CBG MEB

Public Assessment Report

Scientific discussion

Poliomyelitisvaccin multidose, suspension for injection, 2.5 ml

(inactivated poliomyelitis virus type 1,2 and 3)

NL License RVG: 114720

Date: 19 July 2018

This module reflects the scientific discussion for the approval of Poliomyelitisvaccin multidose, suspension for injection 2.5 ml. The marketing authorisation was granted on 12 November 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
GPEI	Global Polio Eradication Initiative
ICH	International Conference of Harmonisation
IPV	Inactivated Polio Vaccine
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Poliomyelitisvaccin multidose, suspension for injection, 2.5 ml from Bilthoven Biologicals B.V.

The product is indicated for the active immunisation against poliomyelitis.

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

This national procedure is a line extension to an existing marketing authorisation. The original product, Poliomyelitisvaccin, suspension for injection, 0.5 ml (NL License RVG 17642), is registered in The Netherlands since 2 December 1993.

The original product is marketed as a single dose, containing 0.5 ml suspension for injection. The line extension enables sufficient supply of the vaccine for the Global Polio Eradication Initiative (GPEI) Strategic Plan. Hence the new 2.5 ml multidose product contains five doses and has the same composition as the single-dose preparation.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC, for which administrative, chemical-pharmaceutical, pre-clinical and clinical data have been submitted. Most of the data in the dossier of Poliomyelitisvaccin multidose, suspension for injection, 2.5 ml was already submitted in the approved dossier of Poliomyelitisvaccin, suspension for injection, 0.5 ml.

II. QUALITY ASPECTS

II.1 Introduction

The multidose product is an orange-yellow to orange-red suspension for injection of formaldehyde inactivated and sterile filtered virus.

The product contains five doses. The active substances in one dose (0.5 ml) correspond to three inactivated polioviruses*:

- type 1 (Mahoney) 40 D-antigen units
- type 2 (MEF 1) 8 D-antigen units
- type 3 (Saukett) 32 D-antigen units

**The viruses are cultured on Vero-cells*

The product is packed in a 4 ml hydrolytic type I glass. Vials are closed with a rubber stopper and an aluminium flip-off cap. Each vial is filled with 3.1-3.2 ml Inactivated Polio Vaccine (IPV) (overfill 28-32%).

The excipients are: formaldehyde (12.5 µg) (E240), 2-phenoxyethanol (2.5 mg), Medium 199 mainly containing amino acids, minerals and vitamins (0.1 ml), disodium hydrogen phosphate dehydrate (E339), sodium chloride, potassium chloride (E508), magnesium sulphate (E518), phenol red, calcium chloride (E509), polysorbate 80 (E433), potassium dihydrogen phosphate (E340) and water for injection.

II.2 Drug Substances

The manufacture, quality control, and stability of the drug substances is identical to the approved 0.5 ml single-dose product. This is acceptable.

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 formulation of IPV's was developed in 1959 to capacitate for both single-dose and multidose presentations. The formulation of IPV contains 2-phenoxyethanol and formaldehyde to ensure microbiological quality during production and storage. Data on the functionality testing of rubber stoppers and container closure integrity testing are provided. Results comply with the requirements. The new IPV multidose product has the same composition as the single-dose preparation. For both presentations, osmolality and chloride content are for information only. If results of sufficient batches are available, a specification will be set. This commitment is noted.

Sufficient additional data has been provided regarding preservative effectiveness, and process validation for filling multidose IPV batches on commercial scale. Pharmaceutical development has been adequately performed.

Microbial attributes
The MAH adequately evaluated the preservative effectiveness of the multidose formulation using tests as described in Ph.Eur. chapter 5.1.3. and drug product samples where the preservative concentration is at or below its lower specification limit.

The MAH performed two studies for the evaluation of the efficacy of the antimicrobial preservative. The first study did not show preservative efficacy of the formulation using tests as described in Ph.Eur. chapter 5.1.3. For the second study, the MAH used a challenge dose, and included drug product samples where the preservative concentration was at or below its lower specification limit. The second study was performed in accordance with Ph.Eur. chapter 5.1.3. Results of this second study are in line with the first study. All results, including those for preservative concentrations at or below the lower specification limit, passed the criteria for efficacy of antimicrobial preservation as prescribed in the Ph.Eur. monograph for human vaccines for justified cases.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. In-process controls and methods for the IPV trivalent are identical for the single-dose and multidose presentations, except for the volume control. A bioburden test prior to sterile filtration of the final bulk before filling has been added as an in-process control. This is in line with an approved variation of the single-dose presentation.
Process validation for full-scale batches will be performed post authorisation. In line with the guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), the MAH provided a process validation scheme for filling of multidose batches on commercial scale. The information provided on the manufacturing process and in process controls is adequate.

Control of excipients
The excipients are the same as for single-dose product. The 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 complies with the Ph.Eur. and includes tests for appearance, identity, sterility, protein, endotoxins, pH, and extractable volume. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Batch analysis data for three consecutive batches have been provided and complied with the specifications. It is noted that process validation was performed at pilot scale. As the manufacturing process and control does not differ between single-dose and multidose (except for the filling volume), this can be accepted.

Stability of drug product
Stability data on the product have been provided in accordance with applicable European guidelines. The MAH has provided 6 months stability data of three batches of drug product manufactured at pilot

scale and stored at 2-8°C. All results complied with the specifications. A commitment has been made by the MAH to place the first three manufacturing scale batches into the long term stability program after approval.

On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “Store at 2-8°C. Do not freeze.” The product remains stable for 28 days following first opening of the container, when stored at 2-8°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Poliomyelitisvaccin multidose, suspension for injection, 2.5 ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- the first three manufacturing scale batches will be placed into the long term stability program.
- the efficacy of antimicrobial preservation will be tested on 3 full scale batches at release and on one full scale batch during the stability period of 36 months.

III. NON-CLINICAL ASPECTS

This product is identical in qualitative composition to the single-dose product, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the application for the single-dose product. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.

III.1 Ecotoxicity/environmental risk assessment (ERA)

The product is intended as a substitute for other products on the market. It is expected that the use of this formulation will replace other available products, and thus the amount of active substance emitted to the environment is not expected to increase.

IV. CLINICAL ASPECTS

This application cross-references to the clinical data approved for the single-dose product. No new clinical studies on efficacy and safety were submitted as the active substance and pharmaceutical form on administration are identical to those approved for the parent product, which is acceptable.

IV.1 Clinical efficacy

The multi-dose product has the same efficacy as the single-dose preparation. The product can be used for the active immunisation against poliomyelitis.

IV.2 Clinical safety

To prevent overdosing, the multidose presentation clearly indicates that it contains more than one dose. The colour of the flip-off cap is also different from that of the single dose.

Also as IPV is not adjuvated with an aluminum salt, it’s unlikely that the local reactions after an overdose will be significantly more severe than after a normal dose. However due to volume of an overdose there is possibility of more pain and/or swelling in infants when the overdose is injected in the relatively small musculus vastus lateralis in infants.

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 Poliomyelitisvaccin multidose.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reaction to persons sensitive neomycin, streptomycin and polymyxin B antibiotics • Apnoea, in very premature infants (<28 weeks of gestation)
Important potential risks	• Medication errors and risk of over-dosing • Potential for contamination of multi dose vial •
Missing information	--

The MEB 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

Poliomyelitisvaccin multidose has proven to be safe and effective for the proposed indication. The multidose product improves the supply of the vaccine for the GPEI Strategic Plan. The content of the product (2.5 ml) provides five doses compared to the single dose of the original 0.5 ml formulation. The multidose product is unlikely to cause overdosing as it can be easily distinguished from the single-dose product and does not contain aluminum salt. No bioequivalence studies were necessary, as it concerns a line extension of the single-dose product packed in multidose vials.

V. USER CONSULTATION

The package leaflet 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 study consisted of a pilot test, followed by two rounds with 10 participants each. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Poliomyelitisvaccin multidose, suspension for injection, 2.5 ml is a line extension of Poliomyelitisvaccin, suspension for injection, 0.5 ml which has a proven chemical-pharmaceutical quality. Poliomyelitisvaccin is a well-known medicinal product with an established favourable efficacy and safety profile.

The new formulation packed in multidose vials is an approvable addition to the original product. The new formulation is considered to improve the supply of the vaccine.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for the multidose product with the reference product, and have therefore granted a marketing authorisation. Poliomyelitisvaccin multidose was authorised in the Netherlands on 12 November 2014.

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
Type II: B.II.d.2.c	Type II variation for deletion of the rat potency test as a release and stability test.		23-7-2015	Approval	Proposal to delete the rat potency test
Type II: B.I.a.2c	The Type II variation concerning the use of commercially purchased media for cell- and virus culture in stead of in-house prepared media and the use of cell- and virus culture media without antibiotics in stead of the current media with antibiotics, can be approved.	SmPC	9-7-2015	Approval	Change the media used in the manufacturing process
Type II: B.II.b.z Type IB: B.II.f.1 .z Type IA: B.II.b.5 .c Type IA: B.II.b.5.b Type IA: B.II.e.1.b.3	The MAH submitted a grouped type II variation to update the dossier with regard to the drug product of IPV vaccine. In parallel, a type II variation to update the drug substance dossier sections was submitted.		23-7-2015	Approval	Update of the dossier with regard to the drug product.
Type II: B.I.a.z Type IA: A.7 Type IA: B.I.b.1.d (2x) Type II: B.I.a.4.e Type IA: B.I.a.4.b (2x) Type II: B.I.b.1.g	The MAH has submitted a grouped type II variation to update the dossier with regard to the drug substance of IPV vaccine (monovalent and trivalent bulks). In parallel, a type II variation (case 442160) to update the drug product dossier sections has been submitted. This DS update consists of several (textual) changes and four actual variations.		7-8-2015	Approval	Dossier update drug substance Deletion of IPC HPD sterility test Removal upper limit D-antigen monovalent pool
Type IB: B.II.f.1.b.2	The MAH has submitted a type IB variation to introduce a change to the in-use period of Poliomyelitis vaccine (multidose; RVG 114720) from 8 hours to 28 days in line with WHO policy to reduce wastage of vaccine in opened vials. The variation is only applicable to the multidose, but since the SPC and PIL of the monodose and multidose are combined, the applicant also filed the variation for the monodose vaccine (RVG 17642).	SmPC	9-7-2015	Approval	Change of the in-use period
Type IB: B.I.a.2a	The variation concerns a change in preparation of the media used for cell culture. At this moment the bovine serum is added aseptically after filtering the rest of the medium. The proposal is to add the bovine serum before filtration. The proposed preparation method reduces the risk of contamination since there is no longer an open handling of the media		1-10-2015	Approval	Change in manufacturing process

Type IB: B.I.b.2.e	Variation on replacement tests for the isoenzyme analysis for testing the VERO cells identity		20-1-2016	Approval	
Type IA: B.I.b.1.d; Type IA: B.I.b.1.z	On the dilution medium (step 18/19 in the production process) several specifications have been set while it was part of the excipients for poliomyelitis vaccine. This medium is no longer seen as an excipient and should therefore be regarded as the other media used in the production of polio trivalent bulk (400-80-320 DU/mL). For these media a sterility test is not required since there will always be a bioburdentest and a filtertest performed. The removal of the sterility test also shortens the lead time for the medium, reducing the costprice of the medium. The bioburden requirement for non-excipient media is set to <10.000 CFU/mL, however when the switch for the dilution medium was made, this was not applied.		18-1-2016	Approval	
Type IA: B.II.e.1.b.3	Update SmPC	SmPC	08-03-2016	Approval	
Type IB: C.I.11.z	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan: change in the RMP and split of RMP for both products.		20-06-2016	Approval	
Type II: B.I.e.2	The type II variation with a post approval change management protocol for manufacturing polio virus type 2 monovalent bulk in a second plant on the same premises is approvable."		29-08-2017	Approval	start production in another plant on the same premises
Type IB: B.I.b.1.z	The MAH has deleted the rat potency test as a release test for the IPV final bulk and DT-IPV final bulk. The MEB has asked the MAH to consider the limit for the potency assay as proposed by the MEB. The MAH has responded to that commitment that it is acceptable to change the lower limit of the rat potency test from ≥ 0.25 to ≥ 0.5. With this variation the MAH would like to submit this change.		14-03-2017	Approval	
Type IB: B.I.b.2.e	The MEB accepts changes detailed in the application including the following: The extraneous agents test is performed on control cells and single harvest on three different cell lines namely;		04-04-2017	Approval	

	Vero- (continuous cell line), MRC5 (human continuous cell line) and (primary) monkey kidney cell line (cynomolgus or Cercopithecus). According to the Ph.Eur. and WHO guidelines the test only needs to be performed on two cell lines namely: Vero and MRC5. With the increase of the polio production we foresee a shortage of cells and to be in accordance with the guidelines the MAH is changing the extraneous agents test from testing three cell lines to the two describes cell lines. The extraneous agents test on the Master Cell Bank (MCB) and Working Cell Bank (WCB) will be unchanged. Also the company's attention is requested to a recent proposal for revision of the Ph. Eur. 2.6.16 "tests for extraneous agents in viral vaccines for human use" published in Pharmeuropa 28.2. In the current monograph the cells in the test cell cultures are incubated at 36 °C and observed for a period of 14 days. In the proposed revision, a subculture of 14 days is carried out followed by a test for haemadsorbing viruses. It was demonstrated that this test procedure is more sensitive to detect some viruses than the 14-day culture period described in the current monograph (Gombold et al, Vaccine 32 (2014), 2916-2926).				
Type IB: B.II.g.4.b	With the implementation of a new SAP system the generation of batch numbering is going to change and therewith also the batch numbering itself. In order to guarantee that batch numbers are absolutely unique it has been chosen to generate meaningless batch numbers instead of meaningful batch numbers as we used in the past. With this variation the MAHwould like to change the coding system as described in the dossier.		09-06-2017	Approval	
Type IAin: B.II.f.1.a.1	Change in calculation of expiry date due to implementation of SAP		23-05-2017	Not approved	
Type IA: B.I.b.1.d	The variation concerns the deletion of two in vivo tests		27-09-2017	Not approved	This variation has been again submitted and approved in

	on the master cell bank (MCB) and working cell bank (WCB).				May 2018
Type IB: B.II.b.3.a	The variation concerns a minor change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product		03-10-2017	Approval	
Type IB: B.I.a.2.a	Medium M199 correction		15-12-2017	Approval	