Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Povidone iodine 5% w/v Eye Drops Solution (povidone iodine)

PL 54537/0001

Alfa Intes Limited

LAY SUMMARY

Povidone iodine 5% w/v Eye Drops Solution (povidone iodine)

This is a summary of the Public Assessment Report (PAR) for Povidone iodine 5% w/v Eye Drops Solution. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Povidone iodine eye drops solution in this lay summary for ease of reading.

For practical information about using Povidone iodine eye drops solution, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Povidone iodine eye drops solution and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK for at least 10 years, with recognised efficacy and an acceptable level of safety.

Povidone iodine eye drops solution is used as a solution for the preparation of the operating ophthalmic field (eyelids, eyelashes and cheeks) and for cleaning the eye and its surroundings in case of eye surgery.

How does Povidone iodine eye drops solution work?
Povidone iodine eye drops solution contains the active substance povidone iodine, which belongs to the group of antimicrobial and antiseptic medicines and works by killing bacteria, spores, fungi and viruses.

How is Povidone iodine eye drops solution used?
The pharmaceutical form of this medicine is eye drops solution.

This medicine will be given to the patient by a doctor or other healthcare professional. They will apply this medicine to the operating ophthalmic field (eyelids, eyelashes and cheeks) and the eye(s) and its surroundings in case of eye surgery.

For further information on how Povidone iodine eye drops solution is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Povidone iodine eye drops solution have been shown in studies?
As the active substance povidone iodine has been in clinical use for over 10 years, data were provided in the form of literature references to show that Povidone iodine eye drops solution is a safe and efficacious treatment as a solution for the preparation of the operating ophthalmic field (eyelids, eyelashes and cheeks) and for cleaning the eye and its surroundings in case of eye surgery.

What are the possible side effects of Povidone iodine eye drops solution?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Povidone iodine eye drops solution approved?
It was concluded that the data provided from literature references had shown that Povidone iodine eye drops solution is effective in the preparation of the operating ophthalmic field (eyelids, eyelashes and cheeks) and for cleaning the eye and its surroundings in case of eye surgery. Furthermore, the well-established use of the active substance povidone iodine has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Povidone iodine eye drops solution?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Povidone iodine eye drops solution. The RMP details the important risks of Povidone iodine eye drops solution, how these risks can be minimised, any uncertainties about Povidone iodine eye drops solution (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Povidone iodine eye drops solution:

Summary of safety concerns	
Important identified risks	• *Anaphylactic reactions*
Important potential risks	• *none*
Missing information	• *none*

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Povidone iodine eye drops solution are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Povidone iodine eye drops solution
A Marketing Authorisation for Povidone iodine eye drops solution was granted in the United Kingdom (UK) on 05 January 2023.

The full PAR for Povidone iodine eye drops solution follows this summary.

This summary was last updated in April 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Povidone iodine 5% w/v Eye Drops Solution (PL 54537/0001) could be approved.

The product is approved for the following indication:

- the pre-operative preparation of the surgical field (eyelids, lashes and cheeks) and irrigation of the ocular surface (cornea, conjunctiva and palpebral fornixes).

The active substance, povidone iodine, is an iodophore that has an established use as a broad-spectrum antiseptic, mainly for the treatment of contaminated wounds and for the preoperative preparation of the skin, mucous membranes and the ocular surface. The organic complex contains approximately 10% of active available iodine.

This application was approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for this application is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national marketing authorisation was granted in the United Kingdom (UK) on 05 January 2023.

II QUALITY ASPECTS

II.1 Introduction

This product contains 200 mg of the active substance povidone iodine in each 4ml single use container. One millilitre of solution contains 50 mg povidone iodine.

In addition to povidone iodine, this product also contains the excipients glycerol, citric acid, polysorbate 20, dibasic sodium phosphate dodecahydrate, sodium chloride, potassium iodate, sodium hydroxide and purified water.

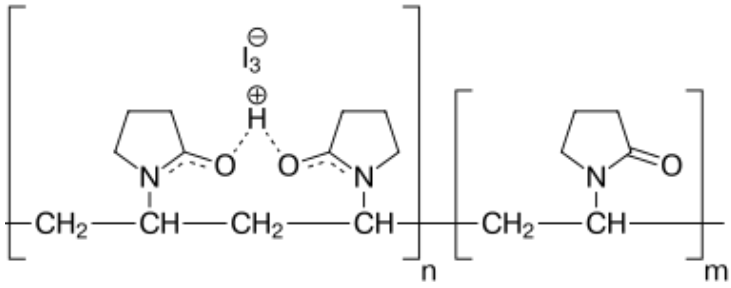
The finished product is packaged in polyethylene sterile, single-use bottles, each containing 4.0 ml eye drops, solution. The bottles are contained in a double sterile sachet. The product is available in a pack size of one bottle. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Povidone iodinate

Chemical Name:	– 2-Pyrrolidinone, 1-ethenyl-homopolymer, compound with iodine; – 1-Vinyl-2-pyrrolidinone polymer, compound with iodine
Other Names:	Iodinated povidone and povidone iodine
Molecular Formula:	$(C_6H_9NO)_n.xI$

Chemical Structure:



Molecular Weight: Approximately 3500 g/mol. It contains not less than 9.0 percent and not more than 12.0 percent of available iodine, calculated on the anhydrous basis.

Appearance: It is a free-flowing, reddish-brown powder.

Povidone iodinate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based

on the results, a shelf-life of 24 months for the unopened product, with the storage conditions 'Do not store above 25°C. Store in the original package and keep away from light.', is acceptable.

Once opened the product should be used immediately-the product should be discarded immediately after first use.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology

No new pharmacology data were submitted, and none were required for this application. A summary of the pharmacology data and the main conclusions of the review are provided in the non-clinical overview is provided below:

Primary pharmacodynamics

Povidone-iodine (PVP-I) is a stable chemical complex of polyvinylpyrrolidone (povidone, PVP) and elemental iodine (I).

The primary pharmacodynamic action of povidone iodine is as a broad-spectrum antimicrobial agent with specific *in vitro* activity against microorganisms including numerous strains of bacteria (both gram-negative and gram-positive), viruses, yeasts, moulds, fungi and protozoa.

The pharmacodynamic action of povidone-iodine is attributed to the small, steady amount of free iodine released into the solution from the povidone-iodine complex. The povidone-iodine complex significantly improves iodine tolerability and minimises iodine toxicity for mammalian cells while maintaining the antimicrobial action of iodine.

Resistance to antiseptics can be intrinsic to the microorganism e.g., chromosomally mediated impermeability or inactivation, or acquired through mutation or acquisition of plasmids and transposons e.g., efflux pumps, target site mutation. However, despite the extensive clinical use of povidone iodine for several decades there have been no reports of resistance, cross-resistance or increased bacterial tolerance to antiseptic treatment with povidone iodine, because iodine probably has multiple modes of action.

The development of bacterial resistance to iodine was studied by the serial passage of two strains of *Pseudomonas aeruginosa*, two strains of *Escherichia coli*, two strains of *Klebsiella aerogenes* and one strain of *Serratia marcescens* in the presence of sub-optimal iodine concentrations that were insufficient to cause cell death. Results showed that, after 20 passages, no detectable change in the required minimum inhibitory iodine concentration was

observed. There was also no detectable change in the time taken until cell death between the parent strain and past subcultures when exposed to effective concentrations of iodine.

Evidence, to date, suggests that povidone iodine does not *in vitro* select resistance among *Staphylococci spp* and *Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli* and Klebsiella aerogenes.

Comment
The non-clinical expert has presented summaries from a range of literature articles to support the proposed mechanism of action of PVP-I as an effective anti-microbial agent that would be useful in the proposed product, as an eye drop and disinfectant solution.

Secondary pharmacodynamics

In vitro studies
Antimicrobial studies on the eye
Coagulase-negative staphylococci are the most common causes of post-cataract endophthalmitis, and these bacteria and viridans streptococci cause most cases of postintravitreal anti-vascular endothelial growth factor (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.

In an evaluation of the antibacterial efficacy of povidone iodine ophthalmic solutions, appropriate quantities of povidone iodine were diluted in in Müller Hinton broth to attain a range of concentrations from 0.005–2.5 per cent w/v per cent w/v. Minimum inhibitory concentration assays assay was performed by adding 50 µl diluted *P. aeruginosa* or *S. aureus* to 50 µl of povidone iodine solution at the various concentrations. The minimum inhibitory concentration was determined by identifying the lowest povidone iodine concentration required to inhibit the bacterial growth. In addition, the minimum bactericidal concentration, which is defined as the minimum povidone iodine concentration required to completely eradicate the bacterial colonies on the Müller Hinton broth agar plates. The growth of *S. aureus* was inhibited at a povidone iodine concentration of 0.078 ±0.020 % w/v whereas the growth of *P. aeruginosa* was inhibited at a much higher povidone iodine concentration of 0.300 ± 0.000 % w/v. Minimum inhibitory and bactericidal concentrations of the compound against a given bacteria were identical.

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.

Povidone iodine 1% w/v was diluted in normal saline, or 0.1 mol/l citrate or phosphate buffers to yield solutions with a pH ranging from 4.0 to 7.0. Antibacterial efficacy was assessed by evaluating povidone-iodine minimum inhibitory concentration and minimum bactericidal concentration at varied pH, povidone iodine formulations diluted in saline and 0.1 mol/l phosphate buffer. Povidone iodine diluted in saline had a minimum inhibitory concentration of 0.25 ± 0.00% w/v against *S. aureus* and of 0.50 ± 0.00% w/v against *P. aeruginosa*. In contrast, povidone iodine diluted in 0.1 mol/l phosphate buffer had a minimum inhibitory concentration of 0.50 ± 0.00% w/v against both bacteria. Minimum bactericidal concentration was identical to minimum inhibitory concentration in all instances.

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 was investigated. 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.

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.

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

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. Virucidal (99.9%, >3-Log10) reductions in titres were produced for 5%, 2%, and 0.4% povidone iodine solutions at 1 minute for adenovirus types Ad5 and Ad7a. Similar reductions were produced at five minutes for types Ad3, Ad4, and Ad8. For type Ad19/ 64, virucidal reductions took 60 min for 5% povidone iodine and 15 minutes for 2% and 0.4%. For type Ad37, 60 minutes (5%), 15 minutes (2%), and five minutes (0.4%) were required to produce virucidal reductions. There were no virucidal reductions in titres produced by 0.001% povidone iodine. The antiviral activity of povidone iodine may be adenovirus type dependent.

A novel application form of povidone iodine was developed by using a povidone iodine liposome complex which demonstrated an excellent antimicrobial efficacy. In this study it could be shown that the novel liposomal formulations containing povidone iodine 2.5 or 5% were as active as the aqueous solution against herpes simplex virus type 1, adenovirus type 8, coxsackievirus A9 and *Chlamydia trachomatis* in cell culture referring to equal povidone iodine concentrations.

In vivo studies

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. Organisms most commonly isolated included: *Staphylococcus aureus*, alpha-haemolytic *Streptococcus sp, S epidermidis*, and *Escherichia coli*. Evaluation of dilute povidone-iodine solutions for effectiveness as ocular surface disinfectants was conducted. Bacterial growth initially detected in 32 of 46 eyes was not detected after disinfection with a 2-minute scrub and 2-minute soaking procedure, using 1:2, 1:10, or 1:50 dilutions 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.

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. In this study, 49 adult male CBA/J mice were used that divided into seven equal groups. The corneas of all mice were scratched and infected with a clinical strain of either S. pneumoniae or *E. coli* topically, except control group. Subgroups received chloramphenicol

0.5% eye drop twice daily in case of S. pneumoniae infection or ciprofloxacin 0.3% eye drop every four hours following *E. coli* infection from or povidone iodine 1% eye drop in both groups, from post infection days 3 to 7. 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.

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*. For the maximum tolerated dose of the study 16 New Zealand albino rabbits, divided into four groups (n = 4 each), were used. Animals were anaesthetised and intravitreally injected with 0.1 mL of 50, 100, 200, or 400 μg of povidone iodine in one eye, and with saline in the other. The animals were examined at days 1, 7, and 14. In the second arm 20 New Zealand albino rabbits were placed into four groups (n = 5 each). Animals were anesthetised and injected with 0.1 mL of *S. epidermidis* containing 3030 colony forming units (CFU) in one eye and saline in the other. Seven hours later, animals were treated with 0.1 mL of 20, 50, and 100 μg of povidone iodine, or no treatment. Bacterial concentrations from extracted vitreous were determined two days following infection. 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*.

Comment

A number of secondary effects are summarised for povidone iodine. Much of this data centres around further activity on the eye; this has limited application as this is secondary to the primary mechanism of action.

Safety pharmacology

No formal non-clinical safety pharmacology studies for povidone iodine as a topical product have been identified in the published literature.

Central nervous system

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.

Cardiovascular system

Antibacterial solutions were irrigated into rabbit pericardium to investigate potential tissue injury. 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.

Respiratory system

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. The lungs of 61 male

Sprague-Dawley rats (150-250 g) were instilled with varying volumes of either phosphate buffered saline or povidone iodine solutions varying in strength from 0.01% to 10%. The lungs were harvested from the rats 1 hour or 1, 3, 5, 7, 14, or 21 days after instillation.

Macroscopically, atelectasis was the primary pulmonary lesion after povidone iodine instillation. The primary light and scanning electron microscopic findings were an initial Povidone-iodine 50 mg/ml Eye Drops and Cutaneous Solution inflammatory phase with oedema, alveolar rupture, and leukocyte infiltration into the pulmonary interstitium, which progressed into a phase of lung parenchyma loss, and then resolved itself with scar tissue formation. Lung tissue viability following 1-day exposure to povidone iodine 0.01%, 0.1%, 1%, or 5% progressively decreased in a significant dose-dependent manner. Povidone iodine aspiration can cause lung injury, including pulmonary fibrosis.

Comment
Safety pharmacology has been briefly described in the non-clinical overview; it is stated that there is a lack of literature data in the public domain. It is acknowledged that there is sufficient information on povidone iodine exposure in humans that preclude the need for extensive safety pharmacology studies to be presented.

Pharmacodynamic drug interactions
No discussion is provided in the non-clinical overview.

III.3 Pharmacokinetics

A summary of the pharmacokinetic data provided in the non-clinical overview is provided below:

Absorption
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 and iodine can both be separately absorbed systemically after topical application.

The topical application of povidone-iodine complex was investigated in dogs to determine whether a relationship exists between povidone iodine topical dose and resultant serum iodide levels. Significant levels of serum iodide resulted from topical application of the higher dose of povidone iodine solution (6 ml of 10% solution per 150 cm^2 versus 3 ml of 10% solution per 75 cm^2). Both doses caused a rapid rise in serum iodide concentrations in the first 2 hours post application, followed by a plateau and then a slight increase at 12, 24 and 48 hours post application. In both groups, significant elevations in serum iodide concentration to >10 μg dL-1 occurred within 90 minutes following application. The pattern of serum iodide levels was similar for both groups; there was no statistically significant difference between these two dosage regimes in the aggregate.

Evidence for absorption of iodine from topically applied povidone-iodine is also provided by experiments with rats and mice. Topical application of povidone-iodine to 15–20 mm^2 of the shaved skin of either rats or mice two hours prior to an injection of radioiodine, decreased radio-iodine uptake in the thyroid by 90%, suggesting competition between the absorbed topically applied iodine and the injected radioiodine for thyroid uptake**.**

Absorption of iodine ingested as povidone-iodine has been studied in rats. Rats that received single gavage doses of ^{125}[I]povidone iodine (dose not specified) absorbed approximately 3%

of the dose, as assessed by measurements of the radioiodine that was retained in the gastrointestinal tract 24 hours after the dose**.** In the same study, absorption was approximately 10 or 5% when the povidone-iodine was administered in 10% ethanol solution and 5% when administered as a 0.2% solution of benzalkonium chloride.

Lugol's solution (strong iodine solution) produces a dark brown staining which cannot be removed by washing with soap and water or by moistening with reducing material. It decreases only very slowly and in the case of strong iodine loads can be observed even after 12 hours. The decrease in the absorbed iodine has two causes: one part diffuses into deeper skin layers where it is reduced to iodide and produces an increase of serum-iodide, while the other part diffuses back out of the skin. An *in-vitro* penetration study of povidone-iodine 10% solution using Franz diffusion static cells with human skin has been conducted. After 24 hours from the beginning of our measurement the iodine concentration in the receiving compartment was 11.59 ± 6.3 µg/cm. The medium flux calculated was 0.73 ± 0.33 µg/cm^2/h with a lag time of 8.9 ± 1.5 h. These *in vitro* results confirmed that povidone iodine could pass through the skin in a relevant amount**.**

Intraperitoneal administration of povidone iodine 10% solution in healthy dogs and rats showed that all titratable iodine was absorbed from the peritoneal cavity within 60 seconds**.**

A rabbit model has been used to investigate the pharmacokinetics in the vitreous of the eye. This model demonstrated that povidone iodine at a concentration of 0.1% after ocular injection has dose-dependent (nonlinear) pharmacokinetics with a half-life (T½) of 3.27 hours. The specific clearance and apparent volume of distribution at a steady state tend to decrease as the dose increased. The T½ values of povidone iodine intravitreal injection at a concentration 0.1% and 0.3% were 3.27 and 3.58 hours, respectively**.**

In a study to determine whether significant amounts of iodine can be absorbed systemically via the mediastinum, povidone iodine 0.5% solution was continuously irrigated into the pericardial sacs of three dogs via catheters for 48 hours. It was shown that the absorption of iodine follows zero-order pharmacokinetics, just as if it were being given by continuous intravenous infusion. The baseline serum iodine concentration was 145.9 ± 64.3 pg/dL, the serum concentration at steady state (Css) 29.290 ± 101.4 kg/dL, urinary clearance (Cl) was 872.4 ± 119.3 ml/hr, and T½ was 6.22 hours. Urinary excretion of iodine increased in proportion to the serum iodine**.**

Distribution

In one study, povidone iodine was radio-labelled as ^{131}I-PVP and rapidly infused intravenously into rats and dogs. The plasma level of radioactivity declined rapidly during the first two hours following infusion. A short inflection phase followed during which the rate of povidone (PVP) disappearance from the plasma changed rapidly. Finally, a straight-line decay curve was reached. In another experiment ^{131}I-PVP was administered by rapid injection to dogs which had thoracic-duct fistulas. Analysis of lymph samples established that the initial rapid fall of serum radioactivity was matched by a rapid rise in extracellular-fluid radioactivity. The inflection point in the blood-disappearance curve coincided with a peak concentration of PVP in the lymph; the levels in the serum and lymph approached one another at a rate that was related to the K-value of the solution**.**

The distribution of povidone was determined by the intravenous injection of six rats with 350 mg of ^{14}C-povidone. Pairs of rats were killed at 2, 4, and 7 hours after infusion. In a similar experiment, rabbits were given 8-9 g of the same preparation daily in seven divided doses. Five moribund human patients received the same preparation of povidone. A similar

distribution pattern was observed in all three species. The skeletal muscle, skin, and subcutaneous tissue contained the largest fraction but lowest concentration of povidone. Samples were taken at different times following infusion; the amount and concentration of PVP retained in the skin and subcutaneous tissue and in skeletal muscle decreased progressively, whereas the values remained constant for organs with large populations of monocytes/macrophages**.**

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 was found in the form of I^- in the plasma of animals treated with $^{125}I^-$ compared to $^{125}I_2$-treated rats in one study. No I_2 could be detected in the plasma. It was determined that 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 maximum 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.

Metabolism

In a metabolism study, radio-labelled povidone was rapidly infused intravenously into rats and dogs. The plasma level of radioactivity declined rapidly during the first two hours following infusion. Approximately 0.3-0.5% of the administered dose appeared in the stool of dog within 24 hours of infusion. Faecal excretion declined thereafter to an average of 0.001%/day. These results concluded that there was no metabolic degradation of povidone iodine**.**

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 iodo compounds 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 iodo compounds within the thyroid.

Excretion

Irrespective of its route of administration (inhalation, subcutaneous or intravenous) iodine is primarily excreted by the kidneys**.** When fasted rats were administered oral gavage tracer doses of ^{131}I as either I2 or NaI 8–9% of the dose was excreted in faeces in 72 hours and 34–35% of the dose was excreted in the urine**.**

In the same study, similar results were obtained in rats that were allowed free access to food before the oral radioiodine dose; 6–7% of the dose was excreted in faeces in 78 hours and 22–29% was excreted in urine (22% of the I2 dose and 29% of the NaI dose).

Pharmacokinetic drug interactions
No formal non-clinical pharmacokinetic drug interaction studies for povidone iodine have been identified in the public domain.

III.4 Toxicology

A number of *in vitro* and *in vivo* studies have been reported for povidone iodine and the individual components (povidone and iodine). These investigative studies are for the most part considered to be either non regulatory or have not been identified as Good Laboratory Practice (GLP) compliant.

No specific toxicology studies on iodine have been performed by the Applicant and none are warranted based on available literature.

A summary of the toxicological data provided in the non-clinical overview is provided below.

Single and Repeat dose toxicity

Acute Toxicity
Acute toxicity studies in rats and mouse have indicated the oral LD_{50} for povidone iodine is > 5000 mg/kg body weight respectively. In an acute toxicity study on gastric exposed mice washing of the povidone-iodine solution (5000 mg /kg), the toxic symptoms and death did not appear in the mice within 14 days after the gastric lavage of Povidone iodine, indicating a LD50 > 5000 mg/kg and no acute toxicity**.**

The results of acute oral toxicity studies performed in animals demonstrate only a very low acute toxicity potential. Iodine has not to be classified and labelled with respect to acute oral toxicity. All non-human LD_{50} values are in the range of 10,000 mg/kg bw or higher and therefore > 2000 mg/kg bw.

In a subacute toxicity study, mice subjected to continuous gastric lavage with povidone-iodine solution (250, 500 and 1000 mg/kg) after 30 days did not show significant difference in weight, routine blood tests, biochemical parameters or visceral examination index compared to control group**.**

Chronic Toxicity
There is little in the public domain over the chronic toxicity of povidone iodine. Studies on the two component elements of povidone have limited chronic toxicity data.

Chronic Toxicity of Iodine/iodide
Metaplasia of the thyroid was reported in rats given potassium iodide in their drinking water for two years. This was thought to occur through a non-genotoxic proliferation dependent mechanism**.**

Repeated administration of iodine via the oral route revealed no evidence for cumulative toxicity in rats. Dose levels of iodine up to 14 mg/kg bw/day and 1.4 mg/kg bw/day did affect the T3/T4 ratios in rats when treated for 10 or 100 days, respectively. Iodide dose levels of 1.4 and 0.42 mg/kg bw/day did not affect the thyroid hormone levels in female rats when treated for 10 or 100 days, respectively. Moreover, for iodide, the thyroid weights of males were significantly increased at a dose level of 1.4 mg/kg bw/day. Hence, the lowest observed adverse effect level (LOAEL) in rats is 14 mg/kg bw/day and 1.4 mg/kg bw/day when treated for 10 or 100 days, respectively**.**

Chronic Toxicity of Povidone
Chronic toxicity studies of povidone were performed on rats (50 males and females per group). Over a four-year period, two groups were treated with povidone 1% (Group 1), povidone 10% (Group 2) with a third group used as a controlled with an unmodified diet (Group 3). All animals in all groups gained weight; the pattern of growth was identical between Groups 1 and 3 while body weight gain was depressed by 10% in animals of Group 2 as compared to controls. Moreover, all haematologic parameters were comparable and urine analysis results were similar among the groups. By 18 months, albumin was noted in the urine of animals from group 2. By 21 months, albumin was detected in the urine from all animals. The animals of group II had diarrhoea. No toxic effects or gross lesions attributable to povidone consumption were noted**.**

Genotoxicity
In an Ames bacterial reversion assay, PVP-I (20 mL/plate) was non-mutagenic to *Salmonella typhimurium* strains TA1530 and TA1538 but showed positive mutagenic activity at higher concentrations against *E.coli* (pol A-). In another study in which test concentrations were not stated, it was reported that PVP-I was capable of producing base-substitution mutations in TA1530 when the test was performed at 4ºC instead of the usual 37ºC. In a further Ames test it was reported that PVP-I was a weak inhibitor of the mutagenicity caused by benzo(a)pyrene in TA98.

In an *in vitro* mouse (TK+/-) lymphoma assay, PVP-I was reported to be non-mutagenic at concentrations of up to 10 mg/mL in the absence of metabolic activation whereas, in the presence of metabolic activation, it caused "aberrant" non-dose related mutations.

However, in a further *in vitro* mouse (TK+/-) lymphoma assay, it was concluded that PVP, PVPI and iodine did not possess any biologically significant cell transforming or mutagenic ability.

In an *in vitro* mammalian cell test, PVP was non-mutagenic in the Balb/c 3T3 transformation assay at concentrations up to 100 mg/mL. Furthermore, three formulations containing PVP-I were not genotoxic in a comet assay or a chromosome aberration test, with or without metabolic activation.

In an investigative study, PVP-I (10% Betaisodona solution) and PVP-I liposomal eye drops were tested for induction of sister chromatid exchanges (SCEs) and structural chromosome aberrations in CHO cells according to the OECD guidelines No. 479 and 473, respectively. A weak non-specific increase in the SCE rates was observed only at the highest concentration (0.1%) of the two PVP-I formulations and it was concluded that there was no evidence of a genotoxic activity.

In vivo studies indicate that single or repeated intraperitoneal administration of PVP-I was non-mutagenic as revealed by the dominant lethal assay (72 mg/kg to mice), the micronucleus test (36 mg/kg to mice) and bone marrow test (82.5 mg/mg to Chinese hamsters).

Taking into account the toxicity of PVP-I to the *in vitro* test systems and the negative findings of *in vivo* studies, the weight of evidence suggests that PVP-I is not genotoxic.

Comment
A range of genotoxicity studies are used to support the weight of evidence approach used by the applicant. *In vitro* studies from Ames and mouse lymphoma assays reveal equivocal results. Further *in vitro* evidence is negative in chromosome aberration/comet assay, and in Chinese Hamster Ovary (CHO) cells following treatment with PVP-I. *In vivo* evidence is presented from mice and hamsters which was supportive of the negative mutagenicity findings.

Carcinogenicity
There are no data on the carcinogenicity of PVP-I available in the literature. However, the potential carcinogenicity effects of PVP and iodine, when tested separately, have been discussed.

It is unlikely that dermal administration of PVP-I is carcinogenic, as it does not cause metastases following repeat dietary administration of PVP-I to rats (repeated-dose toxicity) and it is not reported to be genotoxic. Therefore, due to the relative short-term usage of PVP-I and more than 60 years of use in patients, the carcinogenic risk in humans arising from the normal use of PVP-I is likely to be very low; this is reflected in the SmPC.

Reproductive and developmental toxicity
Fertility
A study was conducted in mice using either the micronucleus test or the dominant lethal assay, and in Chinese hamsters using the bone marrow test. All three assays used a povidone iodine complex (11.2% available iodine) dissolved in distilled water and administered intraperitoneally. The significance of results was determined using the X2 test or U test. In the dominant lethal assay, germ cell mutations in treated male animals are indirectly indicated by changes in the reproductive capacity of untreated females following mating. One group of 20 male mice received 72 mg of povidone iodine/kg. A second group, the vehicle control, received one dose of 10 ml distilled water/kg. A third group was left untreated. Each male was mated with three females for 8 weeks. The animals tolerated a single dosing without incidence. The conception rate in the treated animals decreased significantly in the first week, but the average number of implantations was not affected. In the remaining weeks, all parameters remained similar between control and treated groups. Povidone alone had no teratogenic effects**.**

Povidone iodine solutions have been widely employed in the cleaning of equipment in the *in vitro* fertilisation (IVF) cycle. Exposure of gametes or embryos to potential toxins at any point during the IVF cycle—from vaginal egg retrieval to embryo transfer may have a detrimental effect on embryogenesis and consequent pregnancy rates. In a prospective study, povidone iodine proved embryo-toxic to mouse embryos at all concentrations tested. Total developmental arrest was observed in culture conditions containing povidone iodine at concentrations ranging between 1:100 and 1:100,000. At the lowest povidone iodine concentration of 1:100,000, there was still a significant inhibition of embryonic development, yet several embryos managed to arrive at the blastocyst stage, while others arrested at the 2-6 cell stages. Using the one-cell murine embryo system, povidone iodine solution was found to have an embryo-toxic effect at all concentrations tested**.**

Pregnancy
In a study aimed to investigate the consequences of maternal exposure to iodine excess (0.6 mg NaI/L) throughout pregnancy and lactation on the hypothalamus-pituitary-thyroid axis of the male offspring in adulthood. Maternal iodine excess exposure increased hypothalamic Trh mRNA expression, pituitary Tsh expression and secretion in the adult male offspring.

Moreover, the iodine excess-exposed offspring rats presented reduced thyroid hormones levels, morphological alterations in the thyroid follicles, increased thyroid oxidative stress and decreased expression of thyroid differentiation markers (Tshr, Nis, Tg, Tpo, Mct8) and thyroid transcription factors (Nkx2.1, Pax8). The data strongly suggests that epigenetic mechanisms, as increased DNA methylation, augmented DNA methyltransferases expression, hypermethylation of histone H3, hypo-acetylation of histones H3 and H4, increased expression/activity of histone deacetylases and decreased expression/activity of histone acetyltransferases are involved in the repression of thyroid gene expression in the adult male offspring**.**

Povidone has been studied for its potential teratogenic effect using a technique of injecting agents into the yolk sac of rabbits. After the 9th day of gestation, rabbits were laparotomised with povidone being injected into the yolk sacs in one horn of the uterus, and as control the corresponding solvent was injected into the other horn. On the 28th day of gestation the rabbits were killed, resorptions counted, and foetuses examined for malformations. Physiological saline (n=20) was compared with povidone (n=17), no difference was observed in any of the parameters measured as compared to the saline control. As such povidone was classed as not teratogenic**.**

The effect of a 1% povidone-iodine solution intrauterine infusion on progesterone levels, endometrial histology and estrogen (ERα) and progesterone (PR) receptor distribution by immunohistochemistry was studied in horses. A 1% povidone-iodine infusion during days 0 and 2 post ovulation in healthy mares did not induce histological changes indicating endometritis, but altered progesterone concentrations and reduced the expression of endometrial PR at day 6 without affecting the ERα. These changes could reduce embryo survival**.**

Lactation
In studies to investigate maternal intake of iodine in iodine excess exposed rats, it was determined that the mRNA expression of Slc5a5 and Slc26a4 were reduced in the mammary gland of dams. The results are in accordance with the reduction of prolactin expression and serum levels in iodine excess-treated dams.

Comment
The review concludes that iodine has potential to pass through the placenta and is secreted into breast milk.

The proposed text for section 4.6 of the SmPC is in line with other similarly marketed preparations.

Local tolerance
The non-clinical overview reviews the potential effects of povidone iodide exposure following locally applied drug product; a summary is provided below and is considered acceptable. The clinical use of this preparation would supersede the non-clinical studies.

Otological Toxicity
Povidone iodine preparation is used as a disinfectant in otological surgeries. The ototoxicity of a povidone-iodine preparation was evaluated using infant, young and adult guinea pigs. At 24 hours, the povidone-iodine solution showed a significant toxic effect in the infant group. In the young animal group, no toxic effect was seen. In the adult group, a mild degree of deafness to 2 kHz was found. At 7 days, the young group showed significant hearing loss for all frequencies, but the adult group did not show any hearing loss. Mild hearing loss at 24

hours and seven days when using a 10 % povidone iodine solution, but no hearing loss with a 5% povidone iodine solution at seven days may indicate that rinsing of the middle ear cavity with saline during surgery should minimise the ototoxic effect of povidone iodine.

The ototoxic effects of different concentrations of povidone iodine solutions applied to the middle ear cavity of rats using distortion product otoacoustic emissions was studied**.** 24 healthy adult female Sprague-Dawley rats were randomly divided into three groups. The group A (n = 8 ears) received a povidone iodine 5% solution to the right ear, the group B (n = 8 ears) received povidone iodine 7.5% solution to the right ear and the group C (n = 8 ears) received povidone iodine 10% solution to the right ear. All animals received saline solution to the left ear as a control (n = 24 ears). The animals were tested before, 1 and 10 days after solutions administration to the middle ear. The study revealed that commercially available high concentration povidone-iodine solution may cause significant ototoxic effects when applied topically through a perforated ear drum in rats.

Topical Toxicity – Dermal

Povidone iodine administered clinically through any route can result in systemic absorption of iodine. The amount of iodine absorbed will vary according to the concentration of the solution utilised, the number of applications, and the route of administration**.**

Several cytotoxicity studies, conducted to investigate the potential detrimental effects of povidone iodine on wound healing, typically fibroblasts, keratinocytes and other cell lines, have shown that povidone iodine has very low cytotoxicity compared to other antiseptics when tested on skin (vs. polyhexamethylene biguanide) PHMB, octenidine, chlorhexidine and hydrogen peroxide) and oromucosal (same as octenidine but superior to chlorhexidine) cell lines**.** An *in vivo* study that evaluated the effect of povidone iodine on human polymorphonuclear leukocytes and fibroblasts demonstrated significant inhibition of migration, fibroblastic activity, and wound cellularity in situ at a povidone iodine concentration of 5%. Correspondingly, a 1 % solution showed no significant difference when compared with the control solution of normal saline solution, with good migration and wound cellularity. These results proved that the toxicity of povidone iodine at the cellular level is directly proportional to the concentration of the solution utilized. Therefore, it is recommended that a 1 % solution is the most appropriate dilution for wound**.**

Studies in vivo did not confirm the cytotoxic effect observed with *in vitro* models, particularly at various povidone iodine concentrations**.** Several animal studies of povidone iodine in wound healing, published over thirty years ago, demonstrated that concentrations of up to 10% generally do not inhibit the granulation and epithelialisation processes. No dermal reactions were noted when applying povidone iodine 10% solution to the hairless backs of 25 rabbits for 96 hours of contact and for another 48 hours of contact after 2-weeks of nontreatment**.**

Many animal studies have also investigated the effect of povidone iodine on wound microcirculation, with inconsistent findings. In rabbit ear chamber wounds, the use of a povidone iodine 5% solution was associated with an early but rapidly transient decrease in blood flow. However, use of povidone iodine 10% showed faster neovascularisation compared with silver nitrate, sodium hypochlorite, and untreated controls**.** Another rat model demonstrated no negative effects on capillary blood flow after up to 60 min exposure to a 1% povidone iodine solution.

Topical Toxicity – Ocular

With the use of povidone iodine as the predominant biocidal product for ophthalmological antisepsis, a number of studies have been performed in assessing the local toxicity on the and in the eye. In a study using rabbits, various presurgical skin antiseptics including a povidone iodine 7.5% solution (with detergent) and povidone iodine 10% solution (without detergent) were compared. Each test substance was applied topically to one eye of each of six animals. Five minutes after application, moderate corneal epithelial oedema was noted in all groups except the saline control. After three hours, marked corneal de-epithelialisation, conjunctival chemosis, and anterior stromal oedema were noted in all treated groups except for the povidone iodine 10% solution (without detergent) and the control. After one week, all corneas had returned to normal appearance. These results prove that povidone iodine 10% solution without detergent caused minimal corneal toxicity in rabbits. It was also shown that the other antiseptics tested, including the povidone iodine 7.5% were toxic to the cornea**.**

A most recent study investigated the effects of povidone iodine in different concentrations on the rabbit's cornea. The results show that after conjunctival sac povidone iodine instillation, severe epithelial damage was observed at the concentrations of 2.5% and 5%. After anterior chamber povidone iodine injection, significant corneal oedema was observed at the concentrations of 2.0% and 1.5%**.**

Another study instead investigated the effects of frequent dosing with povidone iodine by evaluating ocular irritation in 18 rabbits according to the McDonald-Shadduck method and corneal epithelial wound healing in 16 rabbits with superficially abraded corneas. Eyes treated with povidone iodine 0.33% had epithelial healing comparable to 0.3% gentamicin treated eyes while povidone iodine, at concentrations of 0.5%, delayed healing by one day. Mild conjunctival congestion and swelling were noted in all eyes**.**

The corneal endothelium may theoretically be exposed to povidone iodine during intraocular surgery or during the repair of a corneal laceration. A study was conducted that explored the changes in corneal endothelial cell density following exposure to povidone iodine 1%, 2%, and 5% solution in a porcine ocular model. Four groups of excised porcine corneas were exposed to povidone iodine 1% (group A), povidone iodine 2% (group B), and povidone iodine 5% (group C) and balanced salt solution (group D) for a 1-minute exposure. Specular microscopy was used to measure endothelial cell density pre- and post-exposure. Group A (1%) had reduction of endothelial cell density from 3870 cells/mm2 to 3604 cells/mm2, group B (2%) 3634 pre-exposure to 3115 post-exposure, group C (5%) 3582 pre-exposure to 2948 post-exposure, and group D (BSS) endothelial cell density was 3639 pre-exposure to 3741 post-exposure. A graded increase in endothelial cell loss is seen with increased povidone iodine concentrations**.**

Investigators undertook an evaluation on *ex-vivo* corneal irritancy and damage with a range of concentrations from 0.5 to 10 % w/v diluted in sodium chloride 0.9 % w/v solution with bovine eyes. Even the lowest tested dilution of povidone iodine of 0.5 % w/v demonstrated some degree of irritation as per the Bovine Corneal Opacity and Permeability (BCOP) assay. While this dilution displayed a BCOP score of 1.8 ± 0.4 (slight-to-moderate irritation), the irritation potential of the compound continued to increase with increasing concentrations. Povidone iodine 1% w/v, demonstrated moderate-to-severe irritation to the cornea (BCOP score: 3.6 ± 0.6). Both positive controls (0.1 mol/l sodium hydroxide and acetone) caused severe irritation to the corneal surface, while sodium chloride 0.9 % w/v (control) was non-irritant. From histological sections, it was observed that povidone iodine up to 0.75 % w/v did not affect corneal epithelial integrity; however, application of the compound resulted in

some stromal swelling at all tested concentrations. Conversely, some detachment of the apical epithelium was seen at the higher 1% concentration.

Using the above study, another investigator repeated the work looking at the effect of pH on povidone iodine formulations. No irritation was observed with saline (BCOP score 0.04 ± 0.10), whereas slight irritation could be seen in some instances when citrate (0.25 ± 0.42) or phosphate (0.42 ± 0.38) buffers were applied to the *ex vivo* bovine eyes. Povidone iodine 1% w/v diluted in saline showed moderate-to-severe corneal irritation (3.00 ± 1.18), which was significantly greater than that observed from the negative controls ($p < 0.001$), whereas povidone iodine dilution in 0.1 mol/l citrate buffer also resulted in significant severe irritation across all replicates (4.58 ± 0.38, $p < 0.0001$). When povidone iodine was diluted in 0.1 mol/l phosphate buffer, the observed BCOP score (0.50 ± 0.55) was not significantly different from that observed in the negative controls ($p > 0.05$). Both positive controls caused notable irritation (0.1% w/v sodium hydroxide BCOP score = 3.92 ± 1.56, 0.1% w/v phosphoric acid BCOP score = 7.00 ± 0.00)**.**

In an *in vitro* study, cultured bovine corneal endothelial cells were exposed to diluted povidone iodine. The degree of cell damage was determined by staining with trypan blue and by comparing the results to those in a control group. In a controlled *in vivo* study, a single dose of diluted povidone iodine was injected into the anterior chamber of rabbit eyes, completely replacing the aqueous humour. *In vitro*, povidone iodine concentrations of 0.05% or less did not induce endothelial cell damage. Significant damage was observed with a povidone iodine concentration of 0.1%. Calf serum concentrations of 1% and higher in the culture media protected the endothelial cell monolayer from cytotoxic damage by the povidone iodine. Aqueous humour did not have a similar effect. *In vivo*, povidone iodine concentrations of 0.1% or less did not induce changes in corneal endothelium morphology or function as assessed by specular microscopy and pachymetry. A povidone iodine concentration of 1% served as a positive control, causing corneal oedema and endothelial cell loss as demonstrated by pachymetry, histopathology, and elevated intraocular pressure**.**

The potential toxicity of povidone iodine on the corneal endothelium after injections into the anterior chamber in a rabbit model was investigated. The 24 eyes of 12 albino rabbits were divided into three groups according to the drugs tested: group A, povidone iodine 5%; group B, povidone iodine 10%; group C, balanced salt solution. The injected eyes were evaluated by bio-microscopy, specular microscopy, corneal pachymetry, and transmission and scanning electron microscopy. Corneal oedema was observed in all eyes of groups A and B. In groups A and C, the endothelial cell morphology was not significantly changed and the mean endothelial cell count of the eyes did not change significantly ($p = 0.5054$). There was no significant difference in corneal thickness between groups A and C ($p = 0.3823$), but there was a significant difference between groups B and C ($p = 0.0002$). Transmission and scanning electron microscopy results were normal in group C but not in groups A and B.

Conclusion

Povidone iodine, in both 5% and 10% concentrations, demonstrates severe toxicity when one drop of either concentration is placed directly in the anterior chamber**.** The toxicity of intravitreal povidone iodine was assessed in rabbit eyes by injecting 0.1 ml of povidone iodine in concentrations of 0.05%, 0.5% and 5% into the vitreous cavity. The injected eyes were evaluated by clinical examination, anterior segment and fundus photography, endothelial cell counts, electroretinography and histopathology. Compared to control eyes, no changes were observed in all 6 eyes injected with 0.1 ml of 0.05% povidone iodine solution. 9 of 10 eyes tolerated a concentration of 0.5% with no detectable adverse changes. One eye developed a temporary mild iritis and mild suppression of the electroretinogram. Intra-retinal

haemorrhages, oedema, arteriolar narrowing and retinal oedema were seen one week following injection. Mild retinal necrosis of the same area was seen on histology. All four eyes injected with 5% povidone-iodine developed temporary hypotony and iridocyclitis. A dense cataract developed in all eyes. Full thickness retinal necrosis and a profound lasting reduction in the electroretinogram was produced in all of these eyes. No corneal epithelial or endothelial changes were observed in any eye in this series. Low concentrations of intravitreal povidone-iodine likely to be produced by instillation prior to surgery are tolerated by rabbit eyes. The concentrations tolerated by the studied eyes are near reported bactericidal levels.

Evaluation of Impurities
No toxicological concerns were raised.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of a complete Environmental Risk Assessment based on the expectation that this product containing an active substance of well-established use is unlikely to significantly impact on the total amount of povidone iodine or it's breakdown products in the environment.

The applicant has provided a partial Phase I Environmental Risk Assessment with a calculated potential environmental exposure in surface water ($PEC_{surfacewater}$) value of 0.000019 μg/L for povidone iodine in the proposed indications.

Assessment of the potential for bioaccumulation has concluded that the potential for persistence, bioaccumulation potential or toxicity (PBT) is very low (logKow < 3). Aquatic effects studies have been reviewed and do not conclude a risk for the environment.

It is not expected that the use of this product will significantly impact on the total amount of povidone iodine or it's breakdown products in the environment.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of povidone iodine are well known. The overview based on a literature review and a review of these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics
The pharmacokinetic properties of povidone iodine are relatively well-known. A summary of the pharmacokinetic data submitted in the clinical overview is provided below:

Absorption
Povidone iodine is a complex of povidone and iodine. Several absorption studies revealed that there is no or very limited absorption of povidone in humans and animals.

Iodine is a common element that is required for the production of thyroid hormones. Iodine that is ingested orally in the form of water-soluble salts, i.e., potassium or sodium iodide, typically results in 100% absorption from the gastro-intestinal tract. In seven euthyroid adults who ingested a single tracer dose of radiolabelled iodine, less than 1% of the administered radiolabel was found in the faeces, suggesting nearly complete absorption of the ingested

radioiodine [9]. In the same study, 20 other euthyroid adults that received daily oral doses of potassium iodide for 13 weeks had daily iodine urinary excretion levels of approximately 80–90% of the estimated daily intake. This also suggests near complete absorption.

In a separate acute ingestion study in nine healthy adults, the urinary and thyroid radioiodine accounted for 97% ± 5% of a single ingested dose of radioiodine. In the same study, two subjects ingested the tracer dose in conjunction with a dose of 5 or 15 mg stable iodide. The recovery of radioiodine in the thyroid and the urine were 96% and 98% respectively. The overall gastrointestinal absorption in different subpopulations (children, adolescents and adults) appears to be similar based upon measurements of 24-hour thyroid uptakes of radioiodine administered orally.

Iodine in food appears to be nearly completely absorbed. In a dietary balance study, 12 healthy adult women were given daily intakes of 170–180 μg for two 7-day periods. The results showed that 96–98% of the daily intake was excreted in the urine, which indicated near-total absorption of the administered dose. Iodine that is incorporated into bovine milk appears to be nearly completely absorbed when ingested.

Distribution

There is little data on the human distribution of povidone in the body. In early toxicokinetic studies, distribution was determined by injecting six rats with 350 mg of 14C-Povidone (K-33) via the intravenous route. In a similar experiment, rabbits were given 8 - 9g of the same preparation daily in seven divided doses. The rabbits were killed at 1, 2, and 6 months after infusion. Five moribund human patients received the same preparation of povidone. A similar distribution pattern was observed in all three species. The skeletal muscle, skin, and subcutaneous tissue contained the largest fraction but lowest concentration of povidone, the organs of the monocytes/macrophages system had the highest concentration. Samples were taken at different times following infusion, the amount and concentration of povidone retained in the skin and subcutaneous tissue and in skeletal muscle decreased progressively, whereas the values remained constant for organs with large populations of monocytes/macrophages.

Irrespective of the route of exposure to inorganic iodine, the distribution of absorbed iodine is similar. This conclusion is supported by a study in which human subjects were orally exposed to tracer levels of radio-labelled iodine as sodium iodide. The results determined that approximately 20–30% iodine was distributed to the thyroid, and 30–60% was excreted in the urine after approximately 10 hours. Essentially the same results were observed after the ingestion of a tracer dose of $Na^{132}I$. Similar results were found in human volunteers that inhaled tracer levels of radioiodine as I_2.

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. Under normal circumstances, the concentration of iodine in serum is approximately 50–100 μg/L. Approximately 5% of the iodine is in inorganic form, with the remaining 95% consisting of the various organic forms of iodine, primarily as protein complexes of the thyroid hormones T4 (tetraiodothyronine) and T3 (triiodothyronine). The tissue distribution of iodide and organic iodine are very different and are interrelated by metabolic pathways that lead to the iodination and deiodination of proteins and thyroid hormones in the body. Iodine is predominantly confined to the extracellular fluid. However, tissues that have specialised transport mechanisms for accumulating iodide are exceptions. These tissues include the thyroid, choroid plexus, mammary glands, salivary glands, gastric mucosa, placenta, and sweat glands.

The concentrations of iodide in serum, which is indicative of extracellular fluid concentrations, normally range from 5 to 15 μg/L. This indicates a total extracellular iodide content of the human body of approximately 85–170 μg, assuming an extracellular fluid volume of approximately 17 L. The concentration of iodide in the thyroid are usually 20-50 times that of serum (0.2–0.4 mg/dL, 15–30 nM). However, concentrations greater than 100 times that of blood occur when the gland is stimulated by thyrotrophin (a TSH) and concentrations in excess of 400 times blood have been observed.

Metabolism
In a metabolism study, ^{14}C-povidone (K-33) was rapidly infused via the intravenous route into rats and dogs as well as being infused into humans over a 45-minute timespan in order avoid rapid expansion of the circulating blood volume. It was concluded that there was no metabolism of povidone in the human system.

The metabolism of absorbed iodine is expected to be similar, irrespective of the route of exposure to inorganic iodine. Molecular iodine and ingested sodium iodide and inhaled methyl iodide all appear to undergo rapid conversion to iodide.

Iodine in the thyroid gland is incorporated into the protein, thyroglobulin. Iodine forms covalent complexes with tyrosine residues. The iodination of thyroglobulin is catalysed by the enzyme thyroid peroxidise. Iodination occurs at the follicular cell-lumen interface and the processes involved are the oxidation of iodide to form a reactive intermediate, the formation of mono-iodotyrosine and diiodotyrosine residues in thyroglobulin, and the coupling of the iodinated tyrosine residues to form T4 (coupling of two diiodotyrosine residues) or T3 (coupling of a mono-iodotyrosine and diiodotyrosine residue) in thyroglobulin. In the thyroid, the T4/T3 ratio is approximately 15:1; however, the relative amounts of T4 and T3 produced can depend on the availability of iodide, as low levels of iodide result in a lower T4/T3 synthesis ratio. The lipophilic T3 and T4 enters the blood via diffusion through the plasma membrane. More than 99% of both T3 and T4 combine with blood transport proteins, predominantly thyroxine binding globulin. The process is regulated by the pituitary hormone, thyroid stimulating hormone (TSH). TSH is released in response to thyrotropin releasing hormone from the hypothalamus as a response to low blood thyroid hormone level or lowered metabolic rate or body temperature.

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; and
- conjugation of the phenolic hydroxyl group on thyronine with glucuronic acid and sulphate.

The mono-deiodination of T4 to T3 is the major source of production of peripheral T3. T3 has a greater potency as a hormone than T4, and, together with the production of 3,3′,5-triiodo-L-thyronine, account for about 80% of total T4 turnover in humans. Iodothyronine deiodinases also catalyse the inactivation of T4 and T3. Deiodination is catalysed by selenium-dependent deiodinase enzymes. In the liver and probably in other tissues, the sulphate conjugation of the phenolic group of iodothyronines occurs. In the human liver, this reaction is catalysed by the enzyme phenolic arylsulphotransferase. Iodothyronines that have one iodine moiety on the phenolic ring preferentially undergo sulphation with the sulphated products then undergoing deiodination.

Excretion and Elimination
It was determined that when a fragmented mixture of povidone with a range of different molecular weight povidones was compared with a single molecular weight povidone (K-33 Povidone) which was infused into humans that during the first 6 hours the excretion of the fragmented mixture was lower than the K-33 povidone. The molecular weight of urinary povidone rose 48-96 hours following infusion to a peak corresponding to a molecular weight of 40,000. Povidone continued to be excreted at the rate of 25 mg/day (0.06% of a clinical dose of 17.5 g) for as long as one year. The excreted dose had a molecular weight between 40,000-120,000 as smaller particles passed rapidly through the glomerulus and larger particles were retained in the monocytes/macrophages system.

The effect of renal impairment
There are no formal studies within the literature, for the proposed indication, that has investigated patients with impaired renal function.

The effect of hepatic impairment
There are no formal studies within the literature, for the proposed indication, that has investigated patients with impaired hepatic function.

The effect of povidone iodine on the elderly
There are no published formal studies that has investigated the pharmacokinetics in elderly patients compared with younger adults within the indication. Human skin changes dramatically with increasing age. Morphological, physiological, and biochemical changes within the tissue have been widely investigated and documented within the literature.

In a study, *in vivo* percutaneous absorption measurements of several molecules with varying physiochemical characteristics were compared between young (18–40 years) and old (>65 years) subjects. Permeation of hydrophilic compounds was found to be significantly lower in aged subjects and therefore it appears that aging can affect percutaneous absorption *in vivo*. The diminished surface lipid content of "old" skin implies a diminished dissolution medium for compounds administered topically. As povidone-iodine is a topical solution, and from general work performed comparing old and young skin, there would be expected that elderly skin was less permeable to povidone-iodine than younger skin.

It is noted that povidone-iodine ointment is widely available across Europe and indicated for the treatment of small wounds, cuts, grazes, superficial burns, abrasions and blisters in adults, adolescents, children, and infants aged 6 months and older. The SmPC states that for adolescents, children and infants aged 6 months and older, the product is used in the same posology and method of administration is the same as in adults.

There is no data regarding ocular absorption of drugs between elderly and younger individuals. The majority of ophthalmic procedures within the literature review showed the efficacy and safety in adults above 60 years of age.

Other Pharmacokinetic studies
Dermal absorption
Povidone iodine is an effective, safe antiseptic, and therefore is used frequently in various fields as a broad-spectrum topical disinfectant. In burn patients and infants, the skin is very thin or permeable, and marked transcutaneous iodine absorption has been reported. However, in adults, healthy skin is much less permeable.

A study was conducted to assess transcutaneous iodine absorption in patients who have single topical application with povidone iodine and the serial changes of the urinary iodine level after total thyroidectomy in patients with thyroid carcinoma in Japanese patients. The urinary iodine levels after skin single preparation of povidone- iodine increased nearly seven times the preoperative urinary level and ranged from 193 to 5120 (mean ± SD: 1504.7 ± 984.9) μg/g of creatinine.

The effect of single dose povidone iodine on serum thyrotropin and thyroxine levels and urinary iodine excretion in 30 preterm, 40 full-term new-borns and 50 infants in a children's hospital was studied. There was no significant change of thyroid function in any of the groups ($p>0.05$). Urinary iodine excretion in pre-term and full-term groups elevated significantly($p>0.05$) indicating that there was substantial dermal absorption.

Mucosal absorption
Whilst povidone iodine has been well established in clinical practice as a mouthwash and more recently as a nasal spray, there are no well controlled pharmacokinetic human studies that highlight the amount of iodine that is absorbed across the buccal or nasal mucosa.

Vaginal absorption
In a study in nonpregnant women, total iodine, protein-bound iodine, inorganic iodine, and thyroxine values were measured in serum before and 15, 30, 45, or 60 minutes after a two-minute vaginal disinfection with povidone iodine (Betadine). Only 15 minutes after application, serum iodine levels were raised and remained significantly elevated 30, 45, and 60 minutes after disinfection. Serum concentrations of total iodine and inorganic iodine were increased up to fivefold to 15-fold, respectively; during the relative short period of observation, thyroxine levels were not altered.

Daily vaginal douching with povidone iodine in 12 euthyroid volunteers for 14 days resulted in a significant increase in serum total iodine concentration and urine iodine excretion. The increase in serum total iodine was associated with a marked decrease in 24-hour iodine 123 uptake by the thyroid and a small but significant increase in serum thyrotropin (TSH) concentration. However, values for serum TSH never rose above the normal range. No significant changes in serum thyroxine (T4), free T4 index (FTI), or triiodothyronine concentrations were observed, although serum T4 and FTI did decrease slightly during treatment. The findings suggest that iodine is absorbed across the vaginal mucosa and that the subsequent increase in serum total iodine does induce subtle increases in serum TSH concentration. There was no evidence, however, of overt hypothyroidism in these euthyroid women.

Wound Absorption
Enhanced absorption of iodine occurs through denuded skin, wounds and abrasions, decubitus ulcers, mucosal surfaces with high absorptive capacity (vagina), or large areas of intact skin. It has been demonstrated that in patients where the burned injury spread over 25% of the skin surface with deep second- and third-degree burns, the serum total iodine levels have been reported to markedly increase to 4500–48,000 mcg/dl and possible systemic complications due to elevated free iodine levels have been reported.

Ocular pharmacokinetics
In adults, application of eye drops did not lead to elevated urinary iodide levels. In a study in neonates, povidone iodine eye drops were compared with silver nitrate, a standard treatment for ophthalmia neonatorum. It was determined that the neonates in the povidone iodine

1.25% eye drops group received approximately 70 μg iodine as compared with iodine uptake of 169 μg for everyone litre of breast milk.

Systemic iodine absorption has been studied in the use of ophthalmic surgery, including cataract surgery. Studies have also been conducted on the intravitreal pharmacokinetics of the molecule.

In one study (n=241) in adult patient, systemic iodine absorption after conjunctival and/or periorbital application of 1.25% and 10% povidone iodine solutions were compared with a non-iodine control. All patients on the povidone iodine 10% application showed, regardless of the application site, a 1.2-1.5-fold increase in urinary iodine excretion after 24 hours ($p = 0.01$). In 17 out of 110 (15.5%) patients in whom the 10% solution was used, the critical threshold of urinary iodine excretion as defined by World Health Organisation (>300 μg/L) was exceeded. In contrast, no significant ioduria was observed with the use of povidone iodine 1.25% solution except in patients after 48 hours ($p = 0.01$) and with a concurrent conjunctival and periorbital application. The proportion of the excreted iodine in urine ranged from 0.24% to 1.77%.

A similar study in adult patients, using five different combinations of povidone iodine alone or in combination with iodine-free antiseptics were applied to the conjunctiva and periorbital skin. An iodine-free product served as control. Iodide and creatinine in urine were analysed before intervention and 24 and 48 h postoperatively. Depending on the concentration and application site, 0.3-4.5% of the total applied iodine or 3.6-45.4% of the free iodine were absorbed. The range of urine iodine excretion was between 11.7 and 71.0 mug iodine/g creatinine, depending on the povidone iodine concentration and the site of application. The increase in iodine excretion was significant at 24 hours postoperatively in trials receiving povidone iodine both periorbitally and conjunctivally, depending on the concentration used.

In the above two studies conducted in adults, it was determined that considerably more iodine was absorbed following cutaneous compared to conjunctival application. This indicates a lower permeability of the conjunctiva with regard to iodine. Where povidone iodine is applied only conjunctivally, the increase in iodide excretion is insignificant, which is also seen in the neonatal study.

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of povidone iodine are well-known. No new pharmacodynamic data have been submitted for this application and none were required.

The applicant has provided sufficient literature reviews of the actions of povidone iodine in a variety of infections in the clinical overview. Povidone iodine is an iodophore that has an established use as a broad-spectrum antiseptic.

A summary of the pharmacodynamic data provided in the clinical overview is provided below:

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-resistant *Staphylococcus aureus* (MRSA) infections. Povidone iodine also has anti-biofilm activity against *Staphylococcus epidermidis* and *Staphylococcus aureus* at sub-inhibitory concentrations. 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.

The iodine release feedback mechanism within the povidone-iodine complex allows for a gradual release of elemental iodine thereby minimising the safety and tolerability issues associated with skin exposure to earlier elemental iodine formulations. It also appears to protect against inhibition of granulation tissue formation.

From *in vitro* studies, it has been suggested that iodine counteracts the inflammation caused from both pathogens and from host response. Such anti-inflammatory effects appear to be multifactorial and to be clinically relevant.

Despite the extensive clinical use of povidone iodine for multiple decades, there have been no reports of resistance, cross-resistance or increased bacterial tolerance to povidone iodine. This has been suggested that this is due to iodine exhibiting multiple modes of action.

The literature suggests that povidone iodine does not, *in vitro*, select resistance among staphylococci and *Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli* and *Klebsiella aerogenes.* The lack of reported resistance to povidone iodine is thought to be due to the sheer diversity of susceptible targets within each pathogen.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application and none were required.

Since its introduction in the 1960's, there has been vast clinical experience with povidone. Many of the clinical efficacy studies were performed prior to the current standards but support the efficacy of the product.

Povidone iodine has been widely indicated as an antiseptic for the treatment and prevention of infection in wounds including ulcers, burns, cuts and other minor injuries. In addition, it is also approved, both as a pharmaceutical medicine and as a biocide for the preparation of skin prior to surgery. It is also approved as a mouthwash/gargle and as vaginal pessaries/ gel/douches.

Povidone iodine has also been approved by numerous countries as an ophthalmic solution for the pre-operative preparation of the surgical field (eyelids, lashes and cheeks) and irrigation of the ocular surface (cornea, conjunctiva and palpebral fornixes).

The main clinical efficacy data provided in the clinical overview to support the use of povidone iodine in the proposed indications is provided below.

Prevention of Surgical Site infection

Surgical site infections remain an important cause of increased morbidity, mortality, hospital length of stay, and care costs. Many infections acquired during surgery originate from the patient's own commensal flora thereby necessitating comprehensive disinfection of the surgical site prior to incision.

The UK National Institute for Health and Care Excellence (NICE) have issued an evidence review for the effectiveness of skin antiseptics in the prevention of surgical site infections. 112 studies were identified, including 28 randomised controlled trials, which included a Cochrane review as being potentially relevant.

From the analysis of the review, the evidence for aqueous povidone iodine in surgical site infections is summarised below.

Surgical Site Infections
Moderate quality evidence from two randomised controlled trials, including 407 people could not differentiate between people who received 5% aqueous povidone iodine for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.
- No significant difference was identified within 30 days (moderate quality)
- No significant difference was identified during three-year follow up (very low quality).

Very low quality evidence from three randomised controlled trials, including 443 people could not differentiate between people who received 10% aqueous povidone iodine for skin preparation before incision and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).
- No significant difference was identified within 30 days surgery (very low quality)
- No significant difference was identified six weeks postoperatively (low quality)
- No significant difference was identified during postoperative phase (very low quality)
- Very low quality evidence from two randomised controlled trials, including 178 people could not differentiate between people who received 10% aqueous povidone iodine for skin preparation before incision during clean surgery and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).
- Very low quality evidence from one randomised controlled trial, including 164 people could not differentiate between people who received 10% aqueous povidone iodine for skin preparation before incision during clean-contaminated surgery and those who received aqueous povidone iodine scrub (7.5%) and paint (10%).

Superficial Surgical Site Infections
Moderate quality evidence from one randomised controlled trial, including 351 people could not differentiate superficial SSI between people who received 5% aqueous povidone iodine for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.

Deep Surgical Site Infections
Low quality evidence from one randomised controlled trial, including 351 people could not differentiate deep SSI between people who received 5% aqueous povidone iodine for skin preparation before incision and those who received 0.5% chlorhexidine with 70% alcohol.

The value and the efficacy preoperative skin antisepsis with povidone iodine were confirmed by a large American study in 7669 clean-contaminated surgical patients. Evidence suggests that the addition of alcohol to povidone iodine involves a little benefit. However, one study of 200 healthy volunteers showed that the use of 70% isopropyl alcohol before or after 10% povidone iodine was more effective in reducing bacterial skin counts than disinfection with a single agent.

A meta-analysis evaluated the efficacy of chlorhexidine and povidone iodine in the prevention of postoperative surgical site infection and the incidence of corresponding skin adverse events. The results showed that chlorhexidine was superior to povidone iodine in preventing postoperative SSI, especially for the clean-contaminated surgery. However, there was no statistically significant difference in the incidence of skin adverse events between chlorhexidine and povidone iodine groups.

As well as surgical site preparation, intraoperative flushing with povidone iodine has been shown to reduce infection rates in sensitive indications including breast surgery, spinal surgery (0.35% dilution), total joint arthroplasty (0.35% dilution), and intraperitoneal irrigation (1% dilution) during laparotomy. A review summarised evidence that suggests efficacy of povidone iodine irrigation, emphasizing as it is a simple and inexpensive solution with the potential to prevent surgical site infection. Such wound irrigation with diluted povidone iodine has been advocated by a recent World Health Organisation guideline.

A comprehensive literature review concluded that 7.5% povidone iodine or 2% triclosan is helpful for the eradication and suppression of skin colonisation for short periods, particularly in preoperative settings.

Treatment of Topical wound infections

For many years, topical povidone iodine has proved its usefulness in the treatment of infected and potentially infected wounds of various types with low possibility of development of resistance by microorganism. Unfortunately, there have been some reports that have suggested that povidone iodine could be detrimental to wound healing due to desiccation of the wound surface and superficial eschar formation. This could be based around a formulation effect as it has been shown that liposomal formulations of povidone iodine could create higher moisture levels at the wound interface with a slower and more targeted release of the povidone iodine with the cell surface.

The results of a clinical trial on patients undergoing split skin grafts, suggested that wounds treated with povidone iodine trended toward lower bacterial counts in comparison to the gauze controls. In addition, the use of povidone iodine ointment medicated gauze did not delay wound healing when compared to simple Vaseline gauze along with evidence for a possible earlier onset of epithelialization with povidone iodine.

Several studies have shown that the use of povidone iodine ointment can lead to a decrease in the incidence of infection and improved patient outcomes.

The efficacy of povidone iodine has been proved in venous and arterio-venous leg ulcers. In an intra-individual comparison study on 51 patients with at least two similar chronic leg ulcers, treated with hydrocolloid dressings, exposure to povidone iodine resulted in a highly significant 2–9 week improvement in healing time, with superior micro-vascularity and dendrocyte density. This has been supported by other studies where lower bacterial load increases faster decreases in ulcer size and inflammation. Similarly, povidone iodine efficacy has also been demonstrated in primarily diabetic foot ulcers.

Prevention of Endophthalmitis

Povidone iodine is routinely used in the preparation of ophthalmic surgery or intraocular injection for prophylaxis against postsurgical endophthalmitis. It has been shown that bacterial culture isolates from patients' vitreous who were diagnosed with postsurgical endophthalmitis are the same bacterial species as found on the eyelids or conjunctiva, *Staphylococcus epidermidis, Staphylococcus aureus,* and *Streptococcus viridans*. These pathogens are able to gain entry into the eye as a result of surgery. The universally adopted strategy for the prophylaxis against postsurgical endophthalmitis is the reduction of the quantity of bacteria on the eyelids and conjunctiva as most of the causative microbes originate there. In addition to the common bacteria, moulds such as *Fusarium sp* and *Aspergillus sp* and yeasts such as *Candida sp* can also be present. Povidone iodine solution has been shown to be clinically effective against these organisms as well as in cases of endophthalmitis due multidrug resistance.

There are almost no published randomised controlled trials evaluating the efficacy of various proposed measures to prevent endophthalmitis, so the optimal methods are largely unknown. Prophylaxis for eye surgery with topical povidone iodine preoperatively and topical antibiotics postoperatively is routinely given, but these measures have not been evaluated by a randomised controlled trial.

Ocular surgery

In terms of ocular surgery and the requirement for pre- and peri-operative antisepsis, povidone iodine solution has been the most studied molecule in cataract surgery and phaecoemulsification procedures.

The European Society of Cataract and Refractive Surgeons (ESCRS) recommends that either povidone iodine 5% or 10% solution should be applied immediately prior to surgery for a duration of a least 3 minutes. In the UK, the National Institute for Clinical Excellence (NICE Guideline NG77, 2017) has published guidelines on cataract surgery. It maintains that surgeons should use preoperative antiseptics in line with standard surgical practice.

The American Academy of Ophthalmology's guideline recommends that povidone iodine 5% solution is applied to the conjunctival cul-de-sac prior to surgery initiation.

Povidone Iodine studies in Ocular Surgery

Povidone iodine has been found useful as part of the immediate preoperative preparation for ophthalmic surgery. It was determined that when povidone iodine 10% solution was diluted to half-strength with sterile saline solution and was subsequently placed in the conjunctival cul-de-sac as part of the preoperative preparation of the eye, the number of bacterial colonies was reduced 91% and the number of species 50% compared with the untreated eye. It was shown through *in vitro* studies that povidone iodine, at a concentration of 2.5% and higher, was effective in eliminating *S epidermidis* with a single application. Three 30-second applications of povidone iodine 1% solution was postulated as being effective for preoperative surface disinfection but has not been tested through a randomised clinical trial. Since the mid-1980's, several studies have been conducted evaluating different strengths and solvent vehicles of povidone iodine and their effectiveness in the prevention of endophthalmitis.

In a large prospective, single-centre, randomised control trial in 242 patients undergoing cataract surgery, patients were randomised to receive 3 drops of povidone iodine 10% into the conjunctival sac (study group) or no povidone iodine drops (control group). Each subject underwent periorbital antisepsis using standard povidone iodine 10% solution for 5 minutes followed by irrigation of the conjunctiva with povidone iodine 1% solution 10 ml. After povidone iodine disinfection, the number of positive cultures was significantly reduced in all groups ($p<.0.0001$) from 69%-93% at presurgical antibiotic treatment to 1%-16% at completion of surgery.

From the study above, a retrospective analysis on the incidence of postoperative endophthalmitis with changes in the preoperative prophylaxis over a 20-year period was conducted at the same single centre. Three groups were chosen for data analysis:

- Period 1 (1990 to 1992), no standardised prophylaxis regimen.
- Period 2 (1993 to 1998), preoperative topical medication, povidone iodine 10.0% periorbitally, and one drop of povidone iodine 1.0% in the conjunctiva sac.
- Period 3 (1999 to 2009), similar to period 2 except with irrigation of the conjunctival sac with 10 mL of povidone iodine 1.0% solution.

It was shown that postoperative endophthalmitis was 0.113% (77/68,323) for all intraocular surgeries. It decreased significantly from 0.291% (16/5,505) in period 1 to 0.170% (33/19,413) in period 2 to 0.065% (28/43,405) in period 3 ($P < 0.001$). In cataract surgery, the overall rate of postoperative endophthalmitis was 0.125% (30/24 034). It decreased in each subsequent period, from 0.338% (9/2,662) in period 1 to 0.224% (15/6,696) in period 2 to 0.041% (6/14,676) in period 3 ($P < 0.001$). Coagulase-negative Staphylococcus was the most commonly isolated organism (47.4%). The evidence showed that from a single centre, the use of povidone iodine when applied topically was an effective antisepsis strategy.

A similar retrospective study was conducted for a total of 10,614 extracapsular cataract surgeries performed between 1992 and 2000. It was found that 12 eyes developed postoperative endophthalmitis were identified and analysed. Another 120 eyes matched for age and gender of the patient were randomly selected as controls. Skin preparation with 5% povidone iodine was associated with an increased risk of postoperative infection, compared to that of povidone iodine 10% solution. On the conjunctiva, a lack of povidone iodine 5% solution disinfection was associated with an increased risk of postoperative infection, compared to povidone iodine 5% disinfection.

A prospective randomised double-blind study was conducted in 105 patients attending for routine cataract surgery who were randomly allocated to have their conjunctival fornixes irrigated preoperatively with either povidone iodine 1% solution (Group A) or povidone iodine 5% solution (Group B). Despite *in vitro* evidence of higher bactericidal efficacy of povidone iodine at more dilute concentrations, povidone iodine at a concentration of 5% is more effective than povidone iodine 1% solution in decreasing the human conjunctival bacterial flora *in vivo* in the clinical setting, particularly in the presence of heavier initial bacterial load. In another similar study comparing povidone iodine 1% with 5% eye drops when applied to the conjunctival cul-de-sac (residence time = 2 minutes), it was found that both concentrations were equally effective for the antiseptic preparation of the eye.

Studies have been conducted to establish the exposure time required for the povidone iodine to be efficacious. One study evaluated recommendation of the ESCRS, with the application of povidone iodine 5% for both skin and conjunctival antisepsis prior to cataract surgery for three minutes. A second study evaluated povidone iodine 10% solution in a similar manner. Both regimens proved to be highly effective with no associated adverse events and thereby supporting the current guidance. Another study showed that repeated irrigation with povidone iodine 0.5% was effective in reducing the risk of developing postoperative endophthalmitis. These results confirm those from an early 1980's study that showed that a concentration of povidone iodine as low as 0.5% has a greater bactericidal activity potentially due to the increase of free iodine levels of microbes isolated from patients with endophthalmitis. It has been shown that instillation of three sequential drops of povidone iodine 5% solution over 30 minutes was associated with a significant increase in the proportion of eyes with all negative cultures, while instillation of a single drop of povidone iodaine was not associated with a significant increase in the number of negative cultures.

It has been shown that irrigation of the fornixes with povidone iodine 5% solution was associated with significantly fewer positive conjunctival cultures at the time of surgery compared with the application of 2 drops on the conjunctiva. Studies have also shown that when povidone iodine 0.25% solution is used as a topical irrigation on the ocular surface there is an associated decrease in the number of conjunctival colony-forming units. This potentially could help prevent both the incidence of scleral buckle infection and the anterior chamber contamination rate. In a study where different strengths of povidone iodine solution (1%, 5%, and 10%) were used as 10 ml irrigation in combination with levofloxacin 0.3% eye

drops, it was shown that povidone iodine 10% was more effective than 5% and 1% irrigation solutions.

The published evidence suggests that povidone iodine 5% solution is a useful method of antisepsis after a single application for disinfection of the eyelids or skin or for early conjunctival lavage when povidone iodine is not used for intraoperative irrigation.

Povidone Iodine Comparative studies
One study compared the antibacterial effect of povidone iodine 5% administered into the conjunctival sac with that of a broad-spectrum antibiotic given for 3 days before surgery, Individually, each regimen caused a similar substantial decrease in the number of colonies and species cultured. There was a more striking decrease when both agents were used in the same eye, however, making 83% of the conjunctivae sterile to culture at the time surgery commenced.

When compared to the application of a topical broad-spectrum antibiotic (polymyxin B sulfate – neomycin sulfate – gramicidin) is compared with topical povidone iodine 1.25% or 2.5% solution both treatments were effective in reducing bacteria over the first week. However, there was little difference in the number of colony forming units between each regimen.

Povidone iodine 5% solution was compared with levofloxacin 0.5% eye drops in a study in a metagenomic analysis. The study results showed that povidone iodine had a significantly reduced biodiversity of corneal flora.

In a study of topical moxifloxacin in combination with povidone iodine 5% versus povidone iodine 5% solution alone, it was shown that the povidone iodine monotherapy when used preoperative antisepsis of the conjunctiva was effective. The addition of a topical antibiotic had no significant effect on the further reduction in bacterial colonisation.

In a study comparing povidone iodine 5% with ciprofloxacin and ofloxacin on the conjunctival bacteria flora, there was no statistical difference between the povidone iodine and ofloxacin, with a slight superiority for ciprofloxacin. As there is no mention of any periorbital antisepsis in the study, it is difficult to determine the clinical significance of the study and whether the clinical end point of a reduction in endophthalmitis was achieved.

A study compared the efficacy and toxicity of povidone iodine 5%, polyhexamethylene biguanide (PHMB) 0.02%, and chlorhexidine 0.02% in patients undergoing phacoemulsification cataract surgery. Pre-treatment with povidone iodine 5% for at least 15 min or repeated applications over 10 minutes was effective in the reduction of conjunctival organisms, and resulted in less postoperative endophthalmitis. It is notable that in none of the patients, acute or chronic postoperative bacterial endophthalmitis was observed. The patients who were exposed to povidone iodine tolerated the treatment well without complications or adverse effects such as corneal oedema or epithelial defects, and sensitivity to the molecule.

Antisepsis for Intraocular Injections
A study comparing topical gatifloxacin eye drops for 3 days use in combination with povidone iodine versus povidone iodine alone, in eliminating conjunctival bacterial flora in patients scheduled to undergo intravitreal injection, highlighted that there was no significant difference between treatment and povidone iodine 5% should be preferred.

In a retrospective study, a total of 35,060 intravitreal injections in 1,854 patients were analysed. 29,281 injections were performed with standard povidone iodine 5% solution, 5,460 injections with diluted povidone iodine solution (3,731 with 2.5%, 1,673 with 1.25%, 56 with 0.625%) with 319 intravitreal injections using no povidone iodine solution. The incidence of patient-reported povidone iodine sensitivity occurred in 15.9% of patients. Fourteen cases of endophthalmitis were identified: 12 in eyes that received povidone iodine 5% solution, one in an eye that received povidone iodine 1.25% solution and one in an eye receiving no povidone iodine. The incidence of endophthalmitis was 0.04% for 5%, 0.02% for diluted povidone iodine, and 0.31% for no povidone iodine prophylaxis.

The guidelines of an expert panel regarding intravitreal injection technique recommend povidone iodine (5–10%) should be the last agent applied to the intended injection site before injection. Povidone iodine may also be applied to the eyelids, including the eyelid margins and eyelashes with a minimum 30 second exposure time.

The use of povidone iodine for conjunctival lavage is also a mandatory step prior to vitrectomy. Investigators showed that using povidone iodine 0.25% solution intraoperatively produced a decrease in positive cultures from the anterior chamber. The same investigators investigated the effects of intraoperative conjunctival irrigation with povidone iodine 1.25% solution compared with pure balanced salt solution (BSS) lavage for 25-Gauge vitrectomy. No endophthalmitis was noted in either group, a total of 4,347 eyes.

There is a lack of a globally uniformly accepted recommendation regarding the exposure time of povidone iodine 5% solution in intraocular procedures. According to the ESCRS guidelines, a 3-minute exposure time is recommended in cataract surgery. On the other hand, the guidelines of an expert panel regarding intravitreal injection technique recommend a minimum 30-second exposure time. Other studies have shown that a 15 second exposure to povidone iodine 5% prior to intravitreal injection did not decrease the concentration of bacterial colony forming units, thus a minimum time of 30 seconds was advised.

Ophthalmia neonatorum

Ophthalmia neonatorum in 19th century Europe was the main cause of childhood blindness. Instillation of silver nitrate solution into the conjunctival sac at birth has significantly reduced the incidence of this complication. Currently in several countries silver nitrate has been replaced by erythromycin or tetracycline preparations because of their superior antibacterial activity against Chlamydia trachomatis and alleged toxicity of the former agent.

Povidone iodine has been compared with silver nitrate solution and other antibiotics such as erythromycin ointment, tetracycline ointment and chloramphenicol ophthalmic ointment. In a study on 100 healthy new-borns, it was found that povidone iodine 2.5% solution was more effective than silver nitrate or erythromycin and less toxic than silver nitrate. Subsequently, a prospective trial conducted on 3,117 infants has confirmed these data.

A more recent study conducted on 330 infants proved that povidone iodine has a pronounced effect on neonatal conjunctivitis.

In another study, povidone iodine 2.5% increased the risk of acquiring chlamydial conjunctivitis in neonates, compared with application of ophthalmic chloramphenicol ointment. In this study, povidone iodine was less efficacious than chloramphenicol in the time range of 3 to 15 days.

Povidone iodine 0.6% plus dexamethasone (DEX) 0.1% ophthalmic suspension has been shown to be efficacious in patients with clinically suspected acute viral conjunctivitis.

Conclusion
Povidone iodine is the most commonly used iodophor that has many characteristics including its broad antimicrobial spectrum, lack of resistance, efficacy against biofilms, good tolerability and its effect on excessive inflammation. Despite new antiseptics in surgery, povidone iodine remains a pre-eminent antiseptic therapy in ophthalmology.

The submitted literature data show that povidone iodine is effective in treating and preventing endophthalmitis. It is a well-known preparation for antisepsis of the periocular and ocular surfaces. Its ability to be active over a wide range of microorganisms, including the predominant bacteria that are responsible for endophthalmitis, help reduce the need for antibiotics in ocular surgery. It is clinically proven and appears easy to use when presented in a ready-to-use format for surgery.

The applicant has provided a reasonable discussion and explanation regarding the bridging data linking the proposed formulation to the formulation used in the publications.

The dosage and administration proposed by the Applicant is in line with the standard practice for antisepsis and the relevant guidelines in cataract and intraocular surgery.

IV.5 Clinical safety

Satisfactory safety information is presented in the clinical overview. Safety data suggest povidone iodine is well tolerated with a good safety profile. Most of the reported adverse events are of mild severity.

The risk of overdose is low as the product is designed to be used by trained healthcare professionals and surgeons skilled in antisepsis procedures.

No new or unexpected safety concerns were raised from the safety data submitted.

A summary of the literature data is provided below:

Ocular toxicity
Many of the clinical trials with povidone iodine were conducted with concomitant medication including anaesthetics, mydriatics and antibiotics, therefore the local reactions cannot be necessarily attributed to povidone iodine alone.

Povidone iodine has been shown to have very good tolerability and safety profile, when used in preoperative application on the occurrence of endophthalmitis after cataract surgery. In one study, after application of topical 5 % povidone iodine, moderate to severe but tolerable eye irritation was reported in 6.6% of subjects (n=4,089).

Lower doses of povidone iodine appear to cause less irritation. A povidone iodine 0.5% solution was employed as a preoperative preparation for intraocular lens surgery; of 929 eyes treated, only 4 demonstrated minor conjunctival irritation attributable to the preparation.

In a study using povidone iodine 5%, there were no adverse events recorded. In another study of 604 patients where povidone iodine 10% was administered for 3 minutes, with monitoring up to 1 month post procedure, there were no complications recorded.

Other common side effects seen with povidone iodine eye drops include local swelling, itching and rash.

With overuse, povidone iodine can have corrosive effects.

A study looking at different timings showed that there was no change in corneal thickness when comparing multi-dose povidone iodine 5% ophthalmic administration to a single dose.

Cases of corneal toxicity have been reported very rarely in association with the ophthalmic use of povidone.

Dermal toxicity
Povidone iodine is well tolerated by the majority of patients, particularly when applied to the skin. Povidone iodine has rarely caused allergic contact dermatitis, urticarial or anaphylactic reactions. In one study, after povidone iodine solution was applied locally on intact skin or mucosa, the incidence of allergy and contact dermatitis in normal subjects was extremely low, with two allergic reactions in 5,000 applications recorded.

Povidone iodine is considered a weak allergen with a prevalence of allergenicity of 0.4%. In a study, 500 patients underwent a human patch insult tested using povidone iodine 1%. The molecule was applied over two days with readings at 2 and 4 days. After two days, 14 (2.8%) patients had a positive patch test to povidone iodine. Tests were still positive after 4 days but with reduced scores. In a second stage (two weeks later), the 14 positive patients were re-evaluated using a different protocol. Povidone iodine 10% was applied twice daily (without occlusion) on the volar aspect of the forearm (5 × 5 cm) for seven days in a repeated open application test. At day 7, only two of the 500 patients were positive (one after four applications, the other after six applications), and the remaining 12 patients (after 14 applications) were negative (false positives using the patch test).

A European Union Safety Assessment Report on povidone iodine assessed data involving the application of 6.9 g of povidone iodine to the hands and forearms for a contact time of less than five minutes. It was concluded that the proposed use of iodine in hand disinfection products is suitable for human health.

Chronic toxicity
Although povidone iodine is generally regarded as very safe; its long-term use could have the potential to cause thyroid dysfunction. Excessive iodine absorption has the ability to induce transient hypothyroidism, or, in patients with latent hypothyroidism, the risk of destabilisation and thyrotoxic crisis. Especially at risk are patients with an autonomous adenoma, localised diffuse autonomy of the thyroid gland, nodular goitre, latent hyperthyroidism of autoimmune origin, or endemic iodine deficiency.

In patients with burns who have been treated with povidone iodine, there is a theoretical risk of hypothyroidism even if changes in the levels of thyroid hormones have not been found. Serum and urine iodine levels after topical application of povidone iodine are related to the size of a burn, renal function and to the length of treatment. The potential risk of hypothyroidism, resulting from iodine exposure after administration of topical povidone iodine within the paediatric setting, has been well documented. Some of studies have concluded that, in order to mitigate the possible risk, the routine use of iodine-containing antiseptics in very-low-birth weight infants should be avoided. This is even if it appears that transient neonatal hypothyroidism could be reflecting differential sensitivity due to prior iodine status. This was demonstrated by a prospective, controlled study with a routine skin-cleansing protocol with topical povidone iodine.

Another prospective study showed the onset of the transient hypothyroidism in four infants out of 20 with delayed sternal closure, exposed to perioperative topical povidone iodine suggesting that although changes in thyroid hormone metabolism in critically ill infants are difficult to interpret, hypothyroidism in the late postoperative period can be caused by exposure to iodine from povidone iodine. Moreover, severe hypothyroidism requiring levothyroxine replacement therapy has been reported in a neonate after prolonged use of an iodinated skin disinfectant.

It has been recommended that patients who do not have a thyroid condition, povidone iodine should not be used for more than seven days due to a risk of thyroid dysfunction.

Reports of other systemic effects following short-term use of povidone iodine are rare. Generally, possible systemic complications are due to elevated free iodine levels and they have occasionally been reported in burn patients treated with topical povidone iodine.

Povidone iodine over a period of time has the potential to also induce hyperthyroidism although this is much rarer than with hypothyroidism. Rare extrathyroidal side effects have been described, such as iodine acne, runny nose, conjunctivitis, gastroenteritis, bronchitis, parotid swelling, and renal impairment.

Therefore, due to potential issues relating to thyroid function with iodine-containing agents, povidone iodine is contraindicated in infants aged <1 month, patients with hyperthyroidism, iodine hypersensitivity or in patients receiving radio-iodine therapy, pregnant women and nursing mothers.

No clinical evidence of cell or organ toxicity in burn patients treated with povidone iodine has been obtained but experimental study showed that large dosages of iodine have produced nephrotoxicity.

Drug Interactions

Pharmacokinetic drug interactions

Povidone iodine is applied topically with minimal transcutaneous absorption of the primary active moiety, iodine. Iodine and iodide in the plasma are not metabolised and will only undergo excretion.

Pharmacodynamic drug interactions

The effects of iodine and iodides on the thyroid may be altered by other compounds which may also have an effect on the thyroid, including amiodarone and lithium. The hypothyroid and goitrogenic effects of lithium carbonate and iodides can be additive if they are given concurrently.

Povidone iodine solutions should not be concomitantly used with ocular formulations that contain mercury-based preservatives. Mercury reacts with the iodine in povidone iodine to form mercury iodide, a caustic compound that can cause corneal damage.

Iodine is absorbed into the body to various degrees, depending on application area and condition of the skin. As such, it interacts with diagnostic tests of the thyroid gland such as radio-iodine diagnostics, as well as with various diagnostic agents used on the urine and stools.

Pregnancy & Lactation

Pregnancy

The application of iodine antiseptics in pregnant women and the subsequent absorption of the iodine releases it into the maternal circulation. This not only has known embryotoxic effects in mouse embryos at all concentrations tested but at the same time, the metabolic effect of the suppression of thyroxin synthesis during the first trimester of pregnancy may lead to a transitory state of maternal hypothyroxinaemia. Maternal hypothyroxinaemia during the first trimester is associated with permanent and irreversible lesions in the cytoarchitecture of the cerebral cortex in the embryo and foetus.

In a study to evaluate the influence of topical iodine-containing antiseptics on neonatal thyroid stimulating hormones (TSH) in 86 full-term infants born by Caesarean section in an iodine sufficient area, it was determined that perinatal iodine exposure did not influence neonatal TSH, although median urinary iodine excretion was higher.

Caution would therefore be advised in the use of any topical povidone iodine preparations in pregnancy.

Lactation

The use of povidone iodine in the mother near term and during breastfeeding increases breast milk iodine levels and can cause transient hypothyroidism in breastfed infants, especially in geographic areas that are iodine deficient. Maternal exposure to povidone iodine near term can sometimes interfere with thyroid studies done as a part of new-born screening tests. Although iodine from povidone iodine is minimally absorbed through intact adult skin, exposure of mothers who are or will be breastfeeding to povidone iodine should be minimised by using lower concentrations of povidone iodine, applying it to the smallest possible surface areas of the body, shortening contact time, and avoiding repeated applications.

Overdose/Acute Toxicity

Although it has been shown through many studies that there is an increase in systemic iodine levels after topical administration there is no real evidence of systemic toxicity on an acute basis. The systemic toxicity of topical povidone iodine is dependent upon the rate of iodine absorption, predisposing medical conditions, concentrations used, number of applications and length of treatment.

Fatalities have been attributed to topical use of povidone iodine in two burns patients and following surgical debridement of a hip wound. Mediastral irrigation with povidone iodine has been reported to result in acute renal failure and seizures.

In patients with known allergies to various substances, including fish and iodine-containing compounds, the incidence of allergic reactions was two in 500 applications, with 16 cases of minor irritation.

Ingestion has been reported to cause stomach upset, vomiting, diarrhoea and irritation of the gastrointestinal tract.

The effect of povidone iodine in infants and children

Ocular surgery (e.g., due to infantile strabismus and childhood cataract) is reasonably common in paediatrics. It is therefore expected that antisepsis measures will be used in ocular surgery in the paediatric community.

The absorption of povidone-iodine across the skin has been well documented and studies have focused upon the difference between neonatal and infant skin compared with the general population.

In new-borns and infants there is an increased risk of developing hypothyroidism after administration of large amounts of iodine. The use of povidone-iodine in new-borns and infants should be limited to an absolute minimum, since their skin is more permeable, and they are more sensitive to iodine. Povidone-iodine can cause foetal or neonatal transient hypothyroidism with increases of TSH (thyroid stimulating hormone).

In a study in infants under the age of three months undergoing cardiac or thoracic procedures, it was found that after povidone-iodine skin preparation covering 20% to 30% of body surface area, plasma total iodine concentrations rose four-fold (range, 160% to 1,440%). This increase was significantly different from the preoperative level at 6, 12, 18, and 24 hours.

An observational study demonstrated that 54% of spontaneously breathing children under general anaesthesia developed apnoea after the topical application of 5% povidone-iodine ophthalmic antibacterial solution to the eye.

A randomised, controlled, single-blinded study compared the effect of balanced salt solution eye drops and povidone-iodine eye drops on respiration in 100 spontaneously breathing children during general anaesthesia. One of the control patients had a significant change in respiration. Thirty of the 50 (60%) povidone-iodine patients had a slowing of respiration within the first 6 breaths after eye drop instillation ($P < .001$). The median time of respiratory pause in those 30 patients was 18.5 seconds (range: 4.36 to 96.2 seconds). Among the povidone-iodine patients, children with a history of a prior tonsillectomy and adenoidectomy and/or bilateral myringotomy had a 7.2 times greater chance of experiencing a change in respiration after instillation of the povidone-iodine eye drops. The average age of the children was 6.62 ± 3.88 years.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The clinical overview contains an adequate review of published clinical data.

Povidone iodine 5% w/v eye drops solution contains the widely used and well-known active substance, povidone iodine, which has a long history of established favourable risk-benefit profile.

There are no indications, in the light of scientific knowledge, that the product differs significantly from the other similar medicinal products with regards to safety and efficacy. The applicant has provided a reasonable discussion and explanation regarding the bridging data, linking the proposed formulation to the formulation used in the publications.

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

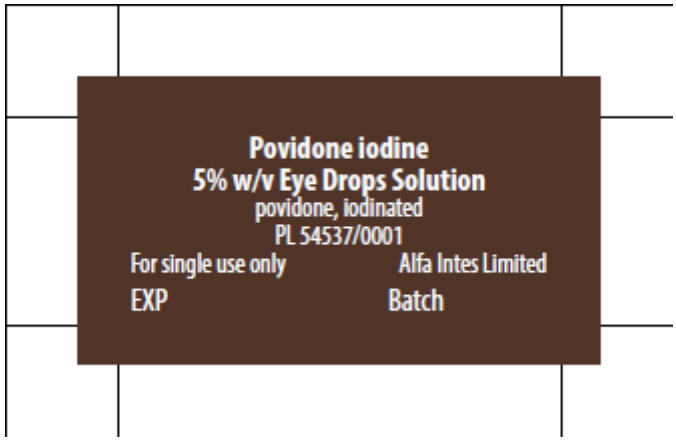
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with povidone iodine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



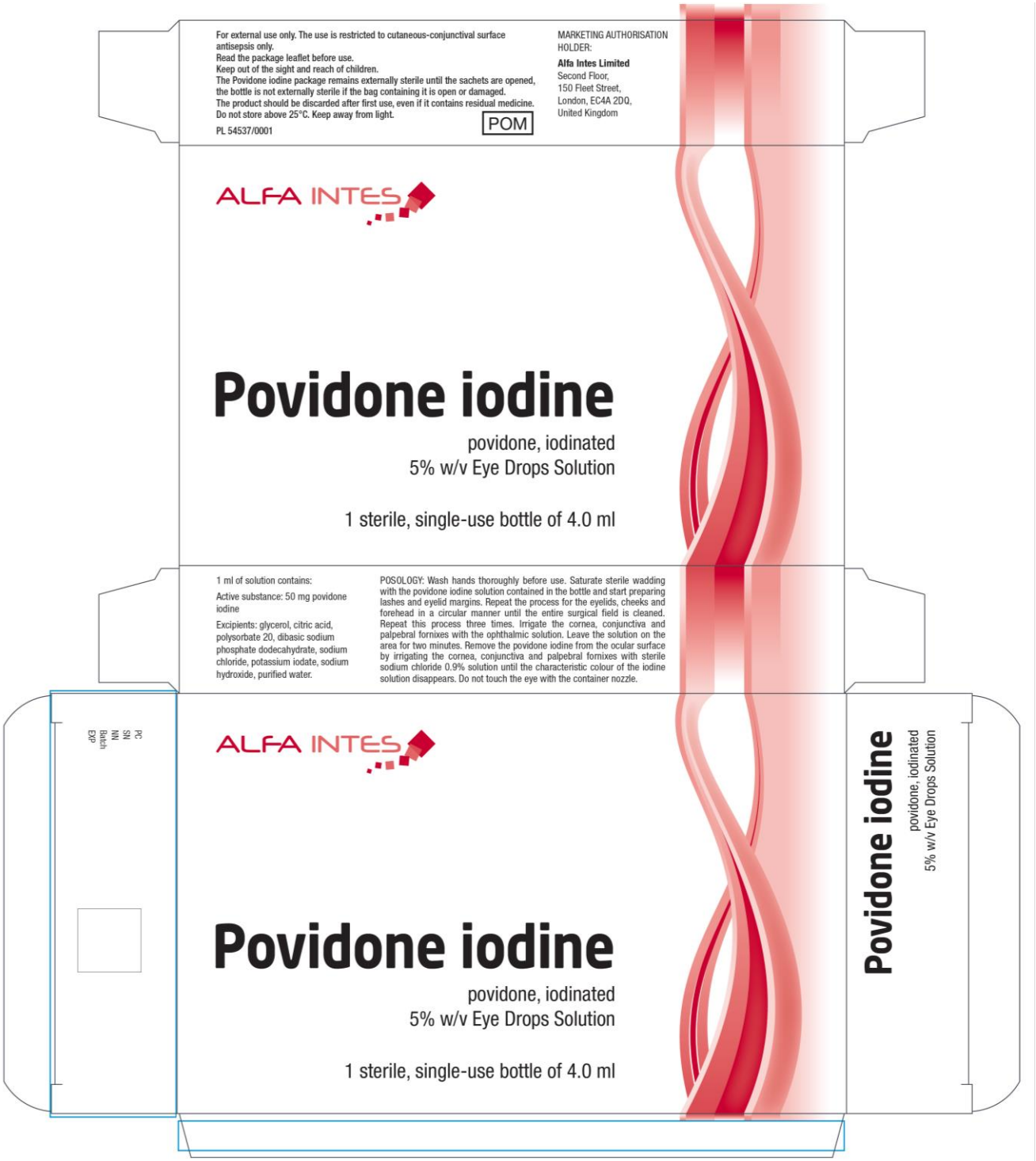

For external use only. The use is restricted to cutaneous-conjunctival surface antisepsis only.
Read the package leaflet before use.
Keep out of the sight and reach of children.
The Povidone iodine package remains externally sterile until the sachets are opened, the bottle is not externally sterile if the bag containing it is open or damaged.
The product should be discarded after first use, even if it contains residual medicine.
Do not store above 25°C. Keep away from light.
PL 54537/0001
POM
MARKETING AUTHORISATION HOLDER:
Alfa Intes Limited
Second Floor,
150 Fleet Street,
London, EC4A 2DQ,
United Kingdom
ALFA INTES
Povidone iodine
povidone, iodinated
5% w/v Eye Drops Solution
1 sterile, single-use bottle of 4.0 ml
1 ml of solution contains:
Active substance: 50 mg povidone iodine
Excipients: glycerol, citric acid, polysorbate 20, dibasic sodium phosphate dodecahydrate, sodium chloride, potassium iodate, sodium hydroxide, purified water.
POSOLOGY: Wash hands thoroughly before use. Saturate sterile wadding with the povidone iodine solution contained in the bottle and start preparing lashes and eyelid margins. Repeat the process for the eyelids, cheeks and forehead in a circular manner until the entire surgical field is cleaned. Repeat this process three times. Irrigate the cornea, conjunctiva and palpebral fornixes with the ophthalmic solution. Leave the solution on the area for two minutes. Remove the povidone iodine from the ocular surface by irrigating the cornea, conjunctiva and palpebral fornixes with sterile sodium chloride 0.9% solution until the characteristic colour of the iodine solution disappears. Do not touch the eye with the container nozzle.
PC
SN
NN
Batch
EXP
ALFA INTES
Povidone iodine
povidone, iodinated
5% w/v Eye Drops Solution
Povidone iodine
povidone, iodinated
5% w/v Eye Drops Solution
1 sterile, single-use bottle of 4.0 ml

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes is made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**