COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Betadine desinfectiedoekjes, impregnated wipes with solution for cutaneous use 350 mg (povidone iodine)

NL License RVG: 125995

Date: 4 November 2021

This module reflects the scientific discussion for the approval of Betadine desinfectiedoekjes. The marketing authorisation was granted on 21 January 2021 For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PE	Polyethylene
PP	Polypropylene
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 Betadine desinfectiedoekjes, impregnated wipes for cutaneous use 350 mg**,** from Mylan Healthcare B.V.

The product is indicated for the disinfection of superficial cuts, abrasions and burns and the skin after injections and blood transfusions. Furthermore, this product is also indicated for the pre- and postoperative disinfection of surgical areas.

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

This national procedure concerns a line extension application of the current marketing authorisation for Betadine, solution for cutaneous use 100 mg/ml (RVG 01331) which has been registered in the Netherlands by Mylan Healthcare B.V. since 1975 (original product). Betadine desinfectiedoekjes is intended for general sales, as povidone iodine based products have been approved for general sales in the Netherlands since November 2007.

A product can be categorized for general sales if the following points are true:

1. The active substance of the drug product has been used in the European community or in the United States of America for at least five years as an active substance in a product that can be obtained without prescription.
2. When using the drug product the risk of damage is negligible.
3. There are no indications for abnormal use.
4. The number of drug products per storage unit are relatively low.
5. The packaging and the package leaflet warn for possible dangerous situations.
6. The availability of oral advice from a pharmacist is not necessary.

It was concluded that all the requirements listed above are true for Betadine desinfectiedoekjes, and that this product can be categorized for general sales.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Betadine desinfectiedoekjes are impregnated wipes with a liquid for cutaneous use. The wipe is folded multiple times and impregnated with a brown-coloured solution. The product contains 350 mg povidone iodine per wipe as the active substance.

The wipe is packed in a sachet (polyinert-aluminium-polyamide-paper).

The excipients are:

Impregnation solution – disodiumhydrogenphosphate (E339), lauromacrogol (polyoxyethylene laurylalcohol ether), glycerol (E422), sodium hydroxide (E524), citric acid (E330), potassium iodate and purified water.

Wipe – non-woven viscose/polyester.

II.2 Drug Substance

The active substance is povidone iodine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Povidone iodine is an amorphous brown-yellow to brown-red powder and is soluble in water and in 96% ethanol, but is practically insoluble in acetone. Polymorphism is not relevant for the product at issue, since it concerns a solution in which the active solution is dissolved. For the active substance the CEP procedure is used.

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 European Pharmacopoeia.

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 and meets the requirements of the monograph in the Ph.Eur. to which is added the additional test for isopropanol. Batch analytical data demonstrating compliance with this specification have been provided for 15 batches.

Stability of drug substance

Stability data on the active substance has been provided from three different manufacturers:

Manufacturer I provided stability data for seven batches under long term conditions (25°C/60% RH) in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. The following stability indication parameters are monitored: available iodine content and iodide content. Based on the data submitted, a retest period could be granted of 60 months when stored in its original container, protected from light.

Manufacturer II provided stability data for three batches under long term conditions (25°C/60% RH) in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. The following stability indication parameters are monitored: available iodine content and iodide content. Based on the data submitted, a retest

period could be granted of 24 months when stored in its original container, protected from light.

Manufacturer III provided a CEP proposing a retest period of 36 months if stored in a polyethylene (PE) bag placed in either a PE drum or a polypropylene (PP) container. This is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The product Betadine desinfectiedoekjes, impregnated wipes for cutaneous use 350 mg relates to a viscose/polyester wipe, impregnated with Betadine dermal solution 10% for skin application as a ready to use application form. The composition of Betadine dermal solution 10% for skin application itself remain unchanged. The wipe is a neutral support for the impregnating solution. There is no interaction between the impregnation solution and the support, shown in a conducted interaction study.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified.

Manufacturing process

The impregnated compresses are manufactured by preparing the active substance solution and transferring the solution by automated machine to the non-woven material. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled batches. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph. Eur. requirements were applicable, or with other relevant compendial requirements. These specifications are acceptable. The wipes as used in the manufacturing process bare no CE-mark. The specification of the gauze is based on the Ph.Eur. monograph “viscose wadding, absorbent” which is considered acceptable. Its specification is generally acceptable. The MAH has committed to add a test on the correct ratio of viscose vs polyester post-approval; at the same time the specification should be updated to include the dimensions.

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, identity, assay, average mass and microbiological quality. 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 two pilot scaled batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for two pilot scaled batches packaged in the proposed container closure system and two pilot scaled batches with a different gauze and different packaging. The batches were stored at 25°C/60% RH (18 months), 30°/65% RH (12 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. Under long-term, intermediate and accelerated conditions all batches remain within specification for 18 months. Given the comparable results it is considered that the gauze and sachet are of no influence to the stability of the betadine solution and the final drug product. Based on the provided data the proposed shelf life of 18 months with storage conditions 'store below 25°C' and 'store in the original packaging in order to protect from light' is acceptable.

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 MEB considers that Betadine desinfectiedoekjes has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitment was made:

1. Addition of a test for the correct ratio of viscose vs polyester.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Betadine desinfectiedoekjes is a topically administered drug that is a complement to the range of the specialty Betadine 10%, solution for cutaneous application. This specialty is therefore intended to be used as an alternative to an existing product, 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 line extension of Betadine, solution for cutaneous use 100 mg/ml 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 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 Betadine desinfectiedoekjes.

Summary table of safety concerns as approved in RMP

Important identified risks	- None
Important potential risks	- None
Missing information	- None

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

IV.2 Discussion on the clinical aspects

For this line extension authorisation, reference is made to the clinical dossier of Betadine, solution for cutaneous use 100 mg/ml. Povidone iodine is a well-known active substance with established efficacy and tolerability. The MEB agreed that no new clinical studies were conducted. Risk management is sufficiently addressed.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to BETADINE 350 mg, compresse imprégnée. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Betadine desinfectiedoekjes, impregnated wipes for cutaneous use 350 mg has a proven chemical-pharmaceutical quality and is an approvable line extension to Betadine, solution for cutaneous use 100 mg/ml. Betadine, solution for cutaneous use 100 mg/ml is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has not been shown for this product, but as it concerns a line extension of a product that has been registered since 1975 and has been marketed for general sales since 2007 the absence of bioequivalence studies is considered acceptable.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted have therefore granted a marketing authorisation. Betadine desinfectiedoekjes was authorised in the Netherlands on 21 January 2021.

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