CLINICAL EVALUATION

Incifilm® Iodine

according to

MEDDEV 2.7.1 rev. 3 (12/2009)

Revision 05

July 2014

Revision History:

Revision No.	Revision date	Explanation	Comment
1	31.08.2010	First revision	N/A
2	01.05.2013	Second revision	N/A
3	01.10.2013	Third revision	To address the deficiencies in SGS ECDE report
4	25.12.2013	Fourth revision	To address the deficiencies in SGS ECDE report rev 2
5	01.07.2014	Fifth revision	N/A

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1. INTRODUCTION

The company Pharmaplast S.A.E, Alexandria, Egypt was founded in 1985 and has since then engaged in the manufacturing of wound care and immobilization products.
As a manufacturer Pharmaplast holds a number of Certificates such as:

- EN ISO 13485:2012
- ISO 9001:2008
- MDD Certificate according to Annex II (excluding Section 4) and Annex V (Sterility aspects only)
- MDD certificate according to Annex II, section 4

The Notified Body of Pharmaplast S.A.E for this tech dossier is LNE-G-MED, France. The following Clinical Evaluation presents the evaluation of clinical data, relevant to assess the products safety and efficacy and is based on the Technical File Incifilm Iodine®, Rev. 04, dated July 2014. The evaluation of clinical data as described in Annex X of the Directive 93/42/EEC as amended by Directive 2007/47/EC is relevant to assess the conformity with the Essential Requirements given in Annex I of the Directive. The clinical data must be based on data that is either derived from clinical investigations, post market experience and/or a compilation of the relevant scientific literature available on the intended purpose of the device and the techniques employed as well. The outline of such a clinical evaluation is given within the MEDDEV 2.7.1 guideline as of December 2009.

For the following clinical evaluation the assessment included a review of relevant clinical literature provided by Pharmaplast S.A.E and searched in the international scientific database Medline, a review of technical product documentation made available as well as an analysis of certain product components and its toxic potentials through the database ChemIDplus database.

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2. PRODUCT DESCRIPTION

2.1. Description

The product Incifilm Iodine® manufactured by Pharmaplast is a theatre incise drape consisting of a yellowish coloured, transparent, polyurethane (PU) film covered with an acrylic adhesive that is impregnated with povidone iodine (PVP-Iodine) as antimicrobial substance (27.25% corresponding to a total iodine concentration of 2.3%).

The PU film is semi-permeable and allows the patient´s skin to breath, so preventing moisture build-up under the drape. As a result Incifilm Iodine® adheres to the surrounding skin throughout long surgical operations and right up to the incision edge.

The antiseptic PVP-Iodine component of the drape which comes into contact with the patient´s skin provides a sterile operative surface and continuous, broad-spectrum antimicrobial activity.

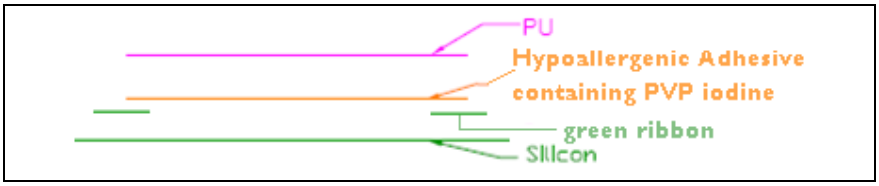
The product line Incifilm Iodine® is available in different sizes and comes with a clay coated white paper (72 gsm) cover for product protection that is removed before the drape is applied to the wound. The products are packed in pouches made of PET/Aluminium/PE. They are sterilized with Gamma radiation and for single use only. Incifilm Iodine® has a claimed shelf life of 2 years.

Fig. 1: Incifilm Iodine®

2.2. Product Components

The following figure gives an overview on the single layers of Incifilm Iodine®:

Fig. 3: Overview about product layers of Incifilm Iodine®



The product line Incifilm Iodine® is available in different sizes and shapes. Detailed information is provided in the Technical File rev. 04 dated July 2014.

3. PRODUCT CLASSIFICATION

The product line of the medical device **Incifilm Iodine®** comprises drapes incorporating PVP-Iodine as an antimicrobial agent and the purpose of this agent is to provide ancillary action on the skin around the site of incision.
Thus, Incifilm Iodine® is classified as class III medical device according to rule no.13 of Annex X of the MDD 93/42/EC as amended by 2007/47/EC since it is a device incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product as defined in Article 1 of the Directive 65/65/EEC, and which is liable to act on the human body with action ancillary to that of the devices.

4. MEDICAL APPLICATION

4.1 Intended Use

Incifilm Iodine incise drapes are intended for use as an incise drape in surgical procedures where there is concern about cross contamination from skin flora to the site of incision and continuous antimicrobial activity is required.

These surgical procedures can include surgeries such as:

- Orthopaedic
- Neurosurgery
- Major abdominal
- Plastic Surgery
- Open Heart and Thoracic
- Ophthalmic

Incifilm Iodine® is intended for single use and for external use only.

4.2 Contraindications, Warnings, Precautions

The following information for the user is provided in the current Instructions for Use for the product line Incifilm Iodine® in the internal leaflet of the product. The information is suitable for the medical devices under consideration and is in line with the information provided for comparable essentially similar products as well as published in the scientific literature reviewed.

Contraindications

- Do not use Incifilm Iodine on patient with known sensitivity to iodine or one of the other components.
- Do not use for children and during pregnancy.

Warnings:

- Don’t re-sterilize or reuse. Re-sterilization and reuse pose risk of infection
- After use, please handle as contaminated waste
- Don’t use on damaged skin or as a wound dressing
- Incifilm Iodine reaches its optimal antimicrobial effect after 3 hours
- Incifilm Iodine doesn’t exhibit any fungicidal activity

5. MATERIAL SPECIFICATIONS AND TESTING REQUIREMENTS

5.1 Material List

Composition Incifilm Iodine®

Component/ Material (from outside to skin contact side)	**Product name**	**Type**	**Supplier / Manufacturer**	**Function**	**Wound contact (y=yes; n=no)**
PU film	Ucecoat AB 5454	Aromatic, once-component polyether-urethane	Cytec Industries SDS, Belgium	Bacterial and water proof	n
Adhesive border containing PVP-Iodine	Acrylic adhesive WD-2184 with PVP-Iodine (27.25%)	Solvent-base acrylic adhesive PVP-Iodine	Everfront, Taiwan BASF Chemicals Devision, Germany	Adhesion Antimicrobial agent	y y
Green ribbon	Green EVA film 0.06 M/M	ethylene vinyl acetate copolymer resin	Everfront, Taiwan	Easy Handling	n
Release liner	Clay coated white paper 72 GSM	white paper 72 GSM silicon coated	Rossella S.r.l., Italy	Protection foil (to be removed before application	n

6. BIOCOMPATIBILITY

The biocompatibility of the medical devices is described in the Technical file section 5. The biocompatibility of the different raw materials was evaluated on the basis of documentation provided by the suppliers as well as on own tests on combination of components. The main materials with the exemption of the PVP-Iodine have been already used within CE marked devices manufactured by Pharmaplast such as for example Pharmafoam Comfort where the same PU film and acrylic adhesive is used.

Supplier documentation on the antiseptic PVP-Iodine is also presented in the Technical File and is in compliance with the requirements of the Common Technical Document Module 2.4. In conclusion, PVP-Iodine is a substance of very low toxicity. It does not cause cutaneous reactions in humans or animals that are not hypersensitive to the substance, and its effect on mucous membranes is mild and of a passing nature. Still, povidone-iodine, regardless of the route it is applied, can cause systemic absorption of iodine and should therefore be contraindicated in case of pregnant or nursing women as well as in newborns and infants. PVP-Iodine has excellent local tolerability and an absence of systemic toxicity. Since PVP-Iodine is a substance of well-

established use the toxicity data of the substance are well-known and further risks associated with the use are not expected.

Summarizing, the documentation on the different raw materials demonstrate that these components which come into contact with the patient´s skin are considered as biocompatible.

The schedule for the biocompatibility tests of the finished product Incifilm Iodine® is complying with the requirements defined in ISO 10993-1. The test results of the cytotoxicity test, irritation test and sensitization test document a good biocompatibility of the Gamma-sterilized product. All test results are within the specifications and show no indication of the release of substances in toxic concentrations.

The sterilization by Gamma irradiation is based on a sterilization validation which is provided in the Technical File. The safety of the sterilization is assured by the validation. Furthermore, the biocompatibility tests have been performed with samples of the sterilized finished medical device and show that the Gamma irradiation does not represent a further risk to the patient's health.

Moreover, the finished products of another product line manufactured by Pharmaplast, i.e. Pharmafoam Comfort, are composed of the identical materials (PU film + acrylic adhesive) and have been marketed and used for many years showing a very safe application. This is reflected by the complaint history of the products where no complaint of biocompatibility has been registered since market launch. A transfer of these results to the Incifilm Iodine® line seems to be reasonable.

Moreover, Pharmaplast has collected post market surveillance data about Incifilm Iodine batches which were sold to non EU customers on 2013 and 2014. The PMS data showed zero complaints. Accordingly, there is enough evidence that the product is biocompatible and safe for its intended use.

Furthermore, Directive 2007/47/EC introduced additional requirements by Essential Requirements section 7.5 which have been especially considered in the biocompatibility assessment of the finished medical device. All raw materials used for the production of Incifilm Iodine® are well documented, controlled and meet the specified quality requirements. The Incifilm Iodine® product line does not contain any substance that is carcinogenic, mutagenic and toxic to reproduction (see product specification). Potential risks due to substances leaking from the device have not been identified in the cytotoxicity test.
Summarizing the Essential Requirements of Directive 93/42/EEC as amended by Directive 2007/47/EC Annex I are fulfilled.

Based on the long-term clinical experience with the raw materials, the documentation provided by the suppliers and the biocompatibility tests performed with the finished product, it is demonstrated that the product line Incifilm Iodine® does not exhibit any toxic potential. Consequently, the product can be regarded as biocompatible and the materials can be considered as suitable for the intended use.

7. RISK ANALYSIS

A risk analysis was performed by Pharmaplast S.A.E and the Steering Committee according to ISO 14971:2012. The manufacturer lays out within the risk analysis potential hazards that may be associated with the device and possible solutions to minimize these risks or address them. Following are possible risks associated with the device but are not limited to:

- Contaminated products
- Different composition of suppliers raw material
- Expired shelf life devices
- Wrong storage
- Long term use instead of short term use
- Multiple use vs. single use
- Manufacturing according to a false recipe
- Wrong product performance during surgery

The possible contamination of the product is minimized through the use of a clean room and through the sterilization by Gamma irradiation. The gamma sterilization process has been validated in accordance with ISO 11137. According to the current risk analysis of Pharmaplast S.A.E, regular bioburden tests are performed. Upon arrival, product components and raw materials are checked against the Certificates of Analysis and Technical Data sheets to confirm the quality of the material.

An accelerated shelf life study was conducted according to the procedures laid down in a Standard Operating Procedure of Pharmaplast S.A.E. which is based on the ICH guideline “Q1A(R2): Stability Testing of New Drug Substances and Products“. The study was performed with samples tested under accelerated ageing conditions at 40ºC ± 2 °C during a period of 36.77 weeks. Several parameters were studied at 4 different points such as the seal integrity, pouch strength, peel adhesion, MVTR and change of colour. The study supported a shelf life of 2 years.

The labelling is implemented in accordance with ISO 15225-1-2012. Therefore, the expiration date, storage conditions and the symbol for ‘single use’ appear on the box thus reducing the risk of a re-use or use of the device beyond its shelf life.

An Instruction for use is also provided by Pharmaplast on the package insert (internal leaflet) so that wrong handling of the product can be minimized.

Internal SOPs and instructions define the manufacturing process and in process controls reduce the possibility of manufacturing mistakes from happening.

In conclusion of the risk analysis, no specific unacceptable patient risks were identified in conjunction with the use and application of the product Incifilm Iodine®.

8. CLINICAL EVALUATION ON THE BASIS OF LITERATURE SEARCH

8.1. Scope

The clinical evaluation was performed in order to fulfill the requirements of Directive 93/42/EEC and 2007/47/EC. This Directive requires an evaluation of the safety and efficacy of the products to be certified during a conformity assessment process and in order to demonstrate the compliance with the Essential Requirements (Annex I). The clinical evaluation is also performed on the basis of the Annex 10 MDD, section 1.1. as well as MEDDEV-Guideline 2.7.1. „Evaluation of Clinical Data“, (12.2009).

The clinical evaluation includes aspects of own tests like biocompatibility tests and literature information on clinical applications.

According to the MEDDEV Guideline the clinical evaluation is based on a literature review. A separate clinical trial was not performed on the product line as there are essentially similar products registered and on the market and a long-year experience with the products is available.

8.2. Literature Search

Several queries for the clinical evaluation of iodine incise theatre drape were performed using different keywords or Medical Subject Headings (MeSH). US National Library of Medicine (NLM), PubMed, Medline, Medline Plus and Google Search were the main sources of literatures.

Keywords/MeSH tags used within the PubMed were among others:

Keywords/MeSH tags	Initial Search Results	Preliminary List	Final Selection
Polyurethane, incise drape	0 Hits	0	0
Plastic, incise drape	8 Hits	2 abstracts	0
Povidone iodine, incise drape	6 Hits	5 abstracts	3 articles
Povidone iodine, toxicity	126 Hits	43 abstracts	5 articles
Povidone iodine, biocompatibility	3 Hits	2 abstracts	1 article
Povidone iodine, clinical efficacy	171 Hits	34 abstracts	2 articles
Povidone iodine, antimicrobial activity	68 Hits	21 abstracts	5 articles
Povidone iodine, clinical trial	450 Hits	130 abstracts	8 articles

Povidone iodine, side effects	53 Hits	26 abstracts	0
Ioban	10 Hits	3 abstracts	2 articles
Total	**895 Hits**	**266 abstracts**	**26 articles**

8.3. Selection criteria to choose articles:

A broad search was conducted and no time limits were set for the search. Since a large body of literature is available on this well-established substance the initial search results were screened and narrowed to form a 'Preliminary List' of articles of potential relevance. The abstracts of the preliminary list were then screened using the above criteria and used to produce a final selection of articles for purchase and/or download. Preference was given to recent articles of clinical significance, peer reviewed journals and systematic reviews/meta-analysis.

The inclusion or exclusion criteria were based on the following:

1. Relativity/applicability of the search results appropriate to the following areas of relevance related to the product:

    a. Therapeutic Area (i.e. surgical operations / surgical incisions)
    b. Chemical Composition (i.e. iodine incise drape)
    c. Classification (i.e. antimicrobial incise drape)
    d. Therapeutic Indications/Uses
    (i.e. Surgical operations e.g. Orthopaedic, Neurosurgery, Major abdominal, Plastic Surgery, Open Heart and Thoracic, Ophthalmic).
    e. Safety and Potential risks

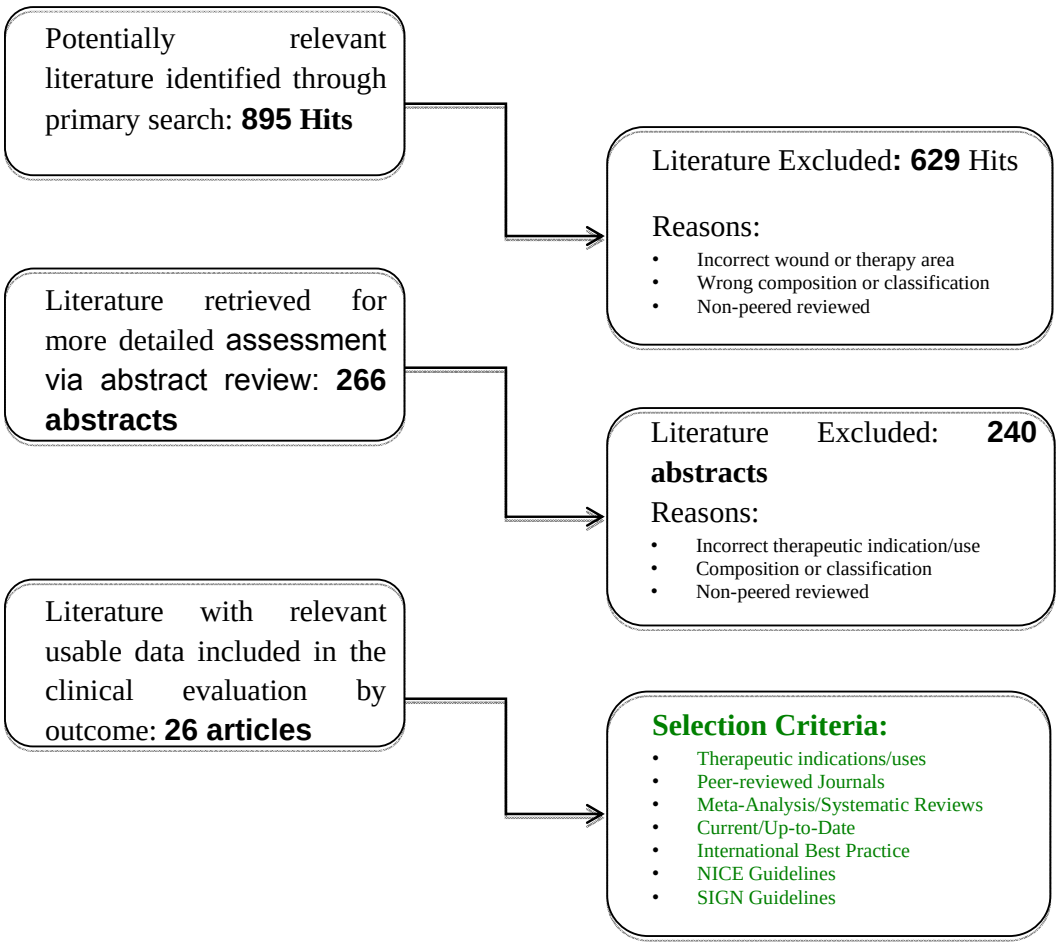
2. Searches focused on recent data, with preference for peer-reviewed journals, meta-analysis and systematic reviews.

3. Google searches focused on 'best clinical practices', international treatment protocols and EU guidelines, such as NICE and SIGN.

All literature articles are publications in international and scientific, peer reviewed journals. All final full articles were thoroughly reviewed and data was collated to provide a clinical evaluation of the evidence.

A review of the 26 final articles purchased was conducted. Where repetition of key concepts occurred, the selection was narrowed to produce the final list of references (23 articles) as shown in section 11 (literature references).

Literature Methodology for the screening and searching of literature was as follows:



All the search results were evaluated and some overlap between articles occurred, whereby the same articles appeared in multiple searches. Where duplication existed, these papers were removed from the final selection of articles (prior to purchasing).

As expected with review articles, repetition of the facts and evidence occurs between publications. Where this occurred the most recent publication was used as the preferred reference source.

8.4. Equivalent Products

In general, incision drapes in various forms are on the market since very long time. In addition to the literature search, a market research was performed for essentially similar PVP-Iodine-impregnated PU incise drapes.

For the clinical evaluation of the characteristics of the Incifilm Iodine® product line, the transfer of results obtained with products considered equivalent following prerequisites exist (in accordance with MEDDEV 2.7.1):

Equivalence with regard to

- Clinical application (same clinical condition/purpose, same site of the body, similar population),
- Technical application (similar conditions of use, similar specifications/properties, similar design, similar principles of action) and
- Biological characteristics (use same materials in contact with the same human tissue or body fluid).

For the clinical application the clinical conditions for the use of Incifilm Iodine® are comparable to those evaluated in the literature section, the same condition exists for the site of the body, where the device is used and also for the intended patient population.

For the technical application of the device the condition of use respectively the principles of action can be considered as comparable, since the procedures applied for the use of those incise drapes are well defined and generally accepted. The product characteristics with regard to the design and the properties will be considered separately in the following section.

The biological characteristics of the device with regard to the contact to human tissue or body fluids is also considered to be equivalent to the cited publications, since the claimed intended use of Incifilm Iodine® is considered using publications with the same intended use.

This market search revealed mainly the product *Ioban 2* manufactured by 3M which is of essentially similar composition and equal total iodine concentration (see attached Product Information by 3M (1) and the Instruction for Use for Ioban 2 (2).

Even if there may be product related differences, a comparison between the two products show that the intended use as well as the composition and properties are almost if not identical. Thus, the products can be considered equivalent when comparing their

- Clinical application (same intended use, similar patient population)
- Technical application (similar mode of action, similar properties)
- Biological characteristics (same or similar composition, contact with human tissue and fluids)

Hence, the clinical and biological application of Incifilm Iodine® can be deemed equivalent to Ioban 2.

Pharmaplast made a comparison between Incifilm Iodine and Ioban 2 of 3M in terms of composition, performance and intended uses. The comparison showed the following info:

	Incifilm Iodine	**Ioban 2**
Composition	Polyurethane film coated with acrylic adhesive. The adhesive contains PVP-Iodine. The adhesive is protected by release liner.	Polyolefin film coated with acrylic adhesive. The adhesive contains Iodophor. The adhesive is protected by release liner

Adhesive coat weight	35-45 gsm	Same
Total Iodine content	1.4-2.4 %w/w (weight of film + adhesive) excluding release liner	Same
Antimicrobial activity	Log_{10} reduction ≥2 against various microorganisms including S.aureus, E-Coli, C.Albicans and P.aeroginosa	Same
Biocompatibility	Non cytotoxic, non-skin irritant and non-sensitizing	Unknown
Packaging	Packed in PET/Alu/PE pouches	Same
Sterilization	Sterile by radiation	Same
Shelf life	2 years	Same
How supplied	Single use individually packed	Same

The above comparison shows that the two products are technically very similar, if not identical. Both Ioban 2 and Incifilm Iodine are used for the same patient population and have the same indications. Both are adhered to the same body sites and come in contact with the same body fluids. Finally both have similar performance in terms of adhesion power. However, Incifilm Iodine is twice the breathability of Ioban 2 which is a big advantage as it prevents accumulation of sweat under the drape and minimizes risk of detachment.

According to the above info, it could be said that Incifilm Iodine is clinically, technically and biologically equivalent to Ioban 2, so clinical data of Ioban 2 could be transferred to Incifilm Iodine.

8.5. Evaluation of Clinical Data

Incisionally-based surgical site infections (SSIs) are estimated to account for 25 - 38% of all nosocomial infections among surgical patients. It is estimated that 2 – 5% of surgical patients will develop a SSI. As a result of these infections, length of patient care is extended and overall cost of care increases. The length of hospitalization is prolonged by an average of 7 days and the charges associated with each individual SSI are respectively high. These infections also significantly increase the risk of more serious complications and potential death of the patient.

Microbial contamination of the surgical site is a necessary precursor of a SSI. Studies have shown the rate of SSIs can be associated with the amount of bacteria present intra-operatively; 1-5% of clean surgeries performed will result in an infection and 10-20% of clean-contaminated surgeries will develop a SSI. While a minority of the contamination sources are exogenous (surgical personnel, operating room environment, and tools, instruments and materials brought into the operating room), the source of pathogens for most SSIs, in the absence of damage to hollow viscera, is the endogenous flora of the patient's skin. When skin is incised, the exposed tissues are at risk for contamination by endogenous skin flora.

A number of preventive measures have been proposed to reduce the risk of SSIs, including patient and skin preparation, surgical team hand/ forearm antisepsis, antimicrobial prophylaxis, operative room management, asepsis and surgical technique, and postoperative incision care. Of the skin preparation products, iodophors, alcohol-containing products, and chlorhexidine gluconate are the most common. PVP-Iodine-impregnated incise drapes have been developed for patients at risk where there is concern about bacterial wound contamination from skin flora and continuous antimicrobial activity is required.

8.5.1. Data referring to Performance

8.5.1.1. Antimicrobial Effects of PVP-Iodine

Since the first discovery of the natural element in 1811, iodine and its compounds have been broadly used to prevent infection and treat wounds (3, 4, 5, 6, 7). However, molecular iodine can be very toxic for tissues, so formulations composed by combination of iodine with a carrier that decreases iodine availability were developed.

In the 1950´s, Povidone iodine (PVP-Iodine) resulted from the combination of molecular iodine and polyvinylpyrrolidone (povidone, PVP). Povidone is a polymer that binds iodine fairly tightly, acting as an iodine-solubilizing carrier that gradually liberates free inorganic iodine in solution to skin and mucous membranes. Povidone iodine is thus a stable chemical complex which contains from 9.0% to 12.0% available iodine, calculated on a dry basis [Unites States Pharmacopoeia, European Pharmacopoeia]. Since its market launch, Povidone iodine has become the universally preferred iodine disinfectant.

Currently, Povidone iodine is a world-wide used antiseptic available commercially in several formulations, e.g. as solution, cream, ointment, dry spray or dressings. The most common brands are Betadine® and Betaisadona®.

The antimicrobial spectrum of PVP-Iodine is very broad: it is effective against bacteria, mycobacteria, fungi, viruses, spores and protozoa (7). Moreover, its efficiency against clinically and epidemiologically significant new pathogens, such as methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* has also been validated. No development of resistance has been determined.

The following table shows an overview on species that have been proven for susceptibility on Povidone iodine.

Table 1: Antimicrobial spectrum of Iodine

Gram-positive bacteria	**Gram-negative bacteria**	**Fungi**	**Viruses**
Bacillus subtilis	*Enterobacter aerogens*	*Aspergillus flavus*	Cytomegalovirus
Clostridium perfringens	*Escherichia coli*	*Candida albicans*	Influenza type A
Clostridium tetani	*Haemophilus vaginilis*	*Cryptococcus neoformans*	Polio type 1, Mahoney and Chat
Corynebacterium diptheriae	*Klebsiella pneumoniae*	*Epidermophyton floccosum*	strains
Diptheroids	*Proteus mirabilis*	*Nocardia asteroides*	*Herpes genitalis*
Diplococcus pneumoniae	*Pseudomonas aeruginosa*		Herpes simplex type 1
Staphylococcus albus	*Pseudomonas pyocyanea*		
Staphylococcus aureus/ haemolytic	*Salmonella typhi*	**Protozoa and other organisms**	
Streptococcus (b-haemolytic)	*Serratia marcesens*	*Entamoeba histoytica*	**Acid-fast bacteria**
Streptococcus faecalis	*Shigella dysenteriae*	*Trichomonas vaginalis*	*Mycobacterium tuberculosis*
Streptococcus pyogenes	*Vibrio comma*	*Treponema pallidum*	
		Chlamydia trachomatis	
		Mycoplasma hominis	
		Rabies	
		Rubella	
		Vaccinia	

(Source: Angel et. al. 2008)

Elemental iodine is rapidly lethal to bacteria, fungi, viruses, and protozoa (7). In the absence of other organic matter that could compete for iodine binding, iodine solution can kill most microorganisms within seconds and rare, partially resistant organisms within minutes. The following table shows the microbicidal short-term effect of disinfection of PVP-Iodine with details of the log-survival rate of 5 test organisms, 2 pH-ranges, 3 different concentrations and 4 contact times.

Table 2: Microbicidal Short-Term Effect (Disinfection) of PVP-Iodine

Test organism	Con-tact time min h	pH 6						pH 8					
		Concentration in %						Concentration in %					
		K	0,025	0,012	0,006			K	0,025	0,012	0,006		
Staphylococcus aureus	5‘	7	2	2	3			7	2	4	5		
	10‘	7	<2	<2	3			7	<2	3	5		
	60‘	7	<2	<2	2			7	<2	3	5		
	4h	7	<2	<2	<2			7	<2	2	5		
Escherichia coli	5‘	7	2	3	3			7	<2	3	5		
	10‘	7	<2	<2	<2			7	<2	3	5		
	60‘	7	<2	<2	<2			7	<2	2	5		
	4h	7	<2	<2	<2			7	<2	2	5		
Pseudomonas aeruginosa	5‘	7	<2	<2	<2			7	4	4	7		
	10‘	7	<2	<2	<2			7	2	4	5		
	60‘	7	<2	<2	<2			7	<2	3	5		
	4h	7	<2	<2	<2			7	<2	3	4		
Candida albicans	5‘	6	<1	<1	<1			6	<1	<1	6		
	10‘	6	<1	<1	<1			6	<1	<1	4		
	60‘	6	<1	<1	<1			6	<1	<1	4		
	4h	6	<1	<1	<1			6	<1	<1	3		
Aspergillus niger	5‘	6	<1	2	2			6	1	3	5		
	10‘	6	<1	<1	1			6	1	2	5		
	60‘	6	<1	<1	<1			6	1	2	5		
	4h	6	<1	<1	<1			6	<1	<1	4		

Source: Wallhäußer, Karl Heinz. Praxis der Sterilisation: Desinfektion – Konservierung, 1995, p.642.

In table 2 the broad range of effects of PVP-Iodine is shown. Notably, the effects of the acidic pH-range are considerably better than the effects of the alkaline range. Already with the very low concentration of 0.025% PVP-Iodine (related to the active ingredient) the 5-5-5-test can be achieved (in-vitro-test for disinfectants: 5 test strains each with 1 x 10^8 bis 3 x 10^8 cells per ml are reduced in their plate-count by a factor of 5 powers of ten in 5 minutes at 21 °C (killing quote = 99.999 %)).

Due to its broad antimicrobial spectrum, Povidone iodine has proved to be a highly efficient microbicide and is used in a wide range of medical applications. Clinical fields exist in prophylaxis and therapy, for either once only or repeated applications: the disinfection of hands and skin, mucosa antisepsis, intra- and postoperative wound treatment, therapy of skin infections, burns and chronic wounds. PVP-Iodine is most commonly used in the surgical setting to ensure preoperative decontamination, thus reducing the risk of surgical wound infection. The risk of operative infection is minimized by decontamination of patient skin surfaces in the area of surgical procedure (7).

Mechanism of the Antimicrobial effect

The antimicrobicidal effect in the Povidone iodine complex is due to iodine; povidone alone has no antibacterial activity (7). Although the precise mechanism of iodine has not been completely determined, it has been suggested that the lethal effect of iodine on microorganisms can be explained as follows: iodine rapidly penetrates the cell wall and proceeds to dislocate protein synthesis, it disrupts the function of respiratory chain enzymes and interferes with lipid membrane and nucleic acid function through several diverse mechanisms of action (3).

Once released from PVP, elemental iodine has several forms in aqueous solutions, with the most effective microbiocidal forms being molecular I_2 and hypoiodous acid (HOI) (7). In these forms, iodine is highly reactive with surrounding organisms via its strong oxidising effects on functional groups of amino acids, nucleotids, and fatty acids. Particularly susceptible are -NH groups, -SH groups, phenol groups, and double bonds of unsaturated fatty acids. Interaction of iodine with these groups in a cell results in rapid partitioning and disintegration of the cytoplasm, enzyme denaturation, pronounced coagulation of chromosomal material leading to nuclear denaturation, membrane pore forming and other loss of cytosolic material. Despite cell wall structural damage, most cells do not undergo lysis or rupture.

The physico-chemical rather than the biological mechanism of action may explain why PVP-Iodine does not generate resistance in microorganisms (7). With regard to increasing bacterial resistance against antibiotics, that is certainly one of the reasons why several authors (see 7) strongly favour and recommend the use of PVP-Iodine in several applications including the pre-operative preparation of the patient's skin. While the earlier clinical literature established the role of PVP-Iodine for general infection control, the more recent literature stresses the special uses of this antiseptic for control of the developing opportunistic pathogens (7).

8.5.1.2. Antimicrobial Activity of Povidone Iodine in Incision Drapes

8.5.1.2.1. Antimicrobial Activity of Ioban 2 by 3 M

3M performed an in-vitro time-kill study (study no. LIMS 7213, 1997) in order to demonstrate the antimicrobial activity of the Povidone iodine in their product Ioban 2. Purpose of this study was to measure the rate of bactericidal activity of available iodine in the Ioban 2 antimicrobial incise drapes compared to a negative control over time. For this study, samples of Ioban 2 and clear incise drapes were directly inoculated with a bacterial suspension, and incubated for 30, 45 and 90 minutes. The samples were neutralized at each time point to stop the antimicrobial reaction and then blended into a solution. Solutions were plated onto a growth medium and incubated for 24-48 hours. Colonies were counted and data was converted to log10 CFU. Log reductions were calculated by subtracting the log10 CFU bacterial recovery of the Ioban 2 drape samples at each time point from the log10 bacterial recovery of the clear incise drape at the corresponding time point.

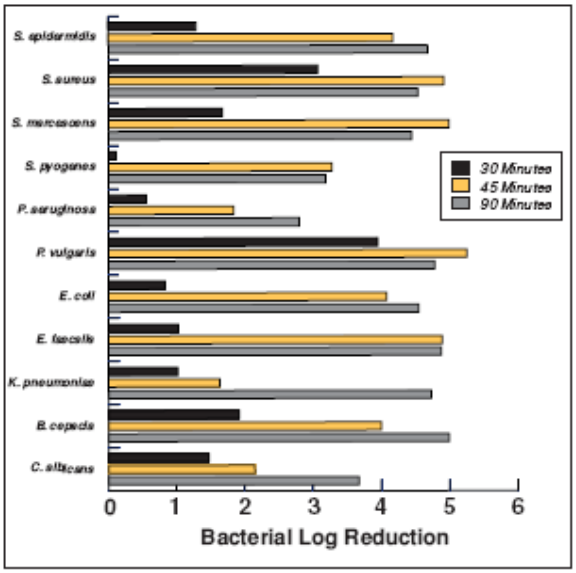
The Ioban 2 drapes were tested against the following different organisms which are typically part of the skin flora or of the endogenous flora:

- *Staphylococcus epidermidis*
- *Staphylococcus aureus*

- *Serratia marcescens*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*
- *Proteus vulgaris*
- *Escherichia coli*
- *Enterococcus faecalis (*also referred to as *Streptococcus faecalis)*
- *Klebsiella pneumoniae*
- *Burkolderia cepacia (*also referred to as *Pseudomonas cepacia)*
- *Candida albicans*

Results shown in Figure 1 indicate the bacterial log reduction of Ioban 2 drapes for each organism. Within 45 minutes of exposure to the Ioban 2 drape, six organisms exhibited greater than a 4-log reduction: *S. epidermidis, S. aureus, S. marcescens, E. coli, E. faecalis*, and *P. vulgaris*. After 90 minutes of exposure, two more organisms exhibited a greater than 4-log reduction: *K. pneumoniae* and *B. cepacia*.

Fig. 1: Log reductions of Ioban 2 by 3M referring to 11 different bacterial organisms



Source: 3M study no. LIMS 7213 (1997) in 3m Incise Drapes: Bibliography of Efficacy and Safety Studies

8.5.1.2.2. Antimicrobial Activity of Incifilm Iodine® by Pharmaplast

Pharmaplast has tested its product Incifilm Iodine® for the antimicrobial activity of the integrated PVP-Iodine in in-vitro antimicrobial activity study at the accredited test laboratory NAMSA, U.S.A. according to the AATCC Test Method 100 (Assessment of Antibacterial Finishes on Textile Materials). The test has been performed within the framework of an accelerated ageing test for the product Incifilm Iodine® to show the antimicrobial activity after 2, 4, 6 and 8 months after an incubation at 40 ± 2°C. The results for the test samples show in average a greater than 2-log reduction for the following organisms after 24 hours contact time:

- *Staphylococcus aureus*

- *Multi-resistant S. aureus (MRSA)*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Candida albicans*

Hence the results presented by Pharmaplast show in general a very good antimicrobial activity of Incifilm Iodine® when referring to the main organisms that cause bacterial contamination in wounds. The results presented by Pharmaplast show a very good antimicrobial activity of Incifilm Iodine® that can be compared to that of Ioban 2 by 3M when referring to the main organisms that cause bacterial contamination in wounds.

The same test was conducted within the framework of real time stability study (product stored at ambient temp) to show the antimicrobial activity after 3 months, 6 months, 9 months, 1 year and 2 years. The results for the tested samples showed in average a greater than log reduction 2 for the following organisms after 24 hours contact time:

- *Staphylococcus aureus*
- *Multi-resistant S. aureus (MRSA)*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Candida albicans*

The starting inoculum concentration at all-time points of the accelerated stability study and the real time stability study was 1-4 x 10^5 except the last time point of the real time stability study when the inoculum concentration was 1-4 x 10^6. This higher inoculation allowed one more fold log reduction, so the antimicrobial efficacy of Incifilm Iodine reached more than log reduction 4 against all the microorganisms set in the final product specifications.

Since the last time point of the real time stability study represents the end of the shelf life of the product, so it could be said that the product Incifilm Iodine should have showed antimicrobial activity of log10 reduction ≥4 if it had been tested against the microorganisms with starting inoculum concentration 1x10^6 rather than 1x10^5. Therefore, there is strong evidence that the antimicrobial activity of Incifilm Iodine is equivalent to Ioban 2 of 3M.

In-Vitro Time – Kill study:

Time – Kill study was conducted at the accredited test laboratory NAMSA, U.S.A. Incifilm Iodine was tested according to the AATCC Test Method 100 (Assessment of Antibacterial Finishes on Textile Materials) after 30 mins, 3 hours and 6 hours against 4 microorganisms. The starting inoculum was between 3 and 6.5 x 10^6. The tested samples managed to inhibit growth of C. albicans by log reduction 1.15 after 30 minutes. After 3 hours, the growth of two more microorganisms (S.aureus and MRSA) was inhibited with log reduction more than 4 and the growth inhibition of C.Albicans reached log reduction more than 4. Finally after 6 hours, one more type (A.brasillinesis) exhibited log reduction more than 4.
This means that Incifilm Iodine remains antimicrobial effective for up to 6 hours which is the average duration of a long surgical operation.

Therefore it is concluded that the PVP-Iodine in the incise drape Incifilm Iodine® shows a good antimicrobial activity in the concentrations that are used. It performs equally to the essentially

similar product Ioban 2 by 3M which is marketed in the same intended use as antimicrobial incise drape since many years.

Data referring to Safety

8.5.1.3. Toxicological Aspects of Povidone Iodine

PVP-Iodine is a substance of well-established use in the European Union. Therefore, non-clinical data on the pharmacodynamics, pharmacokinetics as well as on the toxicity of the substance are largely available and additional own pre-clinical testing is not required. The following data are mainly from acknowledged textbooks, review articles or approved summaries of product characteristics (SPC) that summarize the profile of the substance. Furthermore, there is exhaustive information on the toxicology of the substance in the database of the U.S. National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov) which is also used as source of information.

8.5.1.3.1. Pharmacodynamics

Pharmakotherapeutic Group: Antiseptic, Iodophor
ATC-Code: D08AG02
The PVP-Iodine complex is active at pH values between 2 and 7 [8, 10, 9]. The microbiocidal effect is due to free iodine which is not complex-bound and which is released in aqueous ointments or solutions. Hence, the PVP-Iodine complex can be regarded as a iodine reservoir which constantly releases iodine and thus guarantees a constant concentration of the free active iodine component. Due to the binding in the PVP-Iodine complex the free iodine almost loses its local irritant effect as compared to alcoholic solutions containing iodine. The free iodine is a strong oxidant which reacts on the molecular level mainly with SH- or OH- groups of the amino acids of the bacterial enzymes or structural proteins that can easily be oxidized. This unspecific action is the reason for the broad-spectrum effectivity of the PVP-Iodine against for example gram-positive and gram-negative bacteria, mycobacteria, fungi (esp. *Candida*), numerous viruses and some protozoa. Bacteria spores and some virus species are generally only inactivated after a sufficient residence time. Specific primary resistances against PVP-Iodine as well as the occurrence of secondary resistance after a long-term application are not to be expected.

The use of PVP-Iodine in wound dressings is not for the purpose of exerting any specific pharmacological action. Instead, it acts indirectly as an antiseptic agent by gradual decay due to wound moisture, subsequently leading to the liberation of small amounts of Iodine, acting as a disinfectant.

8.5.1.3.2. Pharmacokinetics

After topical application of PVP-Iodine the absorption of iodine is possible and depends on the way and duration of the application as well as on the amount of substance applied [8, 9,10]. If applied within a short time limit and on intact skin, only a small amount of iodine is absorbed. A significant absorption of PVP-Iodine from medicinal products has been reported after application on mucosa, large wounds with damaged or burned skin and especially after irrigation of visceral cavities or after intraperitoneal application. A resulting elevation of the blood iodine level is in general only temporary. The elevated iodine level does in general not cause any clinically relevant changes in the hormone status of the thyroid gland. The performance of absorbed iodine in the human body is almost identical to that of iodine from other sources.
Absorption of iodine from common treatment of cuts, scrapes, and burns has also been considered by the Unites States Food and Drug Administration FDA.[7]. FDA evaluated the available PVP-Iodine study data and concluded that transient increases in iodine blood levels do not adversely effect thyroid function. However, it was stated that there remains a risk regarding possible systemic

toxicity in the situation in which PVP-Iodine would be applied repeatedly, over a prolongued period, and to a large surface area. Such conditions exist when treating a major burn with PVP-Iodine where serum and urine levels can become pronounced. FDA does not regard thyroid hormone abnormalities as a major health problem despite the risk that exposure to large quantities of iodine could cause hyperthyroidism or induce thyrotoxic crisis in susceptible individuals. It is beleived that abnormal thyroid measurments in this setting are more likely attributed to the stress of the underlying condition than the PVP-Iodine therapy.

The distribution volume of PVP-Iodine is approximately 38 % of the body weight in kilogram, whereas the biological half life after e.g. vaginal application is reported to be 2 days. The normal value for the total iodine content in the blood serum ranges between 3.8 until 6.0 µg/dl, and for anorganic iodine it ranges from 0.01 – 0.5 µg/dl [8]. Elimination is mainly renal with a clearance of 15 to 60 ml plasma/min depending on the serum iodine level and the creatinin clearance (normal value 100 – 300 µg Iodide pro g creatinin). The absorption of iodine and especially the renal elimination depend on the average molecular weight of the mixture: with molecular weights between values from 35.000 to 50.000 the retention in the reticulohistiocytic system is most probable. After topical application there are no thesaurismosis and other changes as they occur after intravenous or subcutaneous application of PVP-Iodine-containing medicinal products.

8.5.1.3.3. Toxicity

Acute toxicity

Povidone-iodine has been found to exhibit significantly lower oral toxicity then do most organic iodine compounds [8, 10]. The intraperitoneal toxicity is clearly higher than the oral effect with an LD_{50} rat (oral) of 5,990 mg/kg and an LD_{50} mouse (i.p.) of 360 mg/kg. BASF publishes a value after dermal application of LD_{50}/rat/male/female: > 2,500 mg/kg (BASF-Test [11]).
In animal experiments (mouse, rat, rabbit, dog) acute toxic effects have only been observed after systemic (oral, subcutaneous, i.v. peritoneal, intraperitoneal) application of excessively high doses that are not relevant for the topical application [10].

Chronic toxicity

The chronic oral toxicity of PVP-Iodine was tested in an animal experiment: two experimental dogs received daily doses of 1.84 g povidone-iodine in enteric coated tablets over a 5-month period [8]. The daily dose corresponded to 370 mg total or 280 mg available iodine. At the end of the study, the sacrificed test animals showed no gross pathology, and their histology was normal.
Further subchronic and chronic toxicity tests have been performed on mainly rats and dogs that received their food supplemented with PVP-Iodine in dosages ranging from 75 to 750 mg PVP-Iodine per day and kg body weight during 12 weeks [9]. After discontinuation of the daily PVP-Iodine the main observations were the reversible and dose-dependent elevation of protein-bound iodine in the serum as well as the unspecific histopathologic modification of the thyroid gland.
The cell toxicity of Povidone-Iodine was tested in rats [8]. One hour incubation of rat hearts in povidone-iodine (containing 0.5 to 5.0% available iodine) produced a cell toxicity that was evidenced by lower growth potential of the subsequently planted cells. On the other hand the healing of skin wounds was not affected by painting with these solutions as long as the level of available iodine was less than 2%. Concentrations of available iodine as high as 5% slowed the healing of the wound without having a permanent effect.

Mutagenicity / Genetic toxicity:

The potential mutagenicity of povidone-iodine was thoroughly investigated using the intraperitoneally administered dominant lethal test, the micronucleus test, the bone marrow test, and animal experiments [9, 12]. In all these tests, even when using extremely high doses of povidone-iodine, no mutagenic effect could be detected.

Developmental toxicity / teratogenicity:

In an animal study pregnant rabbits got an injection of various concentrations (16, 35, and 75 mg/kg/day) of a 15% aqueous povidone-iodine solution intramuscularly for 12 days during the 6-18 days of gestation [9]. The only differences found between the test animals and the controls were some lower weight increases, and lower average weights of fetus and placenta. No toxic or teratogenic effect of povidone-iodine was noticed.

Further tests including the chromosome aberration test, the Rec-assay and the Ames assay did not reveal any conclusive results [13].

On the other hand, it is one of the known characteristics of PVP-Iodine that it can cross the placental barrier. With regard to the fact that the foetus is very susceptible to pharmacologic iodine doses and there is a risk of neonatal hypothyroidism, PVP-Iodine should generally only be given to pregnant or nursing women under compelling circumstances and with proper monitoring [7, 10].

Local tolerance

Whether iodine is administered topically or systemically, it can give rise to allergic reactions such as urticaria, angioedema, eruptions etc.. However, when PVP-Iodine solution is applied locally on intact skin or mucosa, the incidence of allergy and contact dermatitis in normal subjects is extremely low, with 2 allergic reactions in 5,000 applications recorded [10]. Allergy tests, which yielded very severe sensitization with iodine (Lugol's) solution, failed to show any reaction with povidone-iodine [3]. Moreover, in a three year study on 5900 patients, only two allergy cases were observed. The manifested dermatitis healed in 7 days, and no systemic toxicity or iodism was found.

Further studies on the effects of iodophors on intact skin were carried out on 200 patients, exposing them to povidone-iodine solution and tincture of iodine (each containing 2% available iodine) [9]. It was found that while the tincture of iodine soaked patches had to be removed after 24 hours owing to the presence of severe cutaneous reactions, the povidone-iodine patches produced no reactions even after 96 hours.

Other tests on human and rabbit skins abraded with course sandpaper gave results similar to those of the intact skin tests [9]. Moreover, the wounds did not become infected, but were in the process of healing when the povidone-iodine patches were removed.

There were, however, reports about erythema induration and vesicular eruption in special cases, such as patients with diminished immunity or underlying malignancy [9]. The iodine enters the bloodstream attached to serum albumin, and is then eliminated by the kidneys. Depending upon the concentration of the antiseptic solution, the area of the bum, and the frequency of the application, the level of the serum protein-bound iodine and the concentration of the iodine in the urine could increase to several times higher than the normal level. Nevertheless, since the excretion of the iodine is fast, the normal iodine level is usually reached within one week after discontinuation of the treatment [9].

Continuous exposure to povidone-iodine could lead to a decrease in iodine binding, and the spontaneous synthesis of free triiodothyroxine and thyroxine, which is the so called Wolff-Chaikoff-

block [9]. This situation is also transitory by nature, and more likely to occur in individuals with goiter.

Extended studies on guinea pigs showed that the cutaneous irritation caused by povidone-iodine was within acceptable levels [9]. Moreover, chronic application caused a transcutaneous absorption, which led to the saturation of the thyroid gland. This in turn resulted in transient hypersecretion and increased levels of triiodothyroxine and thyroxine. That, however, triggered the activity of the pituitary gland, which lowered the production of TSH by one-half, which in turn achieved the recurrence of euthyroidism after 90 days of treatment.

The effect of PVP-Iodine on the mucous membranes has been studied in 25 patients whose throats including the tonsilar fossae, palate, uvula, and posterior pharingeal wall were painted with povidone-iodine solution [9]. About 60% of the patients showed only a minor reaction (slight reddening of the mucous membranes) which disappeared in about 2 hours, and 40% showed no reaction at all. The test was repeated fifteen times daily with approximately the same results.

BASF [9] publishes the results of the Guinea pig maximization test according to the OECD Guideline 406 where PVP-Iodine was found to be non-sensitizing in this standard test for sensitization.

8.5.1.3.4. Evidence of Adverse Effects From Treated Patients

Information on the safety of iodine in relation to wounds is very broad. Cooper 2007 (14) provides a good review about the situation and the obviously conflicting evidence. According to this summary reports of systemic effects following short-term use of PVP-Iodine are rare. Fatalities have been attributed to topical use of PVP-Iodine in two burns patients and following surgical debridement of a hip wound. Mediastral irrigation with PVP-Iodine has been reported to result in acute renal failure and seizures. Elevated serum iodine has been linked to renal impairment and hyperchloremic acidosis following the use of PVP-Iodine, and it has been suggested that long-term topical treatment with PVP-Iodine on 40 neurological in-patients caused mild thyroid dysfunction. Investigations into the extent of iodine absorption through wounds do not yield conclusive evidence of adverse systemic effects. Iodine levels were monitored in the blood and urine of 33 burns patients and undesirable thyroid or renal effects were not detected.
Changes in the levels of thyroid hormones were not found in 10 patients with extensive third-degree burns that were treated with PVP-Iodine. Moreover, the use of PVP-Iodine in 18 paediatric cardiac patients did also not lead to altered thyroid function.

Serum and urine iodine levels after topical application of PVP-Iodine were deduced to be related to the size of a burn and renal function, but effects on thyroid function were not found. Increased levels of serum iodide in burns patients relate not only to the size of the affected area but also to the length of treatment. Although serum iodide levels can be expected to return to normal following cessation of treatment with PVP-Iodine, patients with existing thyroid disease, pregnant women, nursing mothers and infants were considered unsuitable candidates for long-term topical application of povidone-iodine.

Adverse effects noted in case reports may have been associated with underlying pathologies, rather than Iodine alone because some patients had multiple etiologies. There are recommendations that iodophores should be used in neither patients with renal damage nor those with extensive burns. Allergic reactions to iodine have also been reported, with prevalence reports

ranging from 0.7% to 41%. A high prevalence of sensitisation to topical agents in leg ulcer patients prompted a French group to analyse published studies and to review their own patients (cited in 14). Patch testing in three groups of patients with the European series of standards and an additional series of potential allergens pertinent to leg ulcers showed that PVP-Iodine as Betadine had lower rates than neomycin or other tested substances.

In Hungary, the successful use of Betadine with dermatology patients over many years was reported by Juhász 2002 (15); to determine whether any patients had been sensitised to PVP-Iodine, 50 were challenged by patch testing and no sensitisation was found. Doubts about the validity of positive patch tests where PVP-Iodine (10% solutions in petrolatum, i.e. 1% free iodine) are tested under occlusion caused another scientist to test 500 consecutive patients with conventional patch tests (cited in 14). Only 14 positive patients were found; each of them was retested in a repeated open application test where PVP-Iodine dermal solution was applied to the open forearm twice daily for 7 days. Two of these tests were positive, thus a prevalence rate of 0.4% with true allergic contact dermatitis to PVP-Iodine was deduced. It has been suggested that PVP-Iodine containing detergents caused cytotoxicity and sensitisation in wounds but not intact skin. Concluding the available evidence the authors state that reports of iodine allergy may be exaggerated, especially when looking at the fact that sensitisation may occur before treatment regimes commence and that allergen tests reflect not only health care experiences (14).

Angel et al. (5) made a recent literature review about the use of iodine in wound care in 2008. The authors both reviewed animal and human studies and found over 50 studies that have been conducted on the use of iodine in wound care. There article offers a broad overview about the available studies. The authors come to the conclusion that in the presence of infection, the application of PVP-Iodine proves to be effective at reducing bacteria numbers and decreasing wound infections. Furthermore, they state that there is not enough evidence to support that wound healing is delayed in an infected wound and there are no human clinical studies to support the use of povidone-iodine in non-infected wounds. In view of this, in the absence of infection, the authors recommend that povidone-iodine should be used with caution. They claim that when selecting povidone-iodine in wound care, a holistic approach needs to be taken and the systemic affects needs to be considered.

Summarizing the data on the toxicology of PVP-Iodine it can be stated that in contrast to other iodine-based antiseptics, povidone-iodine is of very low toxicity. It does not cause cutaneous reactions in humans or animals that are not hypersensitive to the substance or that have no have severely damaged skin. Its effect on mucous membranes is mild and of a passing nature (9). Still, povidone-iodine, regardless of the route it is applied, can cause systemic absorption of iodine and should therefore be used carefully in pregnant or nursing women as well as in newborns and infants. PVP-Iodine has excellent local tolerability and an absence of systemic toxicity (9)..

8.5.2. Clinical Studies on PVP-Iodine in Antimicrobial Incise Drapes

Incise drapes are defined as adhesive films used to cover the skin at the site of the incision with the intention of minimizing the contamination of the operative wound by microorganisms colonizing the skin of the patient around the operative site.

Clinical studies on the use of general plastic adhesive drapes (without PVP-Iodine) during surgery for preventing surgical site infection are largely avilable and have recently been evaluated by Webster et al 2007 (20) in a systematic Cochrane review. The authors searched the following databases: Cochrane Wounds Group Specialised Register, the Cochrane Central Register of Controlled Trials, The Cochrane Library, Ovid MEDLINE, Ovid EMBASE, and Ovid CINAHL. Only randomised controlled trials were selected that compare any plastic adhesive drape with no adhesive drape, used alone or in combination with woven (material) drapes or disposable (paper) drapes in patients undergoing any type of surgery. The reviewers' conclude that there was no evidence from the seven trials that plastic adhesive drapes reduces surgical site infection rate and even some evidence that they increase infection rates. Further trials may be justified using blinded outcome assessment to examine the effect of adhesive drapes on surgical site infection based on different wound classifications.

The use of PVP-Iodine-impregnated incise drapes on the other hand, was mainly studied using the product Ioban™ 2 by 3 M which is essentially similar to Incifilm Iodine®. Ioban 2™ has been clinically tested in a number of surgical specialties. The following studies are available in the public domain and have been selected for evaluation of the product safety and efficacy.
Fairclough et al. 1986 (16) studied the wound contamination in 107 patients. Prior to preparing the skin for surgery, samples for bacterial growth were taken from the patients. The same site was sampled after preparation with povidone-iodine. Moreover, at the end of surgical procedure the deep part of the wound was also sampled. In this trial the wounds of 15% of patients became contaminated by organisms present on the skin prior to disinfection. Furthermore, the authors performed another study in which 122 patients undergoing hip surgery received an iodophor impregnated plastic adhesive drape ('Ioban') applied to the operation site 24 hours prior to surgery. Bacterial sampling of the wound at the end of the procedure showed that wound contamination was reduced from 15% to 1.6% by this method. This means a 10-fold decrease of surgical site infections in the group using this iodophor-impregnated plastic adhesive drape. The authors conclude that when patients are to have implant surgery, the protection from contamination by skin organisms afforded by the 'Ioban' drape is likely to prove a valuable tool in the fight to prevent infection

Yoshimura et al. 2003 (17) retrospectively investigated factors associated with wound infection after liver resection for hepatocellular carcinoma, with special reference to use of a plastic adhesive drape impregnated with iodophor. 296 patients underwent liver resection. The authors found that wound infection was significantly less likely with the use of iodophor drapes (3.1%) than for surgery without iodophor drapes (12.1%). In conclusion, the authors state that low BMI, smoking, a long preoperative hospital stay, and the lack of an iodophor drape use were risk factors for wound infection after liver resection for hepatocellular carcinoma. They presume that the drapes prevented contamination from the skin during the operation.

Ritter et al. 1988 (18) studied the incidence of postoperative wound infection following the use of an iodophor-incorporated adhesive wound drape with a preliminary one-minute alcohol cleanse in 649 total arthroplasties. The patients were followed for a minimum of one year to detect signs of

infection. An infection rate of 0.46% was comparable to the incidence previously observed for conventional methods using an iodine spray as a skin preparation.

Further to the above evaluated clinical studies from the public domain, the searches in the internet focused on guidelines referring to the use of PVP-Iodine-impregnated incise drapes. Mainly, one clear guideline referring to the use of PVP-Iodine-impregnated incise drapes was identified:
In 2008, the U.K.´s National Collaborating Centre for Women's and Children's Health performed a review for the National Institute for Health and Clinical Excellence NICE and established a clinical guideline "Surgical site infection" for the prevention and treatment of surgical site infection (SSI)(19). The review included the evaluation of incise drapes the purpose of which was to address the clinical effectiveness of using incise drapes during surgery in the prevention of SSI. *The Clinical questions* referring to Incise drapes in this guideline were defined as follows: „Is the use of incise drapes clinically and cost-effective in reducing the incidence of surgical site infection?" And „Which incise drapes are clinically and cost-effective in reducing the incidence of surgical site infection?" As clinical evidence one systematic review (20) and one Randomized Clinical Trial (21) were identified.

Five trials (*n* = 3082) from the well-conducted systematic review examined the effect of the use of surgical incise drapes without added antimicrobials on the incidence of SSI. Surgery performed included general or abdominal surgery, caesarean sections and hip surgery. The main outcome considered was SSI even if the definition criteria varied among the studies. A meta-analysis performed showed a statistically significant difference between the two groups, with more SSI events in the incise drape group than in the no incise drape group.

The randomized clinical trial evaluated examined the role of adhesive incise drapes in surgical patients for the prevention of SSI *in a total* patient number of n = 577). It found no statistically significant results. The trial did not bring substantial changes to the overall results when added to the previous meta-analysis.

Two randomized clinical trial from the above systematic review were included under the comparison *of the* outcome of use of Iodophor-impregnated incise drapes compared with no incise drapes. The studies with a total of n = 1113 participants investigated whether the use of incise drapes impregnated with the iodophor had an effect in the incidence of SSI when compared with no incise drapes. Participants were patients undergoing abdominal and cardiac surgical procedures. In both studies SSI was reported. The data from the two trials were combined in a meta-analysis which showed no statistically significant difference.

When all the trials were pooled together in a meta-analysis, a statistically significant difference was found that favoured the non-use of incise drapes in the prevention of SSI when compared with the use of an incise drape (whether impregnated with an antimicrobial or not). The review concluded that there is evidence to suggest that the use of non-iodophor-impregnated incise drapes increase the risk of SSI. On the other hand, evidence was found to suggest that there is no difference in risk of SSI between iodophor-impregnated incise drapes and no incise drape. Although the use of non-iodophor-impregnated incise drapes is routine in some operations (such as prosthetic joint or graft surgery), they may marginally increase the risk of SSI.
The guideline recognised that adhesive drapes may have a role in maintaining the integrity of the operative site/field and recommend to use an-iodophor-impregnated incise drape. Summarizing, the recommendations of the guideline are as follows: „Do not use non-iodophor-impregnated incise

drapes routinely for surgery as they may increase the risk of surgical site infection. If an incise drape is required, use an iodophor-impregnated drape unless the patient has an iodine allergy."

A clinical study was also conducted in the Department of Microbiology and University Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW to compare iodine-impregnated ('Ioban') drapes with conventional methods in prevention of bacterial colonization of wounds at operation (22). Forty-five patients undergoing clean elective inguinal surgery, including inguinal and femoral herniorrhaphies and saphenofemoral ligations for varicose veins were entered into the trial. They all had a general anaesthetic. The skin was closed with interrupted fat sutures using plain catgut and a subcuticular continuous proline suture. The patients were randomly allocated to receive one of three skin preparations, (1) alcoholic 10 per cent w/v povidone-iodine containing 1 per cent available iodine ('Betadine', Napp Laboratories), (2) povidone-iodine with an incise drape ('Steri-Drape', 3M United Kingdom plc), (3) 'Ioban' drape with no skin preparation. Two types of microbiological sample were taken to quantitate skin flora: impression cultures and cotton wool swabs. These methods were selected for their practicability.

The results showed decline in the colony counts obtained from the impression cultures, taken before and at the end of the operation in all three groups. However, there was a statistically significant fall in the two groups receiving skin disinfection with 'Betadine', and a less marked reduction in the group receiving 'Ioban' drapes. The results from the swabs showed similar trends but invariably there was not a statistically significant reduction from pre-operative counts in the 'Ioban' drape group. Finally, none of the 45 patients had clinical evidence of a wound infection postoperatively.

The reason for the inferior performance of 'Ioban' drapes may have been that there was less iodine available on the skin to produce a bactericidal effect. There were no clinical postoperative wound infections but this was to be expected in a group of patients undergoing clean surgery of this kind.

The results of this study do not support the use of 'Ioban' drapes **alone,** because the deficiency of antibacterial activity outweighs the practicality and ease of the method.

Pharmaplast has considered the results of the above study in setting the instructions for use of Incifilm Iodine which clearly state that the skin should be prepped by conventional antiseptic method e.g. betadine or alcohol and then the drape can be applied after leaving a chance for the skin to dry i.e. Incifilm Iodine cannot be used directly without prepping of the skin with conventional antiseptics.

The significance of the use of iodine-impregnated incision drape (Ioban(®) 2) for the prevention of postoperative wound infections (SSI) was analysed. A meta-analysis which evaluated four prospective studies and one retrospective study was able to provide significant confirmation of a reduction in the SSI rate. There are no limitations in terms of the biocompatibility of the iodine-impregnated incision drape (23). The meta-analysis concluded that the use of iodine-impregnated incision drape as compared to the use of incision drape with no antiseptic impregnation was not associated with negative consequences in any of the studies. Overall, based on the efficacy strength of the antiseptic incision drape, a reduction of the SSI rate can be confirmed only with a large sample size.

The meta-analysis also has showed the effects of iodine impregnated drape on the skin flora and wound contamination. When comparing the efficacy of skin antiseptics with PVP iodine to the use of the iodine-impregnated drape without preceding skin antiseptics, the skin antiseptics with PVP iodine were more effective than the drape, though the drape also had an antiseptic effect. At the same time, the iodine-impregnated drape reduced wound contamination. Analogous results were shown by the comparison between preoperative antiseptics with PVP iodine/alcohol (betadine), identical antiseptics with subsequent use of the antiseptic incision drape and use of the drape alone. In a comparison of the skin flora at the end of surgery after skin antiseptics with PVP iodine (n=107) and after the use of the iodine-impregnated incision drape 24 h before the start of surgery to the end of surgery (n=122), the wound contamination rate was 15% and 1.6% respectively which means that the iodine-impregnated drape does not only significantly reduce the resident skin flora, but its use also clearly reduces intraoperative wound contamination.

Summarizing the evaluated literature, it can be concluded that PVP-Iodine-impregnated incise drapes are useful and effective in surgical procedures where there is concern about bacterial wound contamination from skin flora and continuous antimicrobial activity is required. This is manifested in the intended use for the product Incifilm Iodine®.

8.5.3. Medical Device Vigilance Data

Pharmaplast has considered post market surveillance the product line Incifilm Iodine according to MEDDEV 2.12-1 rev 8 January 2013. Incifilm Iodine has been sold in different non EU countries where CE mark is not required. A full detailed sheet is annexed with the clinical evaluation report, showing breakdown of sales in different countries and complaints history.

It is clear that Pharmaplast has sold 87,817 pieces of different sizes of Incifilm Iodine 2013 and 2014. The end users of the product have used it as per the indications and the IFUs mentioned in the internal leaflets. During the two years, Pharmaplast has received Zero complaints. This means that the product is safe and effective for its intended purposes.

Further to own vigilance data, this clinical evaluation considers medical device vigilance data for comparable PVP-Iodine-impregnated incise drapes on the international market. For this purpose the vigilance databases of the Competent Authorities in Switzerland (Swissmedic), Germany (BfArM) and USA (FDA) were searched for vigilance data referring to comparable incise drapes. None of the databases contains information on recent recalls of essentially similar devices. Thus, no further risks referring to PVP-Iodine-impregnated incise drapes and their applications in the intended use were identified.

Moreover, the database of the United Kingdom´s MHRA was searched for recalls, incidents and measurements taken by manufacturers in connection with PVP-Iodine incise drapes or incise drapes alone. Under the Medical Device Alerts one recall of a PVP-Iodine-containing Post-OP dressing, e.g. OpSite Post-OP dressings manufactured by Smith and Nephew, has been identified. The recall was due to open / partially sealed primary pouches and was not related to unknown risks of PVP-Iodine.

In addition, the FDA database MAUDE (www.FDA.com) was searched for adverse events that were reported in connection with incise drapes. 4 hits were identified. 3 cases were not an adverse event report but a customer complaint on malfunction. One case referred to the product Ioban manufactured by 3M and is described as follows:

Event Description

„3m was advised of a patient injury from a law firm on (b) (6) 2010. 3m contacted the hospital to obtain additional information involving patient. The following information was provided to 3m from the hospital risk manager on (b) (6) 2010. Date of surgery was (b) (6) 2008 for a partial thickness rotator cuff tear and no complications were recorded. Risk manager stated a tender, u-shaped area with loss of pigment was noted under the right axilla and discovered in the hospital. Risk manager stated, there was also a small blister on patient's back that was healing. Risk manager stated the doctor suggested to the patient, it may have occurred from a combination of the drape, her skin, the adhesive, or betadine. Doctor sent patient for a plastic consult. Risk manager indicated the notes stated the area was "just medial to the anterior axillary fold" and later stated" right anterior to the anterior axillary fold" there were 2 small areas of full thickness skin loss, one triangular in shape and measuring 2x3cm and the other rectangular in shape and measuring 1. 5x3cm. „

No person experienced a severe adverse event due to this intervention. The event referred to the 3m product which is not impregnated with PVP-Iodine. Therefore, a further conclusion for the

product features of Incifilm Iodine® cannot be drawn from this event. In all 4 cases in the MAUDE database there were no further unknown risks related to incise drapes aids identified.

Pharamaplast has also considered post market clinical follow up studies to identify and investigate residual risks associated with the use of the product in the market to ensure the long term safety and performance of devices after marketing. Following a proper premarket clinical evaluation, the decision to conduct PMCF studies must be based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio. PMCF studies may review issues such as long-term performance and/or safety, the occurrence of clinical events, events specific to defined patient populations, or the performance and/or safety of the device in a more representative population of users and patients.

Pharmaplast already have post market clinical data from 14 different countries outside the EU and around 87,817 sold units. The post market clinical data has come with zero complaints in 2 years. Consequently, Pharmaplast believes that there are no residual risks / questions about safety or performance that can be answered by post market clinical follow up. Therefore Pharmaplast has a strong reason to omit PMCF.

Documentation:
Post market surveillance data Incifilm Iodine - Pharmaplast

9. Risk – Benefit Ratio

PVP-Iodine-impregnated incise drapes such as Incifilm Iodine® have shown to aid patients at risk of infection during general surgery. This was confirmed by the several clinical data provided and evaluated in this report.

The Incifilm Iodine® product line provides continuous antimicrobial activity in surgical procedures where there is concern about bacterial wound contamination from skin flora and is thus is intended for the use in exactly this patient group. Using PVP-Iodine as antimicrobial agent, the products can be considered as suitable for the intended use.

Moreover, the Incifilm Iodine® products have proven biocompatibility, so that the materials used and that are in contact with the patients do not potentially harm the patients and are well tolerated.

The risks associated with the products are mainly due to their antiseptic nature. PVP-Iodine has a long history in antisepsis and has demonstrated clinical benefits in the reduction or prevention of contaminations. PVP-Iodine is biocompatible in low concentrations as used in the Incifilm Iodine® product line.

Furthermore, a search for vigilance data referring to PVP-Iodine-impregnated incise drapes in the databases of the Competent Authorities of the Germany, Switzerland, United Kingdom and USA, did not reveal any serious unknown events for this product category.

Finally, the post market surveillance data collected by the manufacturer, Pharmaplast, showed around 87 thousand units sold in 14 different non EU countries during 2013 and 2014 and there were no complaints from any of the customers.

Summarizing this clinical evaluation has extensively shown that safety and efficacy aspects for the Incifilm Iodine® product line have been sufficiently demonstrated and that the benefits outweigh the possible risks for the patient. A positive benefit – risk ratio has been justified for the product line.

Based on the general literature data and own test data for the product it can be concluded that the Incifilm Iodine® product line is safe and efficient for the intended clinical applications.

10. EXPERT STATEMENT AND SIGNATURE

The literature search and the preparation of the clinical evaluation were performed by Dr Mena Zaki (Pharmaplast QA manager). The work was done independently. Efforts have been made to reflect the current scientific status at the time of writing but it is to be indicated that the herein enclosed information may change during the course of time.

Date: 01.07.2014

Dr Mena Zaki
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Annexes

Annex I CV of Mena Zaki

Annex II Literature References

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