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Veterinary Medicines and Product Data Management

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Opinion of the Committee for Medicinal Products for Veterinary Use pursuant to Article 30(3) of Regulation (EC) No 726/2004 of the European Parliament and of the Council on dapsons as an impurity in veterinary medicinal products containing sulphamethoxazole or other sulphonamides

Basis for opinion

On 22 July 2011, The Netherlands requested the Committee for Medicinal Products for Veterinary Use (CVMP) to give an opinion under Article 30(3) of Regulation (EC) No 726/2004 on the implications of animal health and safety of consumers related to dapsons, an impurity formed during the synthesis of sulphamethoxazole, which is used as an active ingredient in veterinary medicinal products

The request followed findings of dapsons in medicated feed for fattening pigs in The Netherlands and a preliminary hazard and risk evaluation carried out by the Dutch authorities concluding that dapsons was very likely to be genotoxic.

Specifically, the CVMP was requested to address the following points:

1. Is dapsons to be considered genotoxic?
2. Does sulphamethoxazole from other suppliers than the ones investigated by The Netherlands contain dapsons? If yes, what are the concentrations?
3. Do the levels of dapsons, present as an impurity in sulphamethoxazole from any supplier, and applied to food producing animals, imply an unacceptable risk for consumers?
4. Do the levels of dapsons, present as an impurity in sulphamethoxazole from any supplier, imply an unacceptable risk for animals?
5. Could the finding of dapsons as impurity in sulphamethoxazole be relevant for other sulphonamides?



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

The procedure started on 15 September 2011.

Opinion

The CVMP having considered the matter, reviewed the report from the Dutch authorities on the issue including the data assessed in the report, the results of a new *in vivo* study (micronucleus test in bone marrow cells of mouse), data made available from studies used in an EFSA opinion concerning dapsone (The EFSA Journal (2005)248, 1-16) and the advice of the ad-hoc expert working group created specifically by the CVMP to assess the genotoxic potential of dapsone, came to the following conclusions:

A significant increase of frequencies of structural aberrations were observed only at the highest doses in two *in vitro* chromosomal aberrations tests which could have been related to cytotoxicity since other *in vitro* tests were found to be negative.

One oral *in vivo* study in mouse was provided. The results showed statistically significant structural chromosomal aberrations in bone marrow, a statistical significant increase in micronuclei and chromosome breaks in spermatocytes were also observed. Studies in rats also showed tumours in multiple sites (spleen, peritoneum and thyroid).

The additional *in vivo* study in mice using the intraperitoneal route showed no significant increase in micronucleated polychromatic erythrocytes. It was concluded that the positive finding in the initial *in vivo* study was most likely related to folate deficiency as folate deficiency can appear in the gut flora microorganisms following oral administration. This conclusion is consistent with the EFSA opinion on dapsone that includes another *in vivo* study in mice, also using the intraperitoneal route.

The CVMP therefore concluded that dapsone does not have a direct genotoxic effect and that the clastogenicity and carcinogenicity seen in laboratory animals after long-term oral exposure to high doses of dapsone are the consequence of a non-genotoxic mode of action.

For substances that have no direct genotoxic mode of action it is considered possible to calculate a margin of safety or a threshold regarding the risk of developing tumours. In this case the rodent carcinogenicity study was considered the most relevant study to calculate the margin of safety or a maximum daily exposure to be considered safe in terms of cancer risk to the consumers based on the lowest concentration used in the rodent study at which effects were still observed (Lowest Observed Effect Level (LOEL)). There was no concentration available at which no effects were observed (No Observed Effect Level (NOEL)).

Based on the pharmacokinetic modelling to derive a (mean) steady state concentration for dapsone in muscle and plasma, consumer exposure to residues based on ingestion of 500g meat per day and on the LOEL, a margin of safety of 9.7×10^5 was estimated. Using the same LOEL and additional safety factors, a maximum daily exposure to be considered safe in terms of cancer risk to the consumer was calculated to be 0.252 mg/person day or 4.2 $\mu\text{g}/\text{kg}$ bw which is considerably higher than the worst case exposure of 0.0433 $\mu\text{g}/\text{kg}$ assuming dapsone impurity of 60 $\mu\text{g}/\text{g}$ (maximum impurity level found by the Dutch authorities in sulphamethoxazole samples).

In addition veterinary medicinal products containing sulfamethoxazole are subject to withdrawal periods over which concentrations of dapsone will decrease which widens the margin of safety. Even considering that a NOEL from the carcinogenicity study could not be identified and that a LOEL was

used in the calculations, the margin of safety estimated and the maximum daily exposure in terms of cancer risk constitute a sufficient margin to conclude that the carcinogenic risk for the consumer from sulfamethoxazole residues contaminated with dapsone is negligible.

With regard to the animal health risk, it is concluded that the risk for chickens and pigs is negligible, due to the short time that these animals live before they are slaughtered. With regard to cattle, in particular dairy cattle, a margin of safety of 6.77×10^4 was calculated which allows to conclude that the risk for cattle in terms of carcinogenicity is also negligible.

From the information received from the national competent authorities in the EU/EEA Member States three suppliers of sulphamethoxazole as active substance for veterinary medicinal products were identified. The assessment reports for the Certificate of Suitability (CEP), available for all three suppliers (EDQM), confirm that the specifications of all sulphamethoxazole suppliers are in line with the European Pharmacopeia monograph requirements. The European Pharmacopeia monograph of sulphamethoxazole mentions limits for six specific impurities, but does not list dapsone. Other individual impurities may be present up to a level of 0.1 %. Analysis performed by the Dutch authorities on sulphamethoxazole available on their market confirmed that dapsone contamination was below the limit of 0.1 % as established in the European Pharmacopeia for non-listed impurities (levels found ranged from 8.4 to 59 µg/g).

Analysis on dapsone contamination in sulphamethoxazole supplied to other EEA-countries, other than The Netherlands, were not available. However from consideration of the manufacturing processes it can be assumed that for sulphamethoxazole as well as other sulphonamides it is likely to expect contamination with dapsone.

The situation might be different from one sulphonamide to another as it will be very much dependent on the synthesis of the compound in question. It can be assumed that levels of dapsone that might be present in other sulfonamides are in the same order of magnitude. It can therefore be concluded that as far as dapsone concentrations in other sulphonamides are in the order of magnitude as observed in the case of sulfamethoxazole, the risk for humans in terms of carcinogenicity is likely to be negligible when consuming meat from pigs, cattle or chickens treated with veterinary medicinal products containing other sulfonamides contaminated with dapsone.

Taking into account that:

- Dapsone is considered not to be a direct genotoxic substance.
- Carcinogenicity and clastogenicity seen in laboratory animals after long-term oral exposure to high doses of dapsone are most probably the consequence of a non-genotoxic mode of action.
- For consumers, the carcinogenic risk from residues from animals that have been treated with products containing sulfamethoxazole contaminated with dapsone is considered to be negligible.
- The carcinogenic risk for chicken, pigs and cattle is considered negligible.

The CVMP considers that specific management measures with regard to dapsone as an impurity in veterinary medicinal products containing sulphonamides are not required because the overall safety assessment has revealed that dapsone when found at impurity levels up to 60 µg/g sulfamethoxazole is neither of consumer safety nor of animal safety concern.

Sulfonamides are used in veterinary and human medicinal products and it is likely that dapsone is also present in sulfonamides used in human medicines. The CVMP therefore recommends that the relevant

elements of this evaluation are brought to the attention of the CHMP for information and further consideration, if considered appropriate.

In addition the CVMP recommends that the Agency liaises with the EDQM for consideration of the relevant parts of this assessment in the context of the monographs in the European Pharmacopeia for sulphamethoxazole and sulphonamides in general.

Taking into account that dapsone is classified as a forbidden substance under the EU MRL legislation (table 2 of the Annex to Commission Regulation (EU) No. 37/2010) consideration could be given to establishing a reference point for action for the substance by the European Commission. The calculations concerning the maximum daily exposure to be considered safe in terms of cancer risk to the consumer could be relevant in this context.

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

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

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

Utrecht, The Netherlands, 12 July 2012

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

Appendix 1: CVMP assessment report -Dapsone