COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

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

Bacicoline-B, powder for eardrops

(colistimethate sodium/E bacitracin/hydrocortisone acetate)

RVG: 01761

Date: 21 January 2019

This module reflects the scientific discussion for the suspension of the marketing authorisation of Bacicoline-B, powder for eardrops following a grouped quality type II variation. The marketing authorisation was suspended on 29 October 2018.

I. RECOMMENDATION

Based on the review of the submitted type II quality variation the Medicines Evaluation Board (MEB) considers that there is a major issue and several 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.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

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 is authorised and marketed.

The MAH submitted a grouped type II variation to change the immediate packaging of one of the components of the finished product, i.e. the powder for suspension, and a change in the manufacturing process. The following types of variations have been submitted:

- B.II.e.1.a.4. - Change in the immediate packaging of the finished product; qualitative and quantitative composition; the change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.
- B.II.f.1.a.1. - Change in the shelf-life or storage conditions of the finished product; reduction of the finished product as packaged for sale.
- B.II.d.1.f. - Change in the specifications parameters and/or limits of the finished product; deletion of a specification parameter which may have significant effect on the overall quality of the finished product.

- B.II.b.3.a. - Change in the manufacturing process of the finished product, including an intermediate used in the manufacturing of the finished product; minor change in the manufacturing process.
- B.II.e.5.b. - Change in pack size of the finished product - deletion of pack size(s).

The proposed amended product consists of a black, opaque bottle containing a non-sterile preparation. During the procedure the MAH launched this unapproved proposed product on the market.

In this Public Assessment Report (PAR), the quality documentation submitted in scope of the variation is discussed. As rejection of the variation led to suspension of the marketing authorisation, the medical need and the possible consequences of shortage of the product have been assessed.

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 change the packaging, for the reduction of the shelf life, deletion of sterility parameter, to bring a minor change in the manufacturing process and to delete one of the two pack sizes.
Based on the review of the quality data and the MAH's response to the questions raised it was concluded that the type II variation is not approvable as several major issues and uncertainties remain. The details of the outstanding major objection and other uncertainties are described below.

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.

<u>Packaging system</u>
The submitted variation to change the packaging in order to use a non-transparent packaging system for the powder is not considered acceptable and therefore a major objection remains (see below).

The currently approved packaging system (amber glass bottle for the powder) and transparent LDPE bottle (for the solvent) allows for a visual check for formation of a homogenous suspension, without lumps or large particles. This is not possible with the proposed black LDPE bottle. After initial preparation of the suspension, the patient should shake the bottle before each use. A visual check on the resuspension of the product is also not possible at this stage of use. This is considered a substantial risk to the patient, as medication errors may occur (e.g. under-dosing) if the product is not fully resuspended.

Quality control of the drug product

The MAH appeared to use a higher limit for a specified impurity in the submitted variation than the limit which has been used for the initial registration. In view of the maximum daily dose (MDD) and the guideline ICH Q3B, a limit above the qualification threshold of 0.5% is not acceptable without further qualification data. Hence the MAH should indicate their proposal of widening the shelf-life limit for an impurity in the application form and provide qualification data. A shelf-life period could not be granted as the limit needed to be fully confirmed first.

Stability of drug product

The in-use stability data of the product from a chemical and physical point of view during the claimed ten days in-use period using the registered analytical procedures, has not been provided.

III.2 Clinical aspects

Rejection of the variation application has led the suspension of the marketing authorisation as the quality of the product can no longer be guaranteed. Therefore, the medical need and possible consequences of shortage of the product have been assessed.

Possible clinical implications of the outstanding major objection

The major concerns with regard to the proposed changes in the manufacturing process and the change of the primary packaging material are of clinical nature. Due to the observed lump formation, the efficacy of the finished product may be affected. To prepare the ear drops, the solvent needs to be added to the bottle containing the powder. When lumps have been formed, it may be difficult to have all the powder reconstituted, which may lead to medication errors, such as underdosing. This problem is further complicated by the fact that the new primary packaging material is a black opaque bottle. After the solvent has been added, it cannot be easily checked whether all powder has been suspended or whether there are unnecessary large particles left in the suspension.

When production of the Bacicoline-B powder is transferred to the alternative production line, it will no longer be aseptically manufactured. Bacicoline-B is indicated for a.o. otitis externa and contra-indicated for otitis media. However, it is known from clinical practice that ear drops indicated for treatment of infection of the outer ear, such as Bacicoline-B, are widely used off-label for the treatment of otitis media. When non-sterile Bacicoline-B is used

off-label in patients with a perforated eardrum, the safety of these patients may no longer be guaranteed.

Otorhinolaryngology physicians indicate that Bacicoline-B is the medicine of first preference in the treatment of acute otitis media ("off-label" indication). There is a need for the product in clinical practice. About 200,000 patients annually use Bacicoline-B. Since 2015 the product has been included in the relevant NHG Standard. In addition, the published study by Van Dongen (2014[1]) can also be used as an objective basis for this indication.

The MAH argues that the possibility of contamination resulting from the use of the non-sterile ear drops is limited. In addition, the risk for patients of an additional infection is very minimal due to the self-preserving effect (for both bacteria and fungi) of Bacicoline-B ear drops. The MEB supports this assessment, where it is noted that sterility is not a requirement since the "otitis media" indication is not in the label. If this is the case in the future, the product must comply with the requirements in the Ph. Eur. and must be sterile.

Availability of alternatives
Alternatives for the use of Bacicoline-B are Sofradex and Otiflox. Sofradex is produced sterile and is currently available. Bacicoline-B has been withdrawn from the market in France and there are no registrations in other countries. Therefore, it is not possible to import Bacicoline-B from abroad. Bacicoline-B s especially used in children and already questions have been raised about its availability.

In accordance with the '*Criteria for classification of critical medicinal products for human and veterinary use*', a medicine is classified as critical on the basis of therapeutic use and availability of alternatives. The indication for this product is not life threatening and given the fact that (only a limited number) of alternatives are available, the product is not labelled critical.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The variation application has been discussed during the MEB Board meetings of 2 June 2016 and 2 August 2018.

The MEB has a strong preference for a sterile manufacturing process for this product. The MAH substantiated why, according to them, the non-sterile product is also acceptable. In June 2016 the MAH was informed that the 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.

[1] Van Dongen et al. A Trial of Treatment for Acute Otorrhea in Children with Tympanostomy Tubes. N Engl J Med 2014; 370:723-733.

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 dated 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.

The suspension can be lifted if the MAH produces the product in accordance with the current (acceptable) dossier or if the company submits a variation for the change of the production process and the assessment shows that the proposed modification of the production process meet the admission requirements. The MEB acknowledges the special position of Bacicoline-B on the Dutch market (product of first preference) and regrets that it is currently no longer available. The Board notes that the product is not (or has not been) on the market in other EU countries, and these countries can substitute with another product (locally or systemically).