COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Natriumcromoglicaat BB 100 mg/5 ml, oral solution

(sodium cromoglicate)

NL/H/4088/001/DC

Date: 13 March 2019

This module reflects the scientific discussion for the approval of Natriumcromoglicaat BB 100 mg/5 ml, oral solution. The procedure was finalised at 13 April 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Natriumcromoglicaat BB 100 mg/5 ml, oral solution from Brown & Burk UK Limited.

The product is indicated for prophylactic treatment of allergic symptoms caused by components of the feed, if these components cannot be avoided.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nalcrom, drank 100 mg (NL License RVG 12446) which has been registered by means of a national procedure in the Netherlands by Sanofi-Aventis Netherlands B.V. since 8 May 1989.

The concerned member state (CMS) involved in this procedure was the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Natriumcromoglicaat BB is a clear colourless solution. Free from any visible particles.

The solution is packed in a 5 ml ampoule of LDPE Blow fill seal (BFS) container with twist off cap. Each 5 ml ampoule of oral solution contains 100 mg sodium cromoglicate.

The excipient is water for injections.

II.2 Drug Substance

The active substance is sodium cromoglicate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Sodium cromoglicate is a white or almost white, crystalline, odourless, hygroscopic powder. It is freely soluble in water, practically insoluble in alcohol, in chloroform and in ether. No polymorphic form has been observed.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the

chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The composition is similar to the reference product and the physicochemical properties are comparable. Biowaiver is granted based on the considerations that the generic product is an aqueous oral solution, same as reference product with same concentration of active substance, same excipient, same method of administration and comparable physicochemical parameters.

Manufacturing process
The drug product is prepared by a non-standard manufacturing process and comprises preparation of the bulk solution, pre-filtration and aseptic filtration and filling in final container with blow-fill-seal process. Information on filters used and some relevant process parameters have been added. The in process controls and control of critical steps are acceptable. Process validation has been adequately performed on one batch of minimum batch size and three batches of maximum batch size. Filter validation has been adequately performed.

Control of excipients
The excipient water for injections complies with Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, extractable volume, colour of solution and particulate contamination, assay, related substances and

sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from four batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability studies at accelerated (6 months), and long-term conditions (36 months) have been provided for one batch at minimum batch size and three batches at maximum batch size. The batches are the same as used in process validation. All stability data comply with the specifications. The product is photostable in the proposed packaging.
On basis of the data submitted, a shelf life was granted of three years. The labelled storage condition is “this medicinal product does not require any special storage condition”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Natriumcromoglicaat BB has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Natriumcromoglicaat BB is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nalcrom, drank which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been

provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sodium cromoglicate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Natriumcromoglicaat BB 100 mg/5 ml, oral solution is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Natriumcromoglicaat BB 100 mg/5 ml, oral solution is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Natriumcromoglicaat BB.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity
Important potential risks	--
Missing information	--

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nalcrom, drank. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Natriumcromoglicaat BB 100 mg/5 ml, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Nalcrom, drank. Nalcrom, drank is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Natriumcromoglicaat BB 100 mg/5 ml, oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 April 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse