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Committee for Medicinal Products for Veterinary Use

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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

For veterinary medicinal products containing gentamicin for parenteral administration to horses

Basis for opinion

On 10 April 2018 the Executive Director of the European Medicines Agency requested the Committee for Medicinal Products for Veterinary Use (CVMP) for a scientific opinion under Article 30(3) of Regulation (EC) 726/2004 concerning veterinary medicinal products containing gentamicin for parenteral administration to horses.

Veterinary medicinal products containing gentamicin for parenteral administration to horses are currently authorised in a number of EU Member States.

The active pharmaceutical ingredient (API) gentamicin sulfate is manufactured via a standard fermentation process that includes the raw material peptone which may be derived from fish. There are three gentamicin sulfate manufacturers who supply the EU market, two of which are holders of a Certificate of Suitability (CEP) to the monograph of the European Pharmacopeia.

Between 2015 and 2017, at least 154 adverse events (AEs) in horses were reported following the use of gentamicin solution for injection in the European Union, the majority of which described anaphylactic-type reactions, a number of which (at least 9) were associated with death.

In the active substance batches of the gentamicin-containing veterinary medicinal products involved in these reported AEs, residues of histamine were found, which were considered to be the underlying cause of the reactions. All AEs are associated with a single manufacturer of API. The investigation by the concerned API manufacturer revealed the root-cause of the high levels of histamine as being related to inappropriate storage conditions of fish at the premises of one fish peptone supplier, which resulted in histamine residues in the API used to manufacture the affected finished products.

Three manufacturers of the active substance for the EU market have been identified, two of whom hold CEPs to the monograph of the European Pharmacopeia. The third supplier does not hold a CEP. A limit



for histamine of 16 ppm was applied by one of the manufacturers of the active substance as an interim limit pending the results of further investigations.

During meetings of the veterinary incident review group and incident review network (for human medicinal products) held in 2017-2018, it was decided that a further consideration of the issue would be necessary.

In light of the above, it was considered necessary to ask the CVMP to provide an opinion under Article 30(3) of Regulation (EC) No 726/2004 on the need for inclusion of a maximum limit for histamine in API specifications for gentamicin sulfate and/or finished product specifications for gentamicin-containing medicinal products for parenteral administration to horses.

Taking into account that the underlying cause is the same for medicinal products for human and veterinary use a parallel procedure for a CHMP Opinion under Article 5(3) of Regulation (EC) No 726/2004 was initiated.

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

- The levels of histamine detected during the manufacture of the API and the finished product where available. In instances where testing for histamine was not carried out for the finished product but was carried out for the API then a reasoned estimate of the levels of histamine present in the finished product was to be established;
- The adverse events reported to the marketing authorisation holders between 1 January 2013 and 31 December 2017, in addition to published research on histamine levels, to ascertain the potential causal association between the reactions that have occurred and the use of gentamicin products containing histamine;
- Drawing from the data provided on the two points above, the Committee was to propose an acceptable level of histamine in the API and/or the finished product of gentamicin containing products used parenterally in horses.

The procedure started on 18 April 2018.

Opinion

The Committee, having considered the matter, reviewed data from published literature, data received from the active substance manufacturer and marketing authorisation holders, and consulted with the Committee for Medicinal Products for Human Use, came to the following conclusions on the issues raised in the request for an opinion.

Based on the information available at this time, it is not possible to state with absolute certainty that finished product manufactured with API batches containing histamine at the interim limit of 16 ppm will not be associated with AEs in the event of parenteral (intravenous) administration to horses. Therefore, the CVMP recommends that the limit be reduced further. Additional measures are also proposed by CVMP to minimise the potential risk of histamine contamination of veterinary medicinal products.

The CVMP recommends the following measures:

1. The interim limit for histamine in gentamicin sulfate which utilises fish peptone as a raw material should be reduced to as low as reasonably practicable in line with safety and pharmacovigilance data, manufacturing capability and batch data. A limit of 8 ppm is below the limit of 0.1 µg/kg bodyweight histamine which is considered to be associated with no or only very mild general

clinical effects according to the work of Eyre and Lewis (1973), is considered to be within the current manufacturing capability of the API manufacturer/supplier based on current batch data and is within the validated range of the analytical method.

2. The EDQM should consider further revision of the Ph. Eur. monograph 1468 on 'Products of Fermentation' with respect to the requirements on the quality of raw materials. The following text is proposed as a possible alternative to the current text in the raw materials section of the monograph:

'Special attention must be paid to minimising the public and animal health risks of histamine and other biogenic amines from fish and fishery products. Where fish-based raw materials are used in the synthesis of the drug substance the manufacturer should carry out a risk assessment and propose suitable limits for histamine levels in the raw material based on experimental purge studies. Additionally, the manufacturing process should include at least one validated step to remove residual histamine and the drug substance specification should include a qualified limit for histamine levels'.

3. The API manufacturer should continue to investigate the use of alternative sources of peptone in order to minimise the presence of histamine in gentamicin sulfate. Results should be presented to the relevant competent authorities with a view to revising the API manufacturing process that is registered for gentamicin sulfate utilising fish peptone.
4. The API manufacturer should continue to optimise the gentamicin sulfate fermentation and purification processes to reduce further the histamine levels in the final API. Results should be presented to the relevant competent authorities with a view to revising the API manufacturing process that is registered for gentamicin sulfate utilising fish peptone.
5. Marketing authorisation holders should continue to monitor any new adverse event reports and to notify regulatory authorities in accordance with pharmacovigilance reporting requirements. Any adverse event reports should include details of the levels of histamine in the relevant API and finished product batches.

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

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

Appendix 1: CVMP assessment report