COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report for the approval of type II variation and lifting of suspension of the Marketing Authorisation

Bacicoline-B, powder for eardrops

(colistimethate sodium/ bacitracin/hydrocortisone acetate)

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This module reflects the scientific discussion for the lifting of suspension of the marketing authorisation of Bacicoline-B, powder for eardrops following a grouped quality type II variation. The marketing authorisation was re-established on 6 November 2020.

I. RECOMMENDATION

Based on the review of the submitted type II quality variations the Medicines Evaluation Board (MEB) considers that all issues and uncertainties regarding the manufacturing, quality control and stability of the product, which has led to the refusal of the type II quality variation and suspension of the marketing authorisation for Bacicoline-B, powder for eardrops from Daleco Pharma b.v., are resolved. Therefore, the MEB has regranted the marketing authorisation for this product on 6 November 2020.

II. EXECUTIVE SUMMARY

II.1 Introduction

Bacicoline-B contains three active substances, namely colistin, bacitracin and hydrocortisone. Colistin is an antibiotic with a bactericidal effect against gram-negative bacteria, in particular against *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *E. coli*, *Moraxella lacunata*. Bacitracin is mainly active against gram-positive bacteria: streptococci, pneumococci and enterococci. The third active substance, hydrocortisone, is a weak-acting corticosteroid with a rapid and reliable efficacy. It decreases the inflammatory symptoms that are usually part of the infection.

The product is indicated for the treatment of inflammatory symptoms and infections of the external auditory canal, otitis externa diffusa, secondary infected eczema of the external auditory canal, such as eczema seborrhoicum and constitutional eczema, caused by bacitracin and colistin sensitive bacteria.

Until recently, Bacicoline-B was marketed in France as a sterile eye drop and in the Netherlands as a sterile ear drop. In January 2015 marketing of the product was ceased in France. Since then, The Netherlands is the only country where Bacicoline-B was authorised and marketed.

Suspension of marketing authorisation
In June 2016 the marketing authorisation holder (MAH) was informed that a submitted type II quality variation could not be approved; there were still questions about the new packaging and stability data were missing. Despite repeated requests, the outstanding questions remained unanswered. Nevertheless, the MAH launched the unapproved black bottle containing a non-sterile preparation after June 2016. Signals were received from the field at the end of May 2018 indicating that Bacicoline-B cannot be prepared for administration in accordance with the package leaflet. This has been reported to the Dutch Healthcare Inspectorate (IGJ).

In June 2018, the MAH submitted data, consisting of a preliminary justification of the use of the black opaque plastic bottles and stability studies in which the product packaged in the new black bottles were used. Results of the stability studies showed levels of impurities above approved limits. Subsequently, the MEB concluded that the quality of the product could no longer be guaranteed as the preparation, packaging and package leaflet of the product did not longer meet the standards required for registration.

The Board decided to suspend the marketing authorisation for Bacicoline-B based on article 51, section 1, title and under d of the Dutch Medicines Act in conjunction with article 49, section 1 and article 50, section 1. In consultation with the Dutch Healthcare Inspectorate (IGJ), the product was recalled from pharmacists in August 2018.

At the hearing concerning the suspension of the product on 1 October 2018, the MAH had the opportunity to present its views in respect to the proposed refusal. After this hearing the Board concluded that the major objection and uncertainties remain. The Board suspended the marketing authorisation for Bacicoline-B on 29 October 2018.

Submitted variation

The MAH submitted a grouped type II variation to change aspects of the production location, production process and packaging and specification of the product. The following types of variations have been submitted:

- B.II.a.3.b.6 Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level
- B.II.b.1.f (x2) Replacement or addition of a site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products
- B.II.b.3.a (x4) Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product
- B.II.b.4.a Change in the batch size (including batch size ranges) of the finished product (up to 10-fold compared to the originally approved batch size)
- B.II.b.4.d Change in the batch size (including batch size ranges) of the finished product (the change relates to all other pharmaceutical forms manufactured by complex manufacturing processes)
- B.II.b.5.z (x2) Change to in-process tests or limits applied during the manufacture of the finished product
- B.II.d.1.e Change in the specification parameters and/or limits of the finished product (change outside the approved specifications limits range)
- B.II.d.2.d (x2) Change in test procedure for the finished product
- B.II.e.1.a.3 Change in immediate packaging of the finished product

In addition, the MAH submitted a Type II variation (B.I.a.1.b) for the introduction of a manufacturer of the active substance hydrocortisone acetate supported by an Active Substance Master File. This supplier has always been used but this was not formally laid down in the dossier.

In this Public Assessment Report (PAR), the quality documentation submitted in scope of the variations is discussed.

This is an exclusively national procedure and no concerned member states are directly involved.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

The MAH has submitted a type II quality variation to introduce a new manufacturer for hydrocortisone acetate and a type II quality variation as the whole production of Bacicoline-B has been transferred to the new manufacturer. In addition, a change in packaging material of the solvent is proposed from an LDPE bottle with LDPE dropper and PP screw cap to a glass bottle with rubber stopper. The manufacturing process has been optimised and the dossier has been updated.

Drug substance
The drug substance hydrocortisone acetate is a well-known drug substance which is described in the Ph.Eur.

Manufacturing process
Sufficient information on the synthesis of the substance has been provided, including the sterilisation. Validation data of the sterilisation process has also been provided.

Quality control of drug substance
The drug substance specification contains tests for identification, loss on drying, specific optical rotation, residue on ignition, related substances, assay, water content melting range, residual solvents, colour in solution, DSC, particle size, sterility and bacterial endotoxins. The specification is acceptable in view of the Ph.Eur. requirements and the synthesis process. The analytical procedures have been adequately described in validated. Batch analysis results have been provided of three commercial scale batches.

Stability
An expiry period for the sterile drug substance of 5 years can be granted based on the provided stability data of four batches stored at 25 C/65% RH (up to 48 months) and 40 C/75% RH (up to 6 months) in aluminium tins inside double polyethylene bags. No specific storage restrictions are necessary.

Drug product

The product was marketed as a powder to be reconstituted using a solvent supplied with the powder. The product was approved in The Netherlands as a pack consisting of:

- one amber glass vial with powder, containing the active substances and excipients as a sterile powder, closed with a chlorobutyl rubber stopper
- one white, transparent LDPE bottle with dropper containing the solvent (purified water), closed with a white HDPE screw cap

There are two pack sizes on the market to yield either 5 or 7.5 ml of suspension.

Packaging system

The variation has been submitted to change the packaging to guarantee a more appropriate packaging, allowing terminal sterilisation. The new immediate packaging consists of:

- Powder supplied in a brown type II glass bottle, closed with a grey bromobutyl rubber stopper, kept in place by an aluminium cap with a blue polypropylene flip off.
- Solvent supplied in a brown type II glass bottle, closed with a grey bromobutyl rubber stopper, kept in place by an aluminium cap with a white polypropylene flip off
- Polyvinyl chloride dropper with high density polyethylene screw cap is supplied in a blister made of cast nylon film, low density polyethylene film, and medical Kraft paper.

According to the old product information, 5-6 drops should be administered (using the old dropper). Based on the obtained results for the old dropper, this would be equivalent to 132.5 to 159 µL. Based on the obtained results for the new dropper, this would be equivalent to approx. 5.9 to 7.1 drops. Therefore, the product information has been updated to and now advices to administer 6-7 drops using the new dropper.
Additionally, a pack size has been deleted. This is considered justified.

Batch size

With the transfer of manufacturing to a different site, batch sizes of the solvent and powder have been increased. This has been appropriately justified.

Manufacturing process

Four minor changes have been made in the manufacturing process of the powder and the solvent. The changes have been appropriately characterised and are acceptable.

Excipients

The composition of the powder has not been changed. For the composition of the solvent the excipient ‘purified water’ has been replaced by ‘water for injections’, which is acceptable.

Quality control of the drug product

Several in-process tests have been added and in-process tests for the solvent have been deleted. In addition, certain in-process limits have been tightened.
‘Conductivity of the solvent’ has been added as specification method with its corresponding test method. This test for purity replaces ‘Freezing point of the solvent’. Therefore,

specification parameter 'Freezing point of the solvent' has been deleted as non-significant (obsolete) specification parameter. The specification 'uniformity of mass' of the powder has been deleted, since the individual fill weight is already checked as in-process control.
The analytical procedure for identification is replaced by new updated test procedures and for content two types of procedures have been deleted.

Stability of drug product
Results from stability testing after 3 months storage at long-term conditions have become available for two batches of powder and two batches of the solvent. These results remained within specifications and no significant changes occurred.
The stability data of reconstituted powder in the amber glass vial with the PVC dropper has been provided (10 days at 5°C and 25°C). The results are within the proposed specification. The previously and currently provided data is sufficient to grant an in-use period of 10 days. No specific storage restriction is necessary for the reconstituted product.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sufficient information has been provided on a new packaging for both the drug product and the solvent. For these new packagings, sufficient stability data has been provided, including in-use stability data with the newly proposed dropper. The suitability of this device has been shown and the drug product can adequately be administered using the dropper. The brown glass vials for the solvent are acceptable to allow for transfer of the full quantity of solvent to the powder and the brown glass vials for the drug product allow for sufficient visual confirmation of a fully homogenised suspension.

Therefore, the Board considers the issues resolved as the MAH produces the product in accordance with the current acceptable dossier and has submitted variations for the change of the production process. As the assessment of the variations shows that the production process meets the admission requirements, the Board has lifted the suspension on 6 November 2020.