COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Povidon Jodium Alfa Intes 50 mg/ml eyedrops, solution (povidone iodine)

NL/H/5430/001/DC

Date: 24 September 2024

This module reflects the scientific discussion for the approval of Povidon Jodium Alfa Intes 50 mg/ml eyedrops, solution. The procedure was finalised on 8 March 2023. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PVP	Povidone
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Povidon Jodium Alfa Intes 50 mg/ml eyedrops, solution, from Industria Terapeutica Splendore S.r.l.

The product is indicated for: cutaneous peri-ocular (including the eyebrows margins) and conjunctival/corneal antisepsis prior to ocular surgery and/or intravitreal injection to support post-procedural infection control.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of povidone iodine. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Both molecule povidone iodine and ophthalmic solution povidone iodine were first introduced into the European market at least ten years ago as preoperative medications for preparation of the surgical field (eyelids, lashes and cheeks) and irrigation of the ocular surface (cornea, conjunctiva and palpebral fornices).

The MAH submitted a justification for bridging between their product and three different products with nearly similar (but not identical) indications:

- Iso-Betadine 5% eyedrops which has been registered in France by Mylan Healthcare B.V. (1992). It is indicated for the preoperative, periocular and conjunctival cutaneous antisepsis in ophthalmic surgery.
- Oftasteril 5% eyedrops which has been registered in Italy by Alfa Intes since 2001. It has indicated for the preparation of the surgical field (eyelids, lashes and cheeks) and irrigation of the ocular surface (cornea, conjunctiva and palpebral fornices).
- Minims Povidone Iodine 5% eyedrops, solution (NL RVG 109310) which has been registered in the Ireland by Bausch & Lomb Ireland Limited via procedure IE/H/0761/001/DC since 2012. It has been indicated for cutaneous peri-ocular and conjunctival antisepsis prior to ocular surgery and/or intravitreal injection to support post-procedural infection control.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Spain, Poland and Portugal.

II. QUALITY ASPECTS

II.1 Introduction

Povidon Jodium Alfa Intes is a clear, red-brown solution with a pH of 4.5 – 7.0. It has an osmolality of 280 – 340 mOsmol/kg. 1 mL of solution contains as active substance 50 mg povidone iodine. Each bottle provides 200 mg of povidone, iodinated in 4.0 ml of solution. One mL of solution contains 50 mg povidone, iodinated. The nominal volume of eye drops contained in the bottle is 4.0 mL corresponding to 133 drops.

The excipients are: glycerol (E422), citric acid monohydrate (E330), polysorbate 20 (E432), disodium phosphate dodecahydrate (E339), sodium chloride, potassium iodate, sodium hydroxide (E524) and purified water.

The solution is packed in a brown, low-density polyethylene (PE) sterile, single-use bottle. The bottle is closed by a PE dropper and PP screw cap. The bottle is contained in a double PE/PET sterile sachet.

II.2 Drug Substance

The active substance is povidone, iodinated, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a yellowish-brown or reddish-brown, amorphous powder and soluble in water. Particle size and polymorphic form are not considered relevant as the product concerns a solution.

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 meets the requirements of the monograph in the Ph.Eur. with stringent limits for pH, loss on drying, sulphated ash and assay. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

Stability data of the active substance have been provided for 21 batches. The stability studies of the drug substance have not all been performed under ICH protocol and ICH storage conditions. Since the product is well known and no known degradation products exist, a retest period of 2 years can be accepted under the stated conditions.

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 has been discussed and their functions have been explained. The main development studies were the characterisation of reference product and formulation optimisation studies. A physicochemical comparison for bridging has been provided with batches of the reference products Iso-Betadine 5% Solution for Ophthalmic Irrigation, Minims Povidone Iodine 5% Ophthalmic Drops; Oftasteril 5% eye drops, solution; Betadine 5% Ophthalmic Solution; Ophthajod 5%; and Povidone-iodine 5% Ophthalmic Solution and the MAHs product. The provided results show that the proposed product has comparable physicochemical properties as the already marketed reference products. This shows the pharmaceutical equivalence of the proposed product to the already marketed reference products.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The main steps of the manufacturing process are dissolution of raw materials, aseptic filtration, filling and packaging. The manufacture of the proposed drug product is regarded as non-standard process, based on aseptic processing. The selected aseptic filtration method has been adequately justified. The process validation data on the product have been presented for three production scale batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with their respective Ph. Eur. monograph, except for potassium iodate which complies with the British Pharmacopeia. These specifications are acceptable.

Microbiological attributes

The product complies with the requirements of Ph. Eur. 1163 eye preparations. Sterility is tested according to Ph. Eur. 2.6.1 sterility. The sterility of the drug product is guaranteed by sterilising of the 'in bulk' product, an aseptic filling and the use of sterile containers. No excipients with specifical antimicrobial activity are included in the proposed formulation. Therefore, after first opening, the product must be discarded.

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 and colour, pH, osmolality, identification of povidone iodine, assay, minimum fill, sterility and sterility of the external bottle. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life specifications are identical.

An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three production scale 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 three production scale batches stored at 25°C/60% RH (20 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). A downward trend in available iodine content is noted when the drug product is stored at all evaluated storage conditions. All other parameters remained relatively stable. All parameters were within the specifications. The stability was tested in accordance with applicable European guidelines. The information provided by the MAH was sufficient to show that the drug substance is packaged protected from light, in line with the required storage condition described in the Ph. Eur. monograph. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are “Do not store above 25°C” “and “Do not refrigerate or freeze”.

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 Povidon Jodium Alfa Intes 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 Introduction

As the active ingredient is widely used, well-known active substance, no further studies are required, and the MAH provides none. A non-clinical overview based on literature review should be appropriate.

Since this a bibliographic application, the non-clinical dossier consists of published literature references only. In cases where literature references are lacking, a justification for absence of literature should be given.

III.2 Pharmacology

Primary pharmacodynamics

Povidone iodine is an iodophore with povidone acting as a carrier of iodine. Iodophors are substances which are capable of taking up iodine and transporting it. The carrier does not react with the substance taken up via a stable chemical bond but rather takes it up due to its electrochemical configuration in its scaffold. The chemical properties of the individual substances are essentially maintained, however the physical properties, i.e. solubility, can change.

Iodine is considered as the active moiety that mediates microbiocidal actions. In aqueous solution, a dynamic equilibrium occurs between free iodine (I_2), the active bactericidal agent, and the povidone iodine complex. When released from the complex, free iodine (I_2) penetrates the cell wall of microorganisms quickly, and the lethal effects are believed to result from disruption of protein and nucleic acid structure and synthesis. After dilution of povidone iodine 10% solution, the iodine levels follow a bell-shaped curve and increase with dilution, reaching a maximum at approximately 0.1% strength solution and then decreasing with further dilution (Rackur, 1985).

There is a good correlation between free iodine concentration – between 9% to 12% available iodine (dried substance) - and the microbiocidal activity of povidone iodine. While the full mechanism of action is not fully elucidated, iodine is thought to inhibit vital bacterial cellular mechanisms and structures, and oxidises nucleotides fatty or amino acids in bacterial cell membranes. The level of free iodine in povidone iodine solutions is pH and solvent dependent (Bigliardi et al., 2017; Prado et al, 2019; Lepelletier et al., 2020; ECHA EU Standing Committee on Biocidal Products, 2013).

As a small molecule, iodine rapidly penetrates into microorganisms and oxidises key proteins, nucleotides, and fatty acids, eventually leading to cell death (Lachapelle et al., 2013; McDonnell & Russell, 1999). Povidone Iodine has a broad antimicrobial spectrum with activity against Gram-positive and Gram-negative bacteria, including antibiotic-resistant and antiseptic-resistant strains (Lepelletier et al, 2020), fungi, and protozoa (Lachapelle et al., 2013). It is also active against a wide range of enveloped and nonenveloped viruses (Lepelletier et al,. 2020; Wutzler et al., 2000), as well as some bacterial spores with increased exposure time (Lachapelle et al., 2013). In addition, Povidone Iodine has been shown to have activity against mature bacterial and fungal biofilms *in vitro* and *ex vivo* (Hoekstra et al., 2017; Capriotti et al., 2018).

The povidone component of povidone iodine increases the antimicrobial efficiency of iodine by delivering it directly into the bacterial cell surface and improving the iodine's ability to pre-penetrate microorganisms. In this way when iodine is complexed with povidone it is constantly released whilst remaining in dynamic equilibrium with the complex. For this reason, microbial membrane penetration of free iodine and intracytoplasmic protein, nucleotides and fatty acids oxidation cannot be stopped, resulting in cell death in seconds (Lachapelle et al., 2013).

Secondary pharmacodynamics

Coagulase-negative staphylococci are the most common causes of post-cataract endophthalmitis, and these bacteria and viridans streptococci cause most cases of post-intravitreal anti- VEGF injection endophthalmitis, *Bacillus cereus* is a major cause of posttraumatic endophthalmitis, and *Staphylococcus aureus* and streptococci are important causes of endogenous endophthalmitis associated with endocarditis (Durand, 2013).

An evaluation of the antibacterial efficacy of povidone iodine ophthalmic solutions demonstrated that the minimum inhibitory and bactericidal concentrations of *S. aureus* and *P. aeruginosa* was of 0.078 ± 0.020 % w/v and 0.300 ± 0.000 % w/v, respectively (Lee et al., 2019).

An *ex vivo* study assessed whether adjusting the pH of povidone iodine ophthalmic would influence its safety, alongside its impact on antibacterial efficacy and storage stability. Minimum bactericidal concentration was identical to minimum inhibitory concentration in all instances (Thakur et al., 2021).

The *in vitro* effectiveness of povidone iodine, an agent with broad antibacterial and antiviral activity, compared to that of chlorhexidine, a cationic antiseptic, on *Acanthamoeba* isolates from patients with amoebic keratitis. The results showed that povidone iodine solution from 0.5 to 2.5% has a better anti-amoebic activity both on trophic and cystic stages of *Acanthamoeba* spp. than does chlorhexidine (Gatti et al., 1998).

It has been shown that an ophthalmic solution containing a low concentration of povidone iodine at 0.6% showed a good, rapid '*in vitro*' antibacterial activity against multi-resistant strains of *S. aureus*, and, to a lesser extent, Candida species (Pinna et al., 2020).

In a comparison of the antimicrobial effect between topical anaesthetics, antivirals, antibiotics, and biocides on the viability of *Acanthamoeb*a cysts and trophozoites *in vitro*, amoebicidal and cysticidal assays were performed against both trophozoites and cysts of *Acanthamoeba castellanii* and *Acanthamoeba polyphaga*. The anti-amoebic effects of povidone iodine is superior to the current diamidines drugs and slightly inferior to the biguanides used in the treatment for *Acanthamoeba keratitis* (Heaselgrave et al., 2019).

A controlled study evaluated the *in vitro* antiviral activity of four povidone iodine concentrations previously used in clinical studies against seven ocular adenovirus types commonly associated with eye infections. There were no virucidal reductions in titres produced by 0.001% povidone iodine. The antiviral activity of povidone iodine may be adenovirus type dependent (Yates et al., 2019).

In a study in dogs, bacterial cultures of specimens from healthy canine eyelids and ocular surfaces were found to demonstrate bacterial growth in 69.7% (53/76) of the eyes sampled. Bacterial growth initially detected in 32 of 46 eyes was not detected after disinfection of a povidone-iodine solution that contained 1% available iodine. The eyelid and ocular surfaces of 16 eyes were disinfected with 1:100 povidone-iodine solution. Bacterial growth initially present in 10 of 16 eyes was present in 1 eye after disinfection and consisted of a single colony of *E coli*. A 1:50 dilution of povidone-iodine is recommended as an ocular surface disinfectant for use in presurgical situations (Roberts et al., 1986).

A study aimed to examine the effectiveness of povidone-iodine eye drop 1% in eye infection caused by inoculation of *Streptococcus pneumoniae* and *Escherichia coli* of mice was performed. Povidone Iodine 1% was effective to decrease *S. pneumoniae* and *E. coli* induced-keratitis symptoms in mice. Treatment with povidone iodine 1% was observed time-dependently and was comparable to common eye drop antibiotics (Jahromy et al., 2019).

In order to determine the maximally tolerated dose of intravitreally injected povidone iodine, an *in vivo* study was conducted with a second arm to test the efficacy of povidone iodine on rabbit eyes infected intravitreally with *Staphylococcus epidermidis*. Phase I of the study observed no retinal damage at any of the concentrations studied. Phase II of the study showed no statistical difference in bacterial counts between treatment and control groups. All infected eyes went on to develop endophthalmitis. results suggest that 400 µg of povidone iodine can be tolerated intravitreally in rabbit eyes with no noticeable damage over a 14-day period. Results further showed that 100 µg of intravitreally injected povidone iodine has no statistically significant effect on rabbit eyes injected intravitreally with 3030 CFU of S. epidermidis (Trost et al., 2007).

Safety pharmacology

No safety pharmacology studies for the central nervous system were identified in the public domain regarding topical administration of povidone iodine. One study was found where povidone iodine was evaluated for its use in local lavage of the epidural space. In 20 rabbits a lumbar laminectomy was performed followed either by local lavage with povidone iodine or with sodium chloride. After one month the meningeal covering of the operated spinal cords revealed no signs of fibrosis or arachnoid adhesions when studied macroscopically or by scanning electron microscopy (Strohecker et al., 1985).

Antibacterial solutions were irrigated into rabbit pericardium to investigate potential tissue injury to the cardiovascular system. Povidone iodine was the only irrigant found to cause substantial damage. These data lend experimental support to clinical observations that suggest a causal relation between pericardial irrigation with povidone iodine and the later development of constrictive pericarditis (Kratz et al., 1983).

Povidone iodine has been reported to cause pneumonia secondary to its pulmonary aspiration. An animal study to analyse the effect and underlying mechanisms of povidone iodine on the lung following its pulmonary instillation was conducted. Povidone iodine aspiration can cause lung injury, including pulmonary fibrosis (Cheong et al., 2012).

Pharmacodynamic drug interactions

Pharmacodynamic interactions with other medicinal products have not been reported.

III.3 Pharmacokinetics

Povidone Iodine is routinely used for topical application as a surgical scrub for skin disinfection and in preparation for ophthalmic surgery or intraocular injection. It has been reported from clinical outcomes that topical iodine preparations can increase iodine plasma levels due to

dermal absorption. Povidone (PVP) and iodine can both be separately absorbed systemically after topical application (Nair, 1998).

Distribution was determined by injecting rats via the intravenous route and rabbits with same preparation doses. A similar distribution pattern was observed in all two species. The skeletal muscle, skin, and subcutaneous tissue contained the largest fraction but lowest concentration of PVP that decreased progressively; the organs of the monocyte/macrophage system had the highest concentration which value remained constant (Nair, 1998). It has been reported that there is differential distribution of radioactivity derived from iodine (I_2) and iodide (I^-) into blood components. Twice as much radio-labelled iodine is in the form of I^- in the plasma of animals treated with ^{125}I- compared to $^{125}I_2$- treated rats. No I_2 could be detected in the plasma. With an increase in dose, increasing amounts of radioactivity derived from $^{125}I_2^-$ treated animals distribute to whole blood compared to equivalent doses of $^{125}I^-$, reaching a maxima at a dose of 15.8 mol I/kg body weight. Most of the radioactivity derived from I_2 associates with serum proteins and lipids, in particular with albumin and cholesteryl iodide. These data indicate a differential distribution of radioactivity depending on whether it is administered as iodide or iodine. This is inconsistent with the commonly held view that iodine (I_2) is reduced to iodide (I^-) before it is absorbed systemically from the gastrointestinal tract (Thrall et al., 1992).

Iodine is a trace element that is naturally present in some foods, is added to some types of salt, and is available as a dietary supplement. Iodine is an essential component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Thyroid hormones regulate many important biochemical reactions, including protein synthesis and enzymatic activity, and are critical determinants of metabolic activity. They are also required for proper skeletal and central nervous system development in foetuses and infants. In a study of iodide metabolism and the effects of moderate dietary iodine deficiency, radio-labelled ^{125}I was administered by prolonged continuous intravenous infusion to rats maintained under iodine-replete conditions and in moderate iodine deficiency. Labelled iodocompounds extracted from various tissues were analysed by thin-layer chromatography. Moderate iodine deficiency resulted in a slight increase in the ratio of mono-iodotyrosine to di-iodotyrosine in the thyroid. No change in the ratio of T3 to T4 was found in thyroid, plasma or skeletal muscle. Faecal excretion of T3 declined appreciably relative to that of T4. Under iodine-replete conditions the ratio of thyroidal secretion rates of T3 and T4 was estimated to be more than three times higher than the ratio of these iodocompounds within the thyroid (Boonnamsiri et al., 1979).

Irrespective of its route of administration (inhalation, subcutaneous or intravenous) iodine is primarily excreted by the kidneys (Nair, 1998).

III.4 Toxicology

Genotoxicity has been adequately addressed, with references to *in vitro* and *in vivo* studies that provide sufficient information on the genotoxic properties of Povidone Iodine.
Carcinogenicity studies are not required for compounds that are intended for single-use, as mentioned in ICH S1A: “Pharmaceuticals administered infrequently or for short duration of exposure (e.g., anaesthetics and radiolabelled imaging agents) do not need carcinogenicity

studies unless there is cause for concern." Therefore, the absence of carcinogenicity studies for Povidone Iodine is considered adequately justified.

The reproductive toxicology studies that are included in the updated non-clinical overview provide only limited information. However, information available from literature suggests that the reproductive toxicology for Povidone Iodine for single use is sufficiently known from clinical use, and thus absence of reproductive toxicology studies is adequately justified.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Substance (INN/Invented Name): Povidone iodine			
CAS-number (if available): 25655-41-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	QSAR estimation	2.49 (iodine) and 0.4 (povidone) <4.5 (povidone-iodine complex)	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.0041	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Conclusions on studies

Povidone iodine is not a persistent, bioaccumulative, and toxic (PBT) nor a very persistent, very bioaccumulative and toxic (vPvB) substance. Considering the above data, povidone iodine is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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

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 member states agreed that no further clinical studies are required.

The MAH did not perform clinical pharmacology studies. The current application is based upon a well-established use application (Article 10a). From the submitted bridging data it is concluded that the free iodine concentrations of the proposed product are comparable and thus representative for the available free iodine concentrations of povidone iodine containing products as described in literature. The addition of polysorbate 20 and potassium iodate to the product is regarded as safe. Detrimental effects with its use are not expected.

IV.2 Pharmacokinetics

Povidone iodine is an iodophore with povidone acting as a carrier of iodine. Iodine is considered as the active moiety that mediates microbicidal actions. In aqueous solution, a dynamic equilibrium occurs between free iodine, the active bactericidal agent, and the povidone iodine complex. When released from the complex, free iodine penetrates the cell wall of micro-organisms quickly, and the lethal effects are believed to result from disruption of protein and nucleic acid structure and synthesis. The 5% concentration as applied for Povidone Iodine Geda 50 mg/ml eyedrops, solution lies well within the range of different povidone iodine solutions as described in the literature for ophthalmic use.

Multiple studies have shown that although orally administered iodine is nearly completely absorbed, absorption of iodine after topical administration to intact skin is generally low. Moreover, in the case of ophthalmic use, the total amount of solution applied is very. Absorbed iodine is mainly excreted renally. Regarding age, impaired renal or liver function, no significant influence on absorption is expected.

The human body contains approximately 10–15 mg of iodine. As a proportion of this amount, approximately 70–90% is in the thyroid gland, which accumulates iodine in producing thyroid hormones for export to the blood and other tissues. Iodine is predominantly confined to the extracellular fluid. It is distributed to thyroid, choroid plexus, mammary glands, salivary glands, gastric mucosa, placenta, and sweat glands. In the thyroid, iodine is incorporated into the protein thyroglobulin and formed to T4 (coupling of two diiodotyrosine residues) or T3 (coupling of a mono-iodotyrosine and diiodotyrosine residue).

The main metabolic pathways for iodine outside the thyroid gland involve the catabolism of T3 and T4 and include:

- Deiodination reactions.
- Ether bond cleavage of thyronine.
- Oxidative deamination and decarboxylation of the side-chain of thyronine;
- Conjugation of the phenolic hydroxyl group on thyronine with glucuronic acid and sulphate.

IV.3 Pharmacodynamics

Povidone iodine is an iodophor solution containing a water-soluble complex of iodine and the biodegradable polymer polyvinylpyrrolidone and has broad microbicidal activity. Iodine, slowly liberated from the polyvinylpyrrolidone iodine complex in solution, kills eukaryotic or prokaryotic cells. This agent exhibits a broad range of microbicidal activity against bacteria, fungi, protozoa, and viruses. Slow release of iodine from the povidone iodine complex in solution minimizes iodine toxicity towards mammalian cells (Teodorescu & Bercea, 2015). It shows effective as iodine against a broad spectrum of microorganisms but is less irritating to the skin and does not require iodides or alcohol to dissolve. Povidone iodine has a prolonged nonselective antimicrobial action due to its microbiocidal activity and is particularly effective in treating mixed infection. Its effectiveness has been clinically proven for all types of topical applications in human medicine (Kumar et al., 2009).

The antimicrobial action of povidone iodine occurs after iodine disassociates from the polymer-iodine reservoir complex. Once in the free form, iodine rapidly penetrates microbial cell membranes and interacts with proteins, nucleotides, and fatty acids in the cytoplasm and cytoplasmic membrane through oxidation reactions as in addition to the cytosolic enzymes involved in the respiratory chain, causing their denaturation and deactivation (Kanagalingam et al., 2015). Iodine binds proteins in several different ways including the oxidation of S–H bonds in amino acids as well as the prevention of hydrogen bonding by reacting with N–H groups. This leads to protein denaturation. Such denaturation affects the structure and function of enzymes and structural proteins alike with the extensive deleterious effect on microbial function. It has furthermore been noted that iodine is able to compromise membrane structure through the reaction of iodine with C=C bonds contained within fatty acids whilst at the same time the hydrogen bonding in nucleic acids is prevented iodine binding to nucleotides. These interactions result in rapid death following exposure to iodine (Cooper, 2007).

Povidone iodine has a wide antimicrobial spectrum with activity against gram-positive and gram-negative bacteria, fungi, protozoa, tubercle bacilli, viruses, and bacterial spores. It has been shown to be effective against resistant micro-organisms such as Methicillin resistance *Staphylococcus aureus* (MRSA) infections (Durani & Leaper, 2008). Povidone iodine also has anti-biofilm activity against *Staphylococcus epidermidis* and *Staphylococcus aureus* at sub-inhibitory concentrations (Oduwole et al., 2010).

Of culture-positive cases, Gram-positive cocci comprise approximately 95% of isolates, with coagulase-negative staphylococci the primary pathogens (70% of cases). Other pathogens include *Staphylococcus aureus* (10%), streptococci (9%), mixed Grampositive bacteria (5%), and Gram-negative bacilli (6%). Fungal postoperative endophthalmitis is rare except in tropical regions (Durand, 2017).

IV.4 Clinical efficacy

Prophylactic peri-operative use of povidone iodine in ophthalmic surgery is primarily aimed to decrease the risk of endophthalmitis. Endophthalmitis is a severe eye infection that may result in permanent loss of useful vision in the affected eye. Most cases are exogenous and occur as a complication of cataract surgery, an intravitreal injection, or penetrating ocular trauma. The rate of endophthalmitis after cataract surgery is approximately 0.1%, for example, while the

rate after penetrating eye trauma is 1 to 18%. Postoperative and posttraumatic endophthalmitis are the major types of endophthalmitis seen worldwide, with postoperative (primarily post-cataract) cases accounting for 40 to 80% and post-traumatic cases comprising 2 to 15% of all endophthalmitis cases seen. Nearly all endophthalmitis patients present with decreased vision, and some also have eye pain.

IV.5 Clinical safety

The incidence and nature of adverse events emerging after topical administration of povidone iodine depend on its clinical use. Important factors are povidone iodine concentration (%) used, the contact time, duration of treatment, the total surface on which the product is applied and which body tissues are treated (skin, mucous membranes, eyes etc.) with their tissue-specific properties (permeability, vulnerability).

The safety profile of povidone iodine is well-established.

IV.6 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 Povidone Jodium Alfa Intes.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.7 Discussion on the clinical aspects

Povidone iodine is an iodophore with povidone acting as a carrier of iodine. It has an established use as a broad-spectrum antiseptic, bactericidal, virucidal and fungicide mainly for the treatment of contaminated wounds and for the preoperative preparation of the skin, mucous membranes and the ocular surface. No specific clinical pharmacokinetic, efficacy or safety trials were performed with the product applied for, which is considered acceptable and in line with the proposed legal base

The MAH concludes that on the basis of the available scientific literature and marketing data on the use of povidone iodine solutions for ophthalmic use of that:

- the use of povidone iodine for antisepsis of the skin and ocular region (incl. the eyes) is well established within the EU for more than 10 years for the proposed indications
- there is a large body of evidence behind the pharmacology, pharmacodynamics, efficacy and safety of povidone iodine for all indications as well as specifically for the

ophthalmic market.

- there is also a large number of studies showing the beneficial effects, with little or no evidence of adverse events or toxicity, associated with povidone iodine and povidone iodine has an excellent safety profile.
- povidone iodine has a positive risk/benefit ratio
- povidone iodine ophthalmic solution can be applied as a bibliographical application based upon the Article 10a of EU Directive 2001/83/EC

Risk management is adequately addressed. The clinical aspects of this product are approvable.

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: a pilot test with 3 participants, followed by 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Povidone Jodium Alfa Intes has a proven chemical-pharmaceutical quality. Povidone Jodium Alfa Intes is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

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 have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 8 March 2023.

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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
NL/H/5430/001 /IB/001	**Type IB: A.2.b** *Change in the (invented) name of the medicinal product* • *for Nationally Authorised Products*	Yes	28-02-2024	Approved	-