Annex

Scientific conclusions and grounds for the suspension of the marketing authorisation of the 1.5 mg/ml presentation

Background information

Further to the 2009 Sampling and Testing Programme, out of specification (OOS) results for assay, dissolution and uniformity of dose of Flexicam 1.5 mg/ml Oral Suspension for dogs were obtained.

These findings were assessed by the Rapporteur and a list of questions was transmitted to the Marketing Authorisation Holder. The answers provided by the Marketing Authorisation Holder were assessed by the Rapporteur and were found to be unsatisfactory in that insufficient data was provided to explain the root cause of the OOS results. The OOS results obtained gave rise to concerns relating to accuracy of dosing and, consequently, safety and efficacy in treated animals. Furthermore, a concern has been raised relating to preparation time (shaking before use) required to achieve a homogenous suspension prior to administration. It was noted that, if required, a prolonged preparation time may be impractical for this product.

Based on the available data, the Rapporteur concluded that there was a fundamental issue with the quality of the product which was likely to adversely affect accurate dosing of the product and that the issue was likely to be applicable to all batches on the market. Following the evaluation of the Rapporteur, the supervisory authority (Danish Medicines Agency) initiated a recall of all batches on the market at pharmacy and/or veterinary surgeon level. In addition, a stop on further sales of batches was agreed until such time as this issue is resolved. The quality defect has been classified as a Class II defect following the Compilation of Community Procedures.

The Rapporteur recommended that the marketing authorisation be suspended until all outstanding issues are satisfactorily resolved by the submission of further data and appropriate variations.

Therefore, in order to allow CVMP to decide on adequate regulatory action, the CVMP asked the European Commission to refer officially the matter to the CVMP for its opinion on the measures necessary to ensure the safe use of Flexicam 1.5 mg/ml Oral Suspension for dogs in accordance with the procedure laid down in Article 45 of Regulation (EC) No 726/2004 (on the basis that the Marketing Authorisation Holder is no longer complying with Title VIII of Directive 2001/82/EC). The European Commission consequently initiated an Article 45 referral procedure and the procedure started on 13 July 2010.

The CVMP has recommended the suspension of the Marketing Authorisation for Flexicam 1.5 mg/ml Oral Suspension for dogs.

Medicinal product no longer authorised

Scientific Conclusions

The Marketing Authorisation Holder concluded that the most likely root cause of the out of specification (OOS) results is incorrect sample preparation procedure due to any one or a combination of the following:

- incorrect re-suspension technique;
- product standing time between re-suspension and sample extraction and/or
- dosage sample too small.

However, no data to support this conclusion is provided. The Marketing Authorisation Holder has not provided data to demonstrate that vigorous shaking and/or prolonged stand time would result in the type of results reported by the OMCL. Such data could have supported the Marketing Authorisation Holder's conclusion. The results of tests to optimise sample preparation are also outstanding, and the Marketing Authorisation Holder has not addressed the practicality of the proposals from a user point of view. Should a 5-10 minute 'preparation time' be required before the product is ready for administration, this has implications for use in the field and is likely to be considered impractical. This issue must be addressed by the Marketing Authorisation Holder.

The Marketing Authorisation Holder has not provided comparative data as requested, to support the contention that use of 1 drop (rather than 2 drops) in the test for the uniformity of individual doses is the most likely cause of the 0MCL 00S finding. As the product is a suspension, it is possible that prolonged storage at temperatures below 25°C may adversely affect re-suspendability, but the applicant has not commented on the request to initiate low temperature stability studies.

The Marketing Authorisation Holder has primarily relied on existing stability and process validation data to support the contention that the product is of appropriate quality. However, this data is not sufficient as it does not address all of the specific questions raised and does not include results for uniformity of dose of oral drops. The Marketing Authorisation Holder's own data from the affected batches show that 2 of the 3 reserve batches tested are not in compliance with Ph. Eur. criteria for this parameter when retested. As this parameter was within specification at release for all 3 batches and is not reported in stability studies, it must be assumed that the issue will also be applicable to other batches on the market.

Grounds for suspension

Based on the available data, the CVMP concludes that there is a fundamental issue with the quality of the product which will adversely affect accurate dosing of the product. The issue is likely to be applicable to all batches on the market. The defect has been classified as a Class II defect. Given that there are alternative products available it is recommended that the authorisation be suspended until all outstanding issues are satisfactorily resolved.

Until the above issues relating to out-of-specification results for assay, dissolution and uniformity of dose of Flexicam 1.5 mg/ml Oral Suspension for dogs have been satisfactorily addressed by the submission of data (via appropriate variation applications) the Marketing Authorisation will remain suspended.

Medicinal product no longer authorised