it necessary to take risk management measures? If yes, what risk management measures and communication does the CVMP consider appropriate?
5. As 2,6-xylylidine can also be formed from xylazine, does the CVMP see any consumer safety concern after human exposure to xylazine and/or its metabolites?

The procedure started on 9 January 2013.

Opinion

The Committee, having

- reviewed the available data relating to the metabolism of lidocaine and the generation of potentially genotoxic metabolites in animals and humans,
- reviewed the existing data on genotoxicity and carcinogenicity and convened an ad hoc expert group specifically to advise on this matter,
- reviewed new residues data generated in cattle along with residue predictions based on a physiologically based pharmacokinetic model,
- considered different approaches for evaluating the risk associated with exposure to lidocaine residues in the absence of standard health based reference values like an acceptable daily intake (ADI),

² Thuesen, L.R., and Friis, C. (2012) *In vitro* metabolism of lidocaine in pig, cattle and rat. Poster presentation EAVPT Congress 2012, The Netherlands

- considered the availability of alternatives to lidocaine for use in large animals and the need for risk mitigation measures in order to minimise potential consumer exposure to lidocaine residues,
- considered possible exposure of consumers to 2,6-xylidine as a result of the use of xylazine,

came to the following conclusions on the five questions raised in the request for an opinion.

Question 1:

Can the CVMP confirm that 2,6-xylidine is a genotoxic carcinogen? From the information available, it appears that 2,6-xylidine is carcinogenic (carcinomas at multiple sites), however, genotoxicity studies suggest that not 2,6-xylidine but actually a further metabolite is responsible for the genotoxic action, as the results of *in vitro* studies were positive with metabolic activation only.

CVMP response:

It is confirmed that 2,6-xylidine is a genotoxic carcinogen in rats and it is assumed that no threshold exists for genotoxicity. A No Observed Effect Level (NOEL) has not been established for carcinogenicity.

2,6-Xylidine can be further metabolised to N-(2,6-dimethylphenyl)hydroxylamine (DMHA) and 4-amino-3,5-dimethylphenol (DMAP). These metabolites lead to the formation of reactive intermediates like a nitrenium ion or iminoquinone. These reactive intermediates have the potential to covalently bind to DNA.

Question 2:

It appears that humans can metabolise lidocaine into 2,6-xylidine. Therefore, even if 2,6-xylidine is not formed in the food producing species (as in horses), the exposure to the parent substance lidocaine via food of animal origin may eventually cause consumer exposure to 2,6-xylidine. Does the CVMP consider that there is a consumer risk for genotoxic and/or carcinogenic effects following exposure to the parent substance lidocaine?

CVMP response:

Lidocaine may undergo metabolism to 2,6-xylidine in humans in intestines and liver. By consequence, even if 2,6-xylidine would not be formed in the food producing species, the exposure to the parent substance lidocaine via food of animal origin may eventually cause consumer exposure to 2,6-xylidine. Therefore there is a potential risk for genotoxic and carcinogenic effects to the consumer following the exposure to lidocaine.

Question 3

What is the consumer risk of exposure to lidocaine-related residues in food resulting from the use of lidocaine in horses, pigs and cattle? Please note that withdrawal periods in horses would be 0 days and the use in other species 28 days for slaughter and 7 days for milk (according to the current rules of the cascade).

CVMP response:

Data from a new residue depletion study in cattle indicate that lidocaine and related residues are present in edible tissues and in milk at early time-points after treatment. However, modelling data indicate that by the minimum cascade withdrawal period of 28 days the total amount of residues remaining in the animal's body will be in the picogram range; even if an entire carcass could be

ingested by a single consumer, exposure to residues would remain below the threshold of toxicological concern³ (TTC) of 0.15 µg.

Regarding milk, the minimum cascade withdrawal period of 7 days does not result in the total elimination of residues or in the elimination of total body residues down to the TTC. To ensure that total residues in the cow's body are below this level requires an interval of 15 days between use of lidocaine and the taking of milk for human consumption. At this time point there is no risk to the consumer.

For pigs no residue data are available and it is therefore not possible to calculate residue levels that will remain following the cascade withdrawal period. However, since metabolism is comparable to that in cattle, it is expected that the minimum cascade withdrawal period of 28 days for meat is sufficient to ensure that residues deplete to negligible levels. Furthermore, considering that lidocaine is used for castration within the first weeks of life, therefore far from slaughter, the risk to the consumer is considered negligible.

For horses, in the absence of residue data it is not possible to conclude with 100% certainty whether a withdrawal period of 0 days is safe. However in the absence of any new residue data, considering the very limited use currently authorised for lidocaine and the extensive metabolism, and considering that new *in vitro* data have further demonstrated that 2,6-xylylidine formation in horses is less significant than in cattle, the risk to the consumer can be considered negligible.

Question 4:

Does the CVMP consider it necessary to take risk management measures? If yes, what risk management measures and communication does the CVMP consider appropriate?

CVMP response:

For horses, considering the very limited use currently authorised (for local/regional anaesthesia only), the extensive metabolism and the fact that new *in vitro* data suggests less significant production of 2,6-xylylidine in horses than in other species, the risk of consumer exposure to residues of lidocaine in horse meat is considered very low. In view of this, the current MRL classification ('No MRL required' for horses and for local/regional anaesthesia only) for lidocaine remains appropriate and no risk mitigation measures are considered necessary. In addition it is also noted that the likelihood of animals being sent for slaughter immediately after treatment is very low, which will further reduce the risk of consumer exposure to residues.

For cattle, considering that the estimated amount of lidocaine residues in the cow's body is negligible (about 10 pg) it can be considered that the minimum cascade withdrawal period of 28 days is appropriate. Therefore, no new risk mitigation measures are needed.

Regarding milk, the safety associated with the minimum cascade withdrawal period of 7 days is uncertain as this time period is not sufficient to ensure that total residues remaining in the cow's body will be below the TTC of 0.15 µg. To ensure that total residues in the cow's body are below this level requires an interval of 15 days between use of lidocaine and the taking of milk for human consumption. At this time point there is no risk to the consumer.

³ The TTC is a risk assessment tool establishing human exposure threshold values for chemicals below which there is a very low probability of adverse effects to human health. The European Food Safety Authority (EFSA) considers that the approach is applicable to substances for which the chemical structure is known but for which there are few or no relevant toxicity data. For substances with a structural alert for genotoxicity EFSA recommends a TTC of 0.15 µg/person/day as the threshold below which human exposure should remain.
<http://www.efsa.europa.eu/en/efsajournal/doc/2750.pdf>

For pigs, considering that metabolism is comparable to that in cattle, it is expected that the minimum cascade withdrawal period of 28 days is sufficient to ensure elimination of residues to a safe level. Moreover considering that the use for castration takes place at a time far from slaughter, the risk to the consumer is considered negligible.

It would seem appropriate to inform lidocaine users via specialised literature for veterinarians or via dedicated websites that an interval of 15 days between use of lidocaine and the taking of milk for human consumption is recommended.

Question 5:

As 2,6-xylidine can also be formed from xylazine, does the CVMP see any consumer safety concern after human exposure to xylazine and/or its metabolites?

CVMP response:

Since 2,6-xylidine has not been detected in cattle milk and tissues, there is no consumer safety concern for this metabolite.

The bioavailability and biotransformation of xylazine in humans following oral administration has not been characterised. However, as oral absorption in rats is nearly 100%, absorption by the oral route may be expected in humans. In addition 2,6-xylidine has been detected in urine following parenteral administration of xylazine in humans.

Therefore there is a risk for genotoxic effects to the consumer following the exposure to xylazine. However, considering the low exposure level (8 to 25 µg) one day after treatment of cattle and the extensive metabolism in cattle and horses, the risk is considered negligible. It is also noted that the likelihood of animals being sent for slaughter immediately after treatment is very low, which will further reduce the risk of consumer exposure to residues.

The Icelandic and the Norwegian CVMP members agree with the above-mentioned recommendation of the CVMP.

This opinion is forwarded to the Netherlands and to the European Commission, all Member States, Iceland and Norway together with its appendix.

The opinion will be published on the Agency website with its appendix.

London, 10 April 2015

Dr A. Holm,
Chair, on behalf of the CVMP

Appendix 1: CVMP assessment report