NOTIFICATION TO THE EUROPEAN MEDICINES AGENCY OF A REFERRAL UNDER ARTICLE 82 OF REGULATION (EU) 2019/6

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This notification is a referral under Article 82 of Regulation (EU) 2019/6 to the European Medicines Agency (the 'Agency') made by Germany:

A range of veterinary medicinal products, all containing the same substance	Veterinary medicinal products containing N-methyl-pyrrolidone (NMP) as an excipient
Target species	All species
Route of administration	All routes of administration
Active substance	Varying active substances in combination with the excipient N-methyl-pyrrolidone (NMP)
Applicant(s)/marketing authorisation holder(s)	To be identified

Detailed explanation of the matter involving Union interest:

This referral procedure concerns the review of a potential serious risk to human and animal health resulting from exposure of users and target animals to veterinary medicinal products containing N-methyl-pyrrolidone (NMP) as an excipient.

According to assessments published by several European scientific committees including the Committee for Veterinary Medicinal Products (CVMP), NMP should be considered as a substance which has the potential to cause developmental toxicity. Germany noted that although a number of veterinary medicinal products authorised in various Member States contain NMP in considerable amounts, only few of them contain appropriate user safety warnings for pregnant women or for target animals for use during pregnancy or lay.

In the revised MRL summary report for NMP, the CVMP described several studies in rats and rabbits that revealed treatment-related malformations (EMEA, 2008). The lowest observed oral NOAEL for developmental toxicity is 125 mg/kg bodyweight/day based on a developmental toxicity study in Sprague-Dawley rats after oral administration. The lowest observed dermal NOAEL for developmental toxicity is 237 mg/kg bodyweight/day based on studies in Sprague-Dawley rats that were reported by different European Committees (Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC) of the European Chemicals Agency (ECHA); Scientific Committee on Consumer Safety (SCCS); Scientific Committee on Occupational Exposure Limits (SCOEL)) (SCCS, 2011; ECHA, 2014; SCOEL, 2016). Overall, NMP was assessed as being developmentally toxic by these European committees. According to the harmonised classification and labelling (ATP09) approved by the European Union, NMP is legally classified as 'Repr. 1B (may damage the unborn child)'.

The potential risk of teratogenic effects is considered a serious concern. The guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) states that "*warnings and safety measures are communicated via the SPC and package leaflet and should inform the user about A. the concerned risk, B. what exposure must be avoided, C. how to avoid it, and D. what to do in the event of exposure (if relevant)*". In consequence, appropriate warnings and safety

measures concerning the teratogenic potential of NMP should be communicated in the product information of the concerned products.

Furthermore, adverse effects on the foetus cannot be detected shortly after exposure. When embryonic development is affected, this can normally only be detected after a prolonged time after exposure and is mostly only noticed if severe effects occur, e.g. spontaneous abortions, still-births or malformations. Additionally, as no safety warnings concerning the teratogenic potential of NMP are included in the product information of most of the concerned veterinary medicinal products yet, users and animal holders might not be sufficiently sensitised of the possibility of related adverse effects. Consequently, it is very unlikely that such potentially occurring effects would be associated and reported as being a consequence of exposure to NMP-containing veterinary medicinal products.

In Germany, there are approximately 69 veterinary medicinal products authorised that contain NMP. However, user safety warnings related to potential teratogenic effects of NMP are only included in the product information of 15 of these products. Quantitative user risk assessment according to the guidelines EMA/CVMP/543/03-Rev.1 and EMA/CVMP/SWP/721059/2014 revealed that most of the NMP-containing products without a warning phrase in their product information pose an unacceptable risk to pregnant women with margins of exposure being substantially below 100. Furthermore, Germany noted that recently authorised generic products contain user safety warnings for NMP, while such warnings are still missing in the product information of the corresponding reference products. The same situation is apparent regarding target animal safety.

In order to review this issue, Germany submitted a non-urgent information (NUI) notification on NMP-containing veterinary medicinal products to European Member States in April 2021. In total, 657 veterinary medicinal products containing the excipient NMP were reported by 20 Member States, belonging to a wide range of therapeutic classes and dosage forms. Safety warnings concerning NMP are included in less than 50% of these products.

In conclusion, in view of the teratogenic potential of NMP and identified inconsistencies in user and target animal safety warnings approved for similar products on the market, Germany considered that it is in the interest of the Union to initiate a review of veterinary medicinal products containing NMP. Where appropriate, risk mitigation measures should be implemented to ensure the safe use of the concerned products on a European level.

Questions to be addressed by the Agency's Committee for Veterinary Medicinal Products (CVMP):

The CVMP is requested to review the available data for veterinary medicinal products containing N-methyl-pyrrolidone (NMP) as an excipient with a view to provide an opinion on the following questions:

- Concerning the teratogenic potential of NMP, does an updated risk assessment performed according to current guidelines (EMA/CVMP/543/03-Rev.1 and EMA/CVMP/SWP/721059/2014) of veterinary medicinal products containing NMP as an excipient result in a potential risk for pregnant users?
- In case a risk for pregnant users is identified, consideration should be given to establishing adequate risk mitigation measures in line with current guidelines (EMA/CVMP/543/03-Rev.1 and EMA/CVMP/SWP/721059/2014) for the concerned veterinary medicinal products.
- Furthermore, providing additional information in the product information on the use of the concerned products in target animals during pregnancy or lay should be considered.

In view of the elements described above and the necessity to take action at EU level, Germany considers that it is in the interest of the Union to refer the matter to the Agency and requests that the CVMP gives its opinion under Article 82 of Regulation (EU) 2019/6 as to whether the marketing authorisations for the above-mentioned products should be maintained, varied, suspended, or revoked.

Signed [redacted] Date 29/04/2022

References:

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EMEA, 1998. Committee for Veterinary Medicinal Products: 1-Methyl-2-Pyrrolidone Summary Report (1), EMEA/MRL/493/98 – FINAL

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EMA, 2010. Committee for Veterinary Medicinal Products. Guideline on user safety for pharmaceutical veterinary medicinal products, EMA/CVMP/543/03-Rev.1

EMA, 2018. Committee for Veterinary Medicinal Products. Guideline on user safety of topically administered veterinary medicinal products, EMA/CVMP/SWP/721059/2014

SCCS, 2011. Opinion on N-Methyl-2-pyrrolidone (NMP) adopted by the Scientific Committee on Consumer Safety; https://op.europa.eu/de/publication-detail/-/publication/b65ed144-015a-4b25-b909-af18a1ef6281

SCOEL, 2016. SCOEL/REC/119 N-Methyl-2-Pyrrolidone. Recommendation from the Scientific Committee on Occupational Exposure Limits; https://op.europa.eu/de/publication-detail/-/publication/c0dbb7a4-0c3a-11e6-ba9a-01aa75ed71a1