

Public Assessment Report

Scientific discussion

Povidonjodium 100 mg/ml Denteck, cutaneous solution

(povidone iodine)

NL License RVG: 120551

Date: 27 November 2019

This module reflects the scientific discussion for the approval of Povidonjodium 100 mg/ml Denteck, cutaneous solution. The procedure was finalised at 12 October 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

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
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 Povidonjodium 100 mg/ml Denteck, cutaneous solution, from Denteck B.V.

The product is indicated for:

- disinfection of skin wounds such as cuts, abrasions and burns; and disinfection of the skin prior to injections or blood transfusions
- Use as an antiseptic for pre-operative and post-operative treatment of skin.

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

This national procedure concerns a bibliographical application based on well-established medicinal use of cutaneous solutions containing the active substance iodinated povidone. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. "Medicinal use" does not exclusively mean "use as an authorised medicinal product", so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the efficacy and/or safety assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

Povidone-iodine solution is an antiseptic. The active substance povidone iodine exerts a quick and prolonged antimicrobial activity. The mechanism of action rests on a gradual release of free iodine which is non-painful in skin contact. The brown colour indicates the presence of iodine at the disinfected area. The antimicrobial activity lasts as long as the brown colour is visible. Povidone-iodine solution is a broad-spectrum antiseptic, effective against bacteria, fungi, several viruses and a few protozoa.

For this well-established use application, the MAH made reference to the long-standing (clinical) experience with reference product Betadine solution 100 mg/ml, cutaneous solution (NL License RVG 01331), registered since 1 May 1975 in the Netherlands by Meda Pharma B.V.

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

II. QUALITY ASPECTS

II.1 Introduction

Povidonjodium 100 mg/ml Denteck is a clear and brown cutaneous solution. Each 1 ml solution for cutaneous use contains approximately 100 mg povidone iodine (corresponding with 10 mg iodine).

The cutaneous solution is packed in amber-coloured PET bottles with HDPE closure and LDPE plug.

The excipients are: purified water, disodium phosphate dihydrate, citric acid and sodium hydroxide.

II.2 Drug Substance

The active substance is povidone iodine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a yellowish-brown or reddish-brown amorphous powder and soluble in water and ethanol (96%) and practically insoluble in acetone.

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 and is in line with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

Stability data on the active substance have been provided for multiple batches over a period of 4 years. Based on the data submitted, a retest period could be granted of 24 months.

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 choice of excipients is justified and their functions explained. The development studies were limited to an upgrading of the quantities and quality of the materials as well as optimisation of mixing times. No clinical or bioequivalence studies have been performed because of the long standing and well known use of 10% iodinated povidone aqueous solutions. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of mixing, dissolving, filling, capping and boxing and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scale batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with the 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, identity, pH, weight loss and assay. 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 three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four full-scale batches 25°C/40%RH (24 months), 30°C/35%RH (12 months) and 40°C/NMT25%RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PET bottles with HDPE caps. All trends and changes remained within limits. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: "Store below 25°C. Store in well-closed, original containers in order to protect from light".

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 Povidonjodium 100 mg/ml Denteck 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)

The approval of this product will not result in an increase in the total quantity of the active substance released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of povidone iodine are well known. As the active substance is widely used and well-known, no further studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Povidone iodine 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 MEB agrees that no further clinical studies are required.

The MAH made reference to the long-standing (clinical) experience with reference product Betadine solution 100 mg/ml, cutaneous solution.

IV.2 Clinical efficacy

Iodine has been used for the prevention or management of wound infections for over 100 years. Since molecular iodine can be very toxic for tissues, formulations were composed by combination of iodine with a carrier (iodophor) that decreases iodine availability. In the early 1950's iodine was complexed with the inert polymer, polyvinylpyrrolidone (Povidone) and this resulting "iodophor" was found to markedly reduce the toxicity of iodine, cease its irritating, sensitizing and staining effects on the skin while still retaining its potent microbiocidal properties.

Povidone iodine (PVP-I) is a powerful antiseptic and disinfectant. In contact with skin and mucous membranes the povidone iodine complex gradually releases the active iodine, which works quickly and has a microbiocidal effect.

Overall, the reported results in above described published studies support the conclusion that 10% povidone-iodine is effective in the reduction of resident skin flora. Moreover, intervention with PVP-I is associated with reduced risk of infection in wounds and when used for skin preparation prior to surgery it seems to perform similarly as other contemporary products.

IV.3 Clinical safety

Povidone iodine has been used widely for decades in hospital and other clinical settings for hand and wound cleansing and skin antisepsis before surgery or other procedures that penetrate these barriers. Formulations of povidone iodine such as aqueous and alcohol-based solutions have been used topically on adult, infant and neonatal skin.

Reported side effects

The topical application of povidone iodine cutaneous solution rarely can cause side effects. However, it may be able to cause local irritation of the skin, followed by redness and irritation, hypersensitivity reactions and anaphylactic reactions. Allergic contact dermatitis has also been reported. After long and frequent topical application neutropenia may be a side effect.

Prolonged use to the skin can result in dysfunction of the thyroid gland (hyperthyroidism). Excessive absorption of iodine after application of Povidone iodine 10% solution to large skin wounds or severe burns can result in systemic adverse effects such as metabolic acidosis, hypernatremia and renal impairment.

Use in special populations

The product may only be used on indication of a doctor in patients with mild nodular goitre or after disorders of the thyroid gland and in patients with a predisposition to autonomous adenoma and/or functional autonomy (especially elderly patients). Caution is needed in patients with thyroid abnormalities. Frequent use must be avoided in patients with renal impairment and regular use in patients that are being treated with lithium.

Paediatric patients

New-borns have an increased risk of developing hyperthyroidism due to the administration of large amounts of iodine. The use of povidone iodine in new-borns should therefore be kept to the absolute minimum.

IV.4 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 Povidonjodium 100 mg/ml Denteck.

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

Important identified risks	<ul style="list-style-type: none"> • Hyperthyroidism after prolonged application to the skin. • Systemic adverse effects such as metabolic acidosis, hypernatremia and renal impairment after excessive absorption of iodine
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.5 Discussion on the clinical aspects

The disinfectant effect of povidone iodine has been extensively described in the literature. The RIVM guideline “RIVM - *WIP Policy on cleaning disinfection and sterilisation*, Revision July 2009” states povidone iodine as skin disinfectant. The use of povidone iodine is recommended for disinfection of skin wounds such as cuts, abrasions and burns; and disinfection of the skin prior to injections or blood transfusions; and use as an antiseptic for pre-operative and post-operative treatment of skin.

There is a lot of (clinical) experience with these products. Local side effects on the skin occur and in rare cases generalised allergic reactions have been described. Within patient risk groups (thyroid abnormalities, renal insufficiency, new-borns/infants), caution should be used when applying povidone iodine agents.

The use of these disinfectant products has been generally accepted for decades. The disinfecting effect is well described and sufficiently documented in literature. The risks associated with the use of this type of substance are considered acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Chloorhexidinedigluconaat 0.5% m/v in Alcohol 70% v/v, cutaneous solution. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Povidonjodium 100 mg/ml Denteck, cutaneous solution has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. The quality of starting material, active substance and finished product as well as the manufacturing, quality control and stability can be considered as sufficient.

From a clinical point of view, the proposed indications, as well as the proposed posology, are in line with current povidone iodine use and recommendations. Based upon clinical data and longstanding clinical experience, the use of this product in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety was shown, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 12 October 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
Type IAIN : C.I.8.a	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use (*); introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	-	24-06-2019	Approval	-
Type IAIN : C.I.2.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the reference product; implementation of change(s) for which no new additional data is required to be submitted by the MAH	yes	30-09-2019	Approval	-