Annex IV

Scientific conclusions and grounds for amendment of the product information

Overall summary of the scientific evaluation of veterinary medicinal products containing N-methyl pyrrolidone as an excipient

Introduction

N-methyl pyrrolidone (NMP) is an excipient which has been used for decades in a number of veterinary medicinal products as a solvent.

It has subsequently been assessed as being developmentally toxic according to 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[1]; ECHA, 2014[2]; SCOEL, 2016[3]).

Moreover, according to Annex VI of the Regulation (EC) No 1272/2008 - classification, labelling and packaging of substances and mixtures (CLP)[4], NMP is legally classified as 'Repr. 1B (may damage the unborn child)'.

Germany noted that a number of veterinary medicinal products containing NMP as an excipient authorised in various Member States do not contain user or target animal safety warnings related to the potential teratogenic effects of NMP in their product information (summary of product characteristics – SPC, labelling and package leaflet).

Quantitative user risk assessment according to the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1)[5] and CVMP guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014)[6] 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 was apparent regarding target animal safety.

In view of the teratogenic potential of NMP and the 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 as an excipient. Where appropriate, risk mitigation measures should be implemented to ensure the safe use of the concerned veterinary medicinal products on a European level.

Therefore, Germany referred the matter to the Agency's Committee for Veterinary Medicinal Products (CVMP) in the interest of protecting user and animal safety in the Union.

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[1] SCCS, 2011. Opinion on N-Methyl-2-pyrrolidone (NMP) adopted by the Scientific Committee on Consumer Safety - link

[2] ECHA, 2014. Background document to the Opinion on the Annex XV dossier proposing restrictions on 1-methyl-2-pyrrolidone (NMP) - link

[3] SCOEL, 2016. SCOEL/REC/119 N-Methyl-2-Pyrrolidone. Recommendation from the Scientific Committee on Occupational Exposure Limits - link

[4] Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures

[5] CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) - link

[6] CVMP guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014)- link

Overall summary of the scientific evaluation

The CVMP was requested to review all available data for veterinary medicinal products containing N-methyl pyrrolidone as an excipient, and to give a scientific opinion on whether the outcome of an updated user risk assessment, performed according to current user safety guidelines (EMA/CVMP/543/03-Rev.1[5] and EMA/CVMP/SWP/721059/2014[6]), for the veterinary medicinal products under consideration would identify a potential risk for pregnant users. In case such a risk was identified, it was requested to establish adequate risk mitigation measures. Furthermore, it was necessary to consider additional information in the product information on the use of the concerned products in target animals during pregnancy or lay.

Veterinary medicinal products containing NMP that are authorised in the European Economic Area are presented in the following pharmaceutical forms: products for injection, solutions for infusion, spot-on products, pour-on products, shampoo, sheep dip products, spray products and concentrates for oral solutions for use in drinking water or for solutions for fish treatment.

User safety

The CVMP was asked to consider the user safety of veterinary medicinal products containing NMP as an excipient with regards to its potential to induce developmental toxicity.

The reproductive and developmental toxicity of NMP following oral exposure was previously described and assessed by the CVMP in the MRL summary report for 1-Methyl-2-pyrrolidone (EMEA/MRL/615/99-FINAL–Rev.1)[7].

In addition, developmental toxicity studies by other routes of administration were previously assessed and published by different European agencies and scientific committees (SCCS, 2011[1]; ECHA, 2014[2]; SCOEL, 2016[3]; Akesson, Bengt & International Programme on Chemical Safety, WHO, 2001[8]). Overall, the CVMP considered that NMP is an established teratogen in laboratory animals following various routes of exposure.

During this referral procedure an updated user risk assessment according to the above-mentioned user safety guidelines was performed by the CVMP for the concerned veterinary medicinal products.

In order to perform the user risk assessment, the N-methyl pyrrolidone concentrations of the individual products concerned by this referral procedure were provided by the national competent authorities of the Member States. Applicants/MAHs were asked to inform the CVMP if the NMP concentrations used in the user risk calculations performed by the Committee were incorrect and when necessary, the calculations were revised. However, for some veterinary medicinal products no information on NMP concentrations was provided and in such cases, the CVMP followed a worst-case assumption, whereby the active substance content was subtracted from the product volume and the remaining volume was assumed to contain 100% of the excipient NMP.

The user risk assessment was performed by pharmaceutical form using the following toxicological reference values for the oral and dermal routes of exposure, respectively:

- lowest oral NOAEL = 125 mg per kg body weight per day, derived from oral developmental toxicity studies with NMP in rats (EMEA/MRL/615/99-FINAL–Rev.1)[7].
- lowest dermal NOAEL = 237 mg per kg body weight per day, derived from dermal developmental toxicity studies with NMP in rats (Becci *et al.*, 1982[9]; SCCS, 2011[1]).

[7] EMEA, 2008. Committee for Veterinary Medicinal Products: 1-Methyl-2-Pyrrolidone Summary Report (2), (EMEA/MRL/615/99-FINAL–Rev.1. May 2008)
[8] Akesson, Bengt & International Programme on Chemical Safety, 2001. N-methyl-2-pyrrolidone. World Health Organization (WHO) - link
[9] Becci P.J., Knickerbocker M.J., Reagan E.L., Parent R.A., Llewellyn W.B. (1982). Teratogenicity study of N-methyl pyrrolidone after dermal application to Sprague-Dawley rats. Fundamental applied toxicology 2: 73–76.

The quantitative user risk assessment was only performed for the dermal and oral exposures. The inhalation exposure was not assessed separately because important parameters for these calculations were missing. However, as the worst-case application rate was very conservative and developmental toxic effects after dermal exposure were more serious than after inhalation exposure, it was anticipated that the user risk assessment following dermal exposure also covers the risk after inhalation exposure.

Although higher margins of exposure (MOEs) are usually considered for teratogenic substances, a MOE of 100 was considered sufficient for the excipient N-Methyl pyrrolidone during the current user risk assessment, due to the conservative assumptions made during the calculations and the use of default values, e.g., 100% dermal absorption.

The quantitative user risk assessment revealed MOEs below 100 for most of the veterinary medicinal products concerned by this referral and consequently, an unacceptable risk for pregnant users. Therefore, the CVMP considered that the implementation of appropriate user safety warnings and risk mitigation measures into the respective product information (summary of product characteristics and package leaflets) for the relevant veterinary medicinal products was necessary for the protection of women of childbearing age, pregnant women or women suspected of being pregnant.

For some veterinary medicinal concerned by this referral (including all products for infusion), the quantitative user risk assessment resulted in MOEs above 100 and hence, the CVMP considered that no user safety warnings should be added in the product information of those products.

Target animal safety

In this referral procedure, the Committee considered whether for veterinary medicinal products containing the excipient N-methyl pyrrolidone, additional information in the product information was necessary for the safe use in target animals during pregnancy or lay.

The excipient NMP has been assessed by different agencies and scientific committees (SCCS, 2011[1]; ECHA, 2014[2]; SCOEL, 2016[3]; Akesson, Bengt & International Programme on Chemical Safety, WHO, 2001[8]) and deemed as an established teratogen according to data derived from laboratory animal species that have shown evidence of foetal malformations due to NMP.

The CVMP considered that the potential of developmental toxicity of NMP should be appropriately reflected in the product information of the concerned veterinary medicinal products, except for those cases where the safe use of the product during pregnancy, lactation or lay has been demonstrated in specific safety studies in the target species, i.e., studies that did not provide evidence of teratogenic effects in the respective target species.

Elanco Animal Health Inc. was the only MAH that presented relevant data on target animal safety in the target species. The MAH provided a study report on 3-times overdose during gestation and lactation in bitches for their product Advantix Spot-on without any signs for developmental toxicity, and this is reflected in the approved product information. This study, in which up to 3 times of the maximum recommended treatment dose was repeatedly administered, was already assessed during the marketing authorisation procedure (IT/V/0114/001) where the statement *"Can be used during pregnancy and lactation"* was agreed to be included in the product information. Therefore, the CVMP agreed that the approved wording was kept in the product information for the Advantix spot-on products since a tolerability study in pregnant and lactating bitches was provided and confirmed that the marketed formulation of the product was used in the study. The Committee further concluded that this sentence should also be kept in the product information of the generic products of Advantix with identical composition to the reference product.

Benefit-risk assessment

Benefit assessment

Efficacy of the concerned products in the target species has not been specifically assessed as part of this referral. The veterinary medicinal products under assessment were assessed at the time of authorisation in centralised and national marketing authorisation application procedures and are considered to be effective in the respective target animals.

Risk assessment

Quality, consumer safety, and the environmental risk for the concerned veterinary medicinal products have not been assessed in this referral procedure.

Due to the teratogenic potential of the excipient NMP, the CVMP reviewed the available data and concluded that there is a risk for pregnant users for some of the veterinary medicinal products concerned by this referral procedure as per the user risk assessment performed by the CVMP. In addition, the Committee concluded that there is a risk for target animals during pregnancy or lay, except for those cases where the safe use of the product during pregnancy or lay has been demonstrated in specific safety studies in the target species.

Risk mitigation measures

Based on the available data, user and target animal safety warnings were established and amendments to sections 3.5 and 3.7 (QRD template v9.0), or sections 4.5 and 4.7 (QRD template v8.2) of the summary of product characteristics and corresponding sections of the package leaflet were proposed for Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution.

Furthermore, as an additional risk mitigation measure, the CVMP concluded that the excipient N-methyl pyrrolidone shall be stated quantitatively in the relevant sections of the product information of Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution, since that knowledge is considered essential for the safe administration of the veterinary medicinal product, where a risk could not be ruled out and consequently SPC sections 3.5/4.5 or 3.7/4.7 are required to include the above-mentioned warnings.

These measures are considered adequate to ensure user and target animal safety.

Evaluation and conclusions on the benefit-risk balance

Having considered the grounds for the referral procedure and the available data, the CVMP concluded that for the veterinary medicinal products Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution, safety warnings are needed to mitigate the risk for pregnant users and/or target animals. The Committee concluded that the benefit-risk balance for these veterinary medicinal products remains favourable subject to the recommended changes in the product information.

Grounds for CVMP opinion

Whereas,

- The CVMP considered the procedure under Article 82 of Regulation (EU) 2019/6 for all veterinary medicinal products containing N-methyl pyrrolidone as an excipient.
- The CVMP reviewed the available data on teratogenic risk for pregnant users associated with the use of veterinary medicinal products containing N-methyl pyrrolidone and an updated user risk assessment was performed according to current user safety guidelines (EMA/CVMP/543/03-Rev.1[5] and EMA/CVMP/SWP/721059/2014[6]).

- The CVMP considered additional information in the product information on the use of the concerned products in target animals during pregnancy or lay.
- On the basis of the available data, the CVMP concluded that for Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution, teratogenic risk is identified either for pregnant users or target animals.
- The CVMP therefore recommended that appropriate safety warnings have to be included in the product information of the veterinary medicinal products Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution, to provide assurance of user and/or target animal safety.

CVMP opinion

In view of the above, the CVMP concluded that the benefit-risk balance of the centrally authorised veterinary medicinal products Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution remains favourable subject to the amendments in their Summary of Product Characteristics and package leaflet which are set out in the respective annexes I and IIIB for Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution.

Therefore, the Committee recommended the variation to the terms of the marketing authorisations for the veterinary medicinal products Melovem 30 mg/ml solution for injection and Vectra 3D spot-on solution.