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Povidone-iodine belongs to the group of active pharmaceutical ingredients (API) that are used in finished pharmaceutical products, so-called antiseptics. Preparations containing povidone-iodine are used in acute surgical care for the prevention and control of infections in various indications.

Povidone (polyvinylpyrrolidone, synthesised in a multi-stage process from acetylene [Reppe chemistry]) is a polyvinyl polymer of different chain lengths; it is used as a suspension and dispersion agent and as a vehicle for pharmaceutical products and also as a volume expander.

H.A. and M.V. Shelanski (1956) developed the so-called « iodophors » for medical use as iodine carriers. These polymers, based on povidone, thus prepared the ground for the use of « povidone-iodine » as an antiseptic substance in a broad medical sphere.

How world-shaking this new concept of the iodophors was at that time can be demonstrated by a small excursion into the pharmacopoeia history of iodine:

- 1821: first introduction of iodine into a pharmacopoeia by Francois Magendie,
- 1890: the 6th edition of « Martindale’s Extra Pharmacopoeia » already mentions 30 iodine-containing medicinal formulations,
- 1928: the « Martindale » lists 128 iodine specialities,
- 1956: an international index devoted exclusively to iodine preparations lists no less than 1700 pharmacopoeia mentions, trade names and synonyms (Sweetman 2005)

Povidone-iodine displays a microbicidal activity equal to that of iodine, but it is considerably more skin-friendly (Reaction mechanism of povidone-iodine, page 13). Considered galenically, its solubility in water is much better than elemental iodine.

The pharmaceutical development of povidone-iodine solutions can be divided historically into two generations:

The first generation, which consisted merely of a solution of povidone-iodine together with some excipients in water, was replaced at the beginning of the 1980s by a sophisticated so-called « second generation » system, in which stabilisation with iodate guarantees a defined release of « free iodine » and greater efficacy and stability of the products. This technique is called standardisation (Iodine chemistry and standardisation, page 10).

In addition, such adapted standardisation and stabilisation of non-complex-bound iodine lead to a constant batch consistency and prevent a decrease in microbicidal efficacy during the storage period (shelf life) (Pinter et al. 1984). Povidone-iodine is safer and easier to use than the classic iodine preparations and displays only very low toxicity.
Among the antiseptic and antimicrobial substances, povidone-iodine still occupies its position of lasting importance in everyday human and veterinary medicine. Povidone-iodine products display the broadest spectrum of antimicrobial effect with high clinical efficacy together with extremely low toxicity in clinical practice. The most recent publications, such as e.g. the «Consensus recommendation on the selection of substances for wound antisepsis» (Kramer et al. 2004) underline the excellent clinical benefit-risk profile of these products.

This brochure describes the characteristics and properties of povidone-iodine and of the B. Braun povidone-iodine range, and emphasises some particular features.
History

«It’s elemental: the element iodine»

Below are some historic facts about one of the most interesting chemical elements, which bring the micro-biological and antiseptic iodine carrier (iodophor) to life.

- Of all the elements known so far to be essential for health, iodine is the most misunderstood and the most feared. Yet, it is by far the safest of all the trace elements known to be essential for human health. (Guy E. Abraham, MD, Professor of Obstetrics, Gynecology and Endocrinology at the UCLA School of Medicine).

Iodine is a rare trace element that fulfills essential functions in biological systems e.g. regulation of the thyroid hormone thyroxine (iodine in the human body, page 8). Present in the earth’s crust in minerals and in seawater in certain types of seaweed (especially brown algae of the genus Phaeophyceae, so-called «kelp»), in the order of frequency of occurrence of the approximately 110 chemical elements on earth known to date it occupies position 62.

Iodine has been used in everyday clinical antiseptic practice for more than 150 years, and is used in various pharmaceutical forms e.g. in the treatment of wounds and the prevention of infections.

And even in the pre-Christian era the advanced civilisations of the ancient Greeks and the Chinese knew how to make use of its positive effects without knowing the identity and mechanism of action of this active substance:

The Greek philosopher Theophrastus (approx. 370-288 B.C.), a student of Aristotle and Plato, was one of the first to experiment with plants for medical purposes («the father of botany»). He reported that the use of seaweed, algae and other plants had a pain-relieving effect after sunburn.


It was French scientists who discovered the halogens fluorine, chlorine, bromine and iodine:

The element iodine was discovered in 1811 by the French chemist Bernard Courtois (1777 – 1838) from Dijon. In his father’s company he devoted himself to the production of gunpowder («black powder») for Napoleon’s armies. The oxidising component in black powder is potassium nitrate, also called (potassium) saltpetre («salt from stone»). France was at war at the time, and there was a great demand for saltpetre, which was obtained from French «nitre beds».

For further processing this required sodium carbonate, which was obtained from seaweed from the coasts of Brittany and Normandy. These seaweeds grow under water by approx. 30 cm per day in gigantic «kelp forests». When Courtois wanted to obtain sodium carbonate from the ash of a kelp harvest and treated it with too much sulphuric acid to remove impurities, he observed dark violet to purple-coloured vapours which condensed on his copper vessels and began to attack and corrode them. Courtois noticed that the vapour crystallised on cold surfaces into black-violet crystals, at which he assumed that this behaviour might be that of a new element. With the assistance of the already famous natural scientists Joseph Louis Gay-Lussac (1778 – 1850) and André-Marie Ampère (1775 – 1836) his discovery was confirmed, and was officially reported to the «Imperial Institute of France» in November 1813.

It was the British chemist Humphrey Davy (1778 – 1829) who, building on this preliminary work, reported to the Royal Society of London at the end of 1813 that a new element had been discovered that resembled chlorine, and it was thus later classified in the periodic system of elements drawn up by Dmitri Ivanovitch Mendelejev (1834 – 1907) in 1869 next to this in the main group of the halogens (salt-formers).

On 1st August 1814 Gay-Lussac published this discovery of the new element, confirmed Courtois as the first to have discovered and isolated it, and gave it its name based on the Greek «ioeides» for «coloured violet-blue», which characterises the intense dark violet colour of the crystals and in particular its vapours.
Courtois’ obtaining of iodine from the ash of seaweed was the first isolation of this element from plant material; compared to the iodine content in minerals (10 to 100 mg per 100 g dry mass), seaweed contains 10,000 times the amount, and is therefore a rich source of iodine.

Nevertheless, this source was exhausted in the 18th century and into the 19th century. Today, this method of obtaining iodine is economically clearly inferior to obtaining it from saltpetre: in 2005, Chile, with two thirds of the world’s iodine yield, was the leading producer and exporter, followed by Japan and the USA (British Geological Survey).

In 1895, further studies of the occurrence of iodine in plants and, associated with this, its analytical identification led to the discovery that iodine is an essential trace element – a component of the thyroid gland (iodine in the human body, page 8).

Phylogenetically, thyroid hormones are very old molecules that are synthesised by most multicellular organisms and even by some unicellular organisms, and act on gene transcription and thus on basal metabolic rate: in cases of under-functioning this can fall to 50% of the normal value, in cases of over-functioning it can increase to double.

The bactericidal efficacy of iodine was scientifically described for the first time in 1880 by French microbiologist and parasitologist Casimir Davaine (1812 – 1882), who became known particularly as a result of his work on the causal pathogenicity of the anthrax organism (Bacillus anthracis).

From the 19th century this discovery led to the use of iodine in medicine for antiseptic skin and wound treatment as the so-called iodine «tincture». Iodine «tinctures», e.g. 2% iodine in ethanol were used in traditional medicine until the middle of the 20th century.

In the 1950s the so-called «iodophors» were conceived by H. A. and M. V. Shelanski (1956) for medical use and developed as iodine carriers. These polymers, based on povidone, to which iodine is ionically bound in the form of the $I_3^-$-species, in 1956 opened up the way for the use of «povidone-iodine» as a microbicidal agent in a wide range of indications.

These historic discoveries and developments therefore ultimately led B. Braun to market medicinal products such as Braunol® since 1985.
The physiological role of iodine in the human body is in the synthesis of thyroid hormones by the thyroid gland. The major thyroid hormone secreted by the thyroid gland is T4 (tetra-iodo-thyronine). T4 in circulation is taken up by the cells and is deiodinated enzymatically to convert it into tri-iodo-thyronine (T3), the active form of thyroid hormone. The physiological actions of thyroid hormones can be categorised as 1) growth and development and 2) control of metabolic processes in the body. Thyroid hormones play a major role in the growth and development of the brain and central nervous systems in humans from the 15th week of gestation to the age of 3 years. The other physiological role of thyroid hormone is to control several metabolic processes in the body. These include carbohydrate, fat, protein, vitamin and mineral metabolism. For example, thyroid hormone increases energy production, increases lipolysis, and regulates neoglucogenesis and glycolysis.

The normal daily requirement ranges from 100 to 300 µg, with quantities from 500 µg to 1 mg daily being normally without effect on the thyroid.

Iodine from the diet is absorbed throughout the gastrointestinal tract. Dietary iodine is converted into the iodide ion before it is absorbed. The iodide ion is bioavailable and is absorbed completely from food and water. This is not true for iodine in thyroid hormones ingested for therapeutic purposes. Iodine enters the circulation as plasma inorganic iodide, which is cleared from the circulation by the thyroid and kidney, which excretes iodine with urine. The excretion of iodine in the urine is a good measure of iodine intake. In a normal population with no evidence of clinical iodine deficiency either in the form of endemic goitre or endemic cretinism (iodine deficiency during pregnancy resulting in thyroid hormone deficiency which causes a disturbance in the development of the brain and central nervous system), urinary iodine excretion reflects the average daily iodine requirement. Therefore, for determining the iodine requirements, the important indexes are serum T4 and TSH levels (indicating normal thyroid status) and urinary iodine excretion. (According to FAO/WHO expert consultation 2001).

Certain areas of the world such as South-East Asia or Africa are seriously affected by iodine deficiency, e.g. due to natural deficiency. Globally, 2.2 billion people (38% of the world’s population) live in areas with iodine deficiency (According to International Council for the Control of Iodine Deficiency Disorders).

Toxicity of iodine
Systemic effects
Iodine and iodides have variable effects on the thyroid (see below) and can produce goitre and hypothyroidism as well as hyperthyroidism (Iodine-Basedow-phenomenon). Goitre and hypothyroidism have also occurred in infants born to mothers who had taken iodides during pregnancy.

Acute systemic toxicity may cause shock, tachycardia, fever, metabolic acidosis and renal failure (Sweetman 2005).

Excess iodine can be effectively removed by haemodialysis or peritoneal dialysis (Zamora 1986).

Effects on the thyroid
Although iodine is essential for the production of thyroid hormones, and iodine deficiency may cause very serious effects, excessive quantities can cause hyperthyroidism or, paradoxically, even goitre and hypothyroidism.

If the daily intake progressively exceeds the tolerated doses (>1 mg daily), there is an initial rise in thyroid hormone production, but at still higher doses (>2 mg daily) production is inhibited (Wolff-Chaikoff effect). The effect is normally transient, since the thyroid adapts to the high iodine levels. In certain individuals a lack of adaptation causes a chronic inhibition of thyroid hormone production, leading to goitre and hypothyroidism.
Absorption of iodine from povidone-iodine

Povidone-iodine administered clinically by any route can result in systemic absorption of iodine. When applied cutaneously there is some uptake. It is obvious that the area of the skin treated, the duration of the treatment and the status of the skin are decisive for the absorption. Clinically it has been confirmed in numerous reports that after application on mature skin with intact barrier function, uptake of iodine from povidone-iodine products was found to be very low (Sweetman 2005).

In contrast, when povidone-iodine is administered into the subcutaneous tissue, mouth, gut, bladder, vagina, peritoneal cavity, and mediastinum, there is significant absorption of iodine with elevation of serum protein-bound iodine. Serum levels return to normal in 3 to 7 days if renal function is normal.

Several studies and case reports show that iodine from povidone-iodine is readily absorbed from the burn wound and in cases of wound irrigation with povidone-iodine solutions. Individual cases of extensive iodine absorption from wound dressings soaked in povidone-iodine have also been reported (e.g. Zellner 1985).

On vaginal application, iodine from povidone-iodine is readily absorbed. The iodine load of the mother may be transmitted to the infant either congenitally or by breast-feeding.

In newborns, the barrier function of the skin is reduced. Several investigations were able to demonstrate that in newborns and children up to the age of one year, iodine from povidone-iodine is readily absorbed not only in cases of broken skin but even in cases of intact skin (Lindner 1997).

Potential adverse drug reactions

Generally, povidone-iodine preparations are well tolerated and reports of cutaneous irritation, sensitisation or allergy are rare. Local irritation, itching, and burning are the most common potential adverse effects reported for povidone-iodine. It has also been suggested that the iodine component of the solution is not likely to be the cause for allergies (Kozuka 2002). This indicates that iodine allergy is either actually very rare or does not exist, or that the methodology used in studies examining iodine allergy was flawed.

In the recently published Consensus «Recommendation for wound antisepsis» which was jointly established by an international group of reputed specialists, povidone-iodine is evaluated as «a medicinal product being the best choice for short-term application in cases of wound infections and contaminated traumatic acute wounds» (Kramer et al. 2004).

Repeated application of povidone-iodine to mucous membranes may result in burning sensations (Isenberg 2002). Prolonged exposure of the skin to povidone-iodine results in an irritant effect, which increases over the first 1.5 - 6.5 h of exposure, and may result in skin burns if the solution is trapped on the body or e.g. under a tourniquet and is not allowed to dry (Nahlieli 2001). Occlusive patch testing may give false-positive results due to skin irritation.

When 2.5% povidone-iodine eye drops were used several times a day, occasionally a mild stinging was observed which was not the case with the use of 1.25% povidone-iodine eye drops. Single use of 2.5% povidone-iodine eye drops was well tolerated. In addition to this finding is the observation that in the period from 1994 - 2000 about 8,000 eyes were treated with 0.75% povidone-iodine without the occurrence of any adverse reaction (Jacobi 2000).
Iodine chemistry

Iodine as a chemical element is classified among the halogens, the VII\textsuperscript{th} main group of the periodic system, together with fluorine, chlorine, bromine and astatine.

At room temperature, elemental iodine forms black-violet crystals and tends to « sublimation », i.e. the crystals immediately change their state of aggregation, forming dark violet vapours, which on cooler surfaces can precipitate again in solid form.

The solubility of iodine in water is very low: only 1:3000, but very good in alcohols. In addition to its use in medicine, iodine is used in photography and in the computer and dye industries.

Iodine can be identified very rapidly and clearly with starch, with which it forms a deep blue iodine-starch complex.

In quantitative analysis it is determined by titration with sodium thiosulphate. Sodium thiosulphate is also used to rapidly remove the unpleasant stains caused by iodine; the violet-brown iodine, which has a high Redox potential, is reduced to the colourless iodine species such as iodine I\textsuperscript{-} (Service, page 30).

It has been shown that at least seven iodine subspecies react with each other in aqueous solution within complex equilibriums; however, among these, elemental iodine is the species that displays the highest microbicidal activity (Reaction mechanism of povidone-iodine, page 13).

Additionally, with increasing dilution of aqueous povidone-iodine, more elemental iodine is paradoxically released (up to a maximum dilution of 1:100). This principle was first investigated and described in detail by Professor W. Gottardi from Austria (1985 and 1991). The maximum iodine release is achieved with a 0.1 % povidone-iodine concentration (see Figure 1).

Rackur explained this dilution phenomenon by the formation of polymer aggregates that « store » uncomplexed iodine as in an accumulator (1985). With increasing aqueous dilution, these aggregates dissociate and release the previously « stored » iodine, as a result of which the microbicidal efficacy of the solution is increased.

The combination of the study results of Gottardi (1985 and 2001), Atemnkeng et al. (2006), Atemnkeng and Plaizier-Vercammen (2006) and Rackur (1985) confirm this phenomenon and show that the release of iodine is essential for the microbicidal efficacy of the antiseptic solution as shown figure 2 (Reaction mechanism of povidone-iodine, page 13).
Standardisation of aqueous povidone-iodine solutions

The galenic formulation of an aqueous povidone-iodine solution is one of the key elements for optimal microbicidal efficacy. With so-called «standardisation», it was achieved galenically, i.e. in the particular quality of the formulation, that Braunol® solutions display the following special properties:

- constantly uniform high antimicrobial performance against all micro-organisms, de facto already after 15 sec., «rapid onset of action»
- guarantee of a constant release of elemental «free» iodine, which is the active agent of the povidone-iodine complex, over the entire shelf life
- constant skin-friendly pH value of the solution
- with regard to the mentioned parameters «microbicidia», «free iodine» and «pH» the Braunol® solution exhibits constant stability over the period of storage and thus guarantees batch consistency, one of the most fundamental requirements of a pharmaceutical product.

The effects that the use of non-standardised aqueous povidone-iodine solutions can have are confirmed by reports and a whole series of publications from the USA in the 1980s and 1990s (Berkelman et al. 1981):

A generics manufacturer had unknowingly used contaminated water for the production of povidone-iodine solutions, after which *Pseudomonas cepacia* was identified in certain batches. It was subsequently reported from several hospitals that the use of these improperly produced batches which were released into the market had led to pseudobacteraemias in false-positive blood cultures; in some cases patients were even infected as a result of the disinfection with these povidone-iodine solutions prior to blood samples being taken.

An intensive investigation of these incidents and analysis of the iodine release from the batches in question showed that the content of free, microbicidally acting iodine was only 1 ppm, an amount that was obviously insufficient to counteract any contamination.

<table>
<thead>
<tr>
<th>Test product</th>
<th>Log₁₀ reduction factors at specified time (s)³</th>
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<tbody>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Braunol®</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Unstandardised iso-Betadine®</td>
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<tr>
<td>Standardised Betadine®</td>
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<tr>
<td></td>
<td>1.51</td>
</tr>
<tr>
<td>Standardised Betadine®</td>
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</tbody>
</table>

³Each assay was performed three times.
Properties of povidone-iodine

Stability
In powder form povidone-iodine can be stored without significant loss of iodine. However, the substance should be stored in a dry place protected from light. As a result of this excellent stability of the pharmaceutical substance povidone-iodine, for Braunol®, for example, stability for 3 years can be guaranteed for containers smaller than 500 ml and for 5 years for all larger containers.

pH value
Povidone-iodine is microbicidally active over a pH range of 2.5 to 7.0, with the pH optimum being between 3 and 6.

Fig. 3: Monomer part of proposed povidone-iodine-structure (3-D-model)

Fig. 4: Proposed structure of povidone-iodine (Schenk et al. 1979)
Reaction mechanism of povidone-iodine

The chemistry of iodine is complex, as a large number of reactions are possible. H+ ions have an important influence on various reactions, therefore the adjustment of the pH value is very important for the course of these reactions, including the biocidal activity of the iodine compounds. In aqueous solutions iodine can occur in no less than seven different forms, of which, however, only hydrated molecular iodine (I2), hypoiodic acid (HOI) and iodine ions (I-) have a microbicidal effect (Rackur 1985, Gottardi 1972).

The biocidal effect of iodine is due to its ability to react with various functional groups e.g. –OH (reaction with the phenolic group of amino acid tyrosine), –NH2, (amino acids and nucleotide bases), -SH (amino acid cysteine) and carbon-carbon double bonds of unsaturated fatty acids. This reactive groups have essential functions in the metabolic processes of the target organisms such as bacteria and yeasts (Gottardi 1985). These metabolic processes are interrupted by the binding of iodine and the micro-organisms are thus inactivated.

If polymers, which have the ability to bind iodine and thus possess so-called iodophor properties, are present in a system, the iodine chemistry becomes even more interesting (Iodine chemistry, page 10). In the case of povidone-iodine (also called PVP-iodine) – the active substance in all B. Braun iodine products – the iodophor is poly (N-vinyl-2-pyrrolidone). The difference between conventional iodine solutions and an iodophor is that approx. 99.9% of the iodine is present in complexed form. This effect markedly reduces the disadvantages of elemental iodine, e.g. toxicity and irritation potential, and staining power.

In pharmaceutical formulations such as Braunol® (B. Braun povidone-iodine products, page 17), which contain both iodine and iodide, the microbicidal effect can be attributed almost completely to the properties of the free molecular iodine, which in Braunol® is present in a concentration of > 8 ppm for the entire shelf life of the product (Atemnkeng et al. 2006, Standardisation of aqueous povidone-iodine solutions, page 11).

Iodine is mainly present in the form of tri-iodide, which is in chemical equilibrium with iodide and active iodine. In the povidone-iodine complex the iodine is present in various forms:

- **available iodine** contains all iodine types that can be titrated with sodium thiosulphate.
- **iodide** negatively charged ion; necessary for complexing iodine
- **total iodine** sum of all available iodine species
- **free iodine** responsible for the microbicidal effect of aqueous povidone-iodine solutions. Can be extracted from aqueous povidone-iodine solutions by means of a complicated procedure.

The polymer poly (N-vinyl-2-pyrrolidone), povidone-iodine and all other iodophors alone display no microbicidal activity. The microbicidal properties are due to the release of elemental iodine. The determining factor for the microbicidal effect is not only the concentration of free iodine in the solution, but more importantly the concentration of free iodine at the cell wall – the site of action – of the target organisms. The povidone binds rapidly and firmly to the cell walls and ensures that the actual active substance (free iodine) is transported to the site of action (see illustration).
Comparison of substances

**Chlorhexidine**

**Molecule**
The chlorhexidine molecule is an aromatic cationic biguanide carrying two p-chlorophenol rings. For medical applications the gluconate is mostly used.

**Mechanism of action**
Chlorhexidine develops its antimicrobial effect by adhering to the bacterial cell wall and causing disruption of the cytoplasmic membrane of the bacterial cell. This in turn causes interruption of the respiratory chain and inhibition of the membrane-bound ATP-ase. In higher concentrations lysis of the bacterial cell can even occur.

**Characteristics**
Chlorhexidine is a frequently used antiseptic, above all in dental medicine. Chlorhexidine possesses moderate to high cell toxicity, and when used in the oral cavity yellow discoloration of the teeth can occur. Allergic reactions can be caused by chlorhexidine. A further problem with the antiseptic use of chlorhexidine is the development of resistance.

**Octenidine**

**Molecule**
Octenidine dihydrochloride is a surface-active substance (cation-active bispyridine) that is currently used for antisepsis in combination with 2% phenoxyethanol (no mono-preparation).

**Mechanism of action**
The mechanism of action of octenidine has not yet been clarified completely. It is a surface-active substance, therefore it will adhere to the bacteriell cell wall. The mode of action is probably comparable to that of quaternary ammonium compounds.

**Characteristics**
With use on wounds no absorption is detectable, so that according to the present knowledge risks of toxicity as a result of absorption can be excluded. Not yet fully elucidated is the question of increased cytotoxicity in comparison with the iodophors or polihexanide; its use should therefore be restricted to two weeks. There are good clinical experiences in the initial treatment of grazes, bites and cuts, and with a 1+1 diluted solution on burns. With topical use octenidine can cause a slight burning sensation. Contraindications are irrigations of the abdominal cavity and the urinary bladder, and use on the tympanic membrane.
**Polihexanide**

**Molecule**
The polihexanide molecule (Poly-amino-propyl-biguanide) is an aliphatic cationic biguanide.

**Mechanism of action**
Polihexanide exerts its effect on the cell wall of bacteria through non-specific electrostatic interactions. This mechanism of action is due to the strong basic nature of polihexanide and the distribution of electric charge along the elongated polihexanide molecule. In accordance with the principle of electromagnetic interaction between charge carriers (electrical attraction and repulsion), polihexanide is attracted and attached by other charged substances. If these substances are parts of a biological system, e.g. acidic, negatively charged phospholipids in the cell wall of bacteria, their spatial structure and charge structure are affected by the attachment of polihexanide. A disturbance of the biological system « bacteria » occurs.

**Characteristics**
Compared with povidone-iodine and octenidine, its onset of effect is slower, and is dependent on micro-organism and concentration. On account of its good tissue-compatibility, polihexanide is one of the preferred substances for sensitive and poorly healing chronic wounds, also after initial treatment with the previously mentioned substances. Its good tolerability also permits longer use in lavages and under semi-occlusive and occlusive dressings, e.g. for keeping wounds moist. In addition to possible allergy to the substance, the contraindications are: use on hyaline cartilage and on the peritoneum, in the middle and inner ear, in the eye and in the region of the CNS, and also during the first four months of pregnancy. Later in pregnancy, during the lactation period, on infants and babies, it should be used only if there is a compelling indication. It must not be used in combination with anionic surfactants, soaps, oils or ointments.

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**Comparison of antimicrobial efficacy of different active agents for antiseptics**

<table>
<thead>
<tr>
<th></th>
<th>Bactericidal gram+</th>
<th>Bactericidal gram-</th>
<th>Sporicidal bacterial spores</th>
<th>Tuberculocidal</th>
<th>Leurocidal yeasts</th>
<th>Fungicidal fungi</th>
<th>Virus inactivating enveloped</th>
<th>Virus inactivating non-enveloped</th>
</tr>
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<tr>
<td>Povidone-iodine</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Octenidine dihydrochloride</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Polihexanide</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>

+  = effective  
-  = not effective  
+/−  = partially effective
Povidone-iodine–products

Braunol®
Antiseptic for skin, mucous membrane and wound treatment

Units of sale
30 ml bottle, 100 ml bottle, 200 ml foam bottle, 250 spray bottle, 500 ml bottle, 1000 ml bottle, 5 litre canister

Product description
Aqueous solution for antiseptic skin, mucous membrane and wound treatment and for hygienic and surgical hand disinfection.

Product efficacy & applications*
Antiseptic treatment of mucous membranes
Antiseptic treatment of wounds (e.g. pressure sores, diabetic ulcers), burns, infected and superinfected dermatoses
Antiseptic presurgical treatment of eyes
Antiseptic irrigation, washing, bathing e.g. for wound treatment, perioperative infection prophylaxis (dilutions 1:2 to 1:100)
Skin disinfection of intact skin e.g. preoperatively, before biopsies, injections, punctures, blood sampling and catheterisations
Sebaceous-gland-poor skin within 15 sec (before infections and punctures)
Sebaceous-gland-poor skin within ≥ 60 sec (before punctures of joints, body cavities and hollow organs, and surgical interventions)
Sebaceous-gland-rich skin within 10 min
Hygienic hand disinfection within 60 sec
Surgical hand disinfection within 5 min
Active against bacteria, mycobacteria, fungi, viruses (Rota, HBV, HIV)
Rapid activity against MRSA and CA-MRSA within 15 sec even in a dilution of 1:10
Compatible with most wound dressings except for silver–containing dressings

Ingredients
7.5 g povidone-iodine (0.75 g available iodine, active ingredient) per 100 g; sodium hydrogen phosphate dihydrate, sodium iodate, macrogol lauryl ether 9 EO (Ph. Eur.), sodium hydroxide, purified water

Product properties
| Colour: | brown |
| Odour: | characteristic |
| Density: | app. 1.025 g/cm² |
| pH-value: | app. 5.7 |

Highlights
Brown colour shows already disinfected areas
Very broad spectrum of effect even with diluted product
Rapid onset of effect within 15 sec and lasting effect
Standardised povidone-iodine solution for safe use and effect within a shelf life of 3 years (containers < 500 ml) or 5 years (containers ≥ 500 ml)
Braunoderm®

Skin disinfection

**Product description**

Ready-to-use alcoholic skin disinfectant

**Product efficacy & applications***

Skin disinfection of intact skin e.g. preoperatively, before biopsies, injections, punctures, blood sampling and catheterisations

Sebaceous-gland-poor skin within 15 sec (before infections and punctures)

Sebaceous-gland-poor skin within ≥ 60 sec (before punctures of joints, body cavities and hollow organs, and surgical interventions)

Sebaceous-gland-poor skin within 10 min

Active against bacteria including MRSA, mycobacteria, fungi

Active against enveloped viruses (incl. Vaccinia, HBV, HCV, HIV) and the non-enveloped Polio-virus

Can be supplied coloured and uncoloured

**Ingredients**

50.0 g 2-propanol, 1.0 g povidone-iodine (0.1 g available iodine, active ingredient) per 100 g; buffer, stabiliser, purified water

**Product properties**

Colour: clear, orange-brown (colour added) or brown (no colour added)

Odour: alcoholic

Density: app. 0.910 g/cm³

Flash point: 21 – 22 °C (DIN 51755)

**Highlights**

Combines rapid effectiveness of propan-2-ol with the broad spectrum activity of povidone-iodine

Rapid activity within 15 sec and good sustained effect

Active against MRSA and Polio-virus

Facilitates the perfect adhesion of incision foil

**Units of sale**

250 ml bottle, 250 ml spray bottle,
1000 ml bottle, 5 litre canister
## Product description
Ointment for antiseptic skin and wound treatment

## Product efficacy & applications*
- Antiseptic treatment of damaged skin
- Antiseptic treatment of wounds (e.g. pressure sores, diabetic ulcers), burns, superficial skin wounds
- Antiseptic treatment of infected and super-infected dermatosis
- Active against MRSA
- Compatible with most wound dressings except for silver – containing dressings

## Ingredients
10.0 g povidone-iodine (1.0 g available iodine, active ingredient) per 100 g; macrogol 400, macrogol 4000, purified water, sodium hydrogen carbonate

## Product properties
- Appearance: viscose ointment
- Colour: brown
- Odour: characteristic

## Highlights
- Spreads easily due to soft fluid consistency
- Liquefies at body temperature and facilitates unhindered elimination of wound exudates

### Units of sale
- 20 g tube, 100 g tube, 250 g tube, 250 g pot
Braunovidon® Ointment Gauze

Antiseptic for wound treatment

**Product description**

Impregnated dressing for antiseptic skin and wound treatment

**Product efficacy & applications***

Antiseptic treatment of damaged skin
Antiseptic treatment of wounds (e.g. pressure sores, diabetic ulcers), burns, superficial skin wounds
Antiseptic treatment of infected and super-infected dermatosis
Active against MRSA
Allows application of therapeutically correct amount of active ingredient onto the wound

**Ingredients**

10.0 g povidone-iodine (1.0 g available iodine, active ingredient) per 100 g ointment; macrogol 400, macrogol 4000, purified water, sodium hydrogen carbonate, cotton fabric, white soft paraffin

1 piece of ointment gauze 7.5 x 10 cm contains: 10.5 g ointment
1 piece of ointment gauze 10 x 20 cm contains: 28.0 g ointment

**Product properties**

Appearance: gauze with Braunovidon® ointment
Odour: characteristic

**Highlights**

Spreads easily due to soft fluid consistency
Liquefies at body temperature and facilitates unhindered elimination of wound exudates
Easy & fast application: Combines the advantages of the therapeutically established antiseptic Braunovidon® Ointment with a practical and easy method of application

*The descriptions of the products Braunol®, Braunovidon® and Braunoderm® have been produced on the basis of their German authorisations as medicinal products. Both the product names and the authorised indications can vary from one country to another. For exact information, the country-specific summary of product characteristics should always be consulted.*
## Applications of povidone-iodine

### Range of uses for Braunol®

<table>
<thead>
<tr>
<th>Applications</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Preoperative) skin disinfection</strong></td>
<td>Concentrate</td>
</tr>
<tr>
<td>Surgical and hygienic hand disinfection</td>
<td>Concentrate (pre-heat to body temperature if necessary)</td>
</tr>
<tr>
<td>Disinfection of the patient by washing</td>
<td>1:2 - 1:25 with water</td>
</tr>
<tr>
<td>Whole body disinfection in the bath</td>
<td>1:100 with water, allow to act for 15 min</td>
</tr>
<tr>
<td>Prior to injection, aspiration, blood sampling and catheterisation</td>
<td>Concentrate</td>
</tr>
<tr>
<td>Prior to biopsies, incision and punctures</td>
<td>Concentrate</td>
</tr>
</tbody>
</table>

**Wound and mucous membrane antisepsis**

<table>
<thead>
<tr>
<th>Applications</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound disinfection</td>
<td>Concentrate (pre-heat to body temperature if necessary)</td>
</tr>
<tr>
<td>Mucous membrane antisepsis</td>
<td>Concentrate – 1:10**</td>
</tr>
<tr>
<td>Infected and superinfected dermatoses</td>
<td>Concentrate</td>
</tr>
<tr>
<td>Wound cleansing in cases of increased microbial risk</td>
<td>Concentrate (pre-heat to body temperature if necessary)</td>
</tr>
<tr>
<td>Cleansing of burn wounds</td>
<td>Concentrate for disinfectant wash (pre-heat to body temperature if necessary) then rinse with warm saline solution</td>
</tr>
</tbody>
</table>

* In general, care must be taken to ensure that in pre-operative skin and mucous membrane antisepsis no amounts of liquid accumulate under the patient (pooling). Otherwise when high-frequency devices are used and/or in cases of occlusion of Braunol® burns or skin irritations can occur.

** Dilution with NaCl or Ringer’s solution

### Povidone-iodine solutions are indicated for further clinical uses

<table>
<thead>
<tr>
<th>Povidone-iodine solutions</th>
<th>Usual concentrations</th>
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</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Prevention and treatment of infections of vascular prostheses</td>
<td>1:2** as continuous topical wound irrigation, with fixed irrigation device, concentrate for washing the wound</td>
</tr>
<tr>
<td>Preparation for large bowel operations</td>
<td>1:2** to 1:4** as an enema the night before and on the day of the operation</td>
</tr>
<tr>
<td>Antiseptis for large bowel resections</td>
<td>Concentrate</td>
</tr>
<tr>
<td>Reduction of the risk of postoperative infection</td>
<td>1:10** single irrigation of the surgical wound for 60 seconds</td>
</tr>
<tr>
<td><strong>Gynaecology and obstetrics</strong></td>
<td></td>
</tr>
<tr>
<td>Disinfection of the vagina and vulva prior to surgical and other procedures</td>
<td>1:10**</td>
</tr>
<tr>
<td>Vaginal douches</td>
<td>1:10**</td>
</tr>
<tr>
<td>Antiseptic in cases of premature rupture of the membranes and intensive monitoring sub partu</td>
<td>1:20** as intrauterine catheter irrigation at 20 ml/hour</td>
</tr>
</tbody>
</table>
Povidone-iodine solutions are indicated for further clinical uses

<table>
<thead>
<tr>
<th></th>
<th>Usual concentrations</th>
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</thead>
<tbody>
<tr>
<td><strong>Urology</strong></td>
<td></td>
</tr>
<tr>
<td>Hospital prophylaxis and before examinations</td>
<td>1: 20** (as Irrigation Solution)</td>
</tr>
<tr>
<td>Catheter drainage</td>
<td>Concentrate for external use, 1:10* to 1:100* for irrigation</td>
</tr>
<tr>
<td><strong>Orthopaedics</strong></td>
<td></td>
</tr>
<tr>
<td>Irrigation of surgical wounds</td>
<td>1: 20** for irrigating wounds using 3-4 litres solution</td>
</tr>
<tr>
<td>Disinfection of open fractures</td>
<td>1:10** as irrigation drainage</td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment of viral conditions (<em>keratoconjunctivitis epidemica</em>)</td>
<td>1: 3 – 1: 6***</td>
</tr>
<tr>
<td>Credé’s prophylaxis (<em>Ophthalmia neonatorum</em>)</td>
<td>1: 3 – 1: 6***</td>
</tr>
<tr>
<td>Preoperative periocular disinfection</td>
<td>1: 3 – 1: 6***</td>
</tr>
<tr>
<td>Preoperative ocular antisepsis</td>
<td>1: 3 – 1: 6***</td>
</tr>
<tr>
<td>Post-exposure prophylaxis in case of HIV</td>
<td>1: 3 – 1: 6***</td>
</tr>
<tr>
<td>Eye rinse after accidental contamination</td>
<td>1: 1, 5</td>
</tr>
<tr>
<td><strong>ORL (Otorhinolaryngology)</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic suppurative Otitis Media</td>
<td>1: 1, 5</td>
</tr>
<tr>
<td><strong>Dental and maxillo–facial surgery</strong></td>
<td>1:10**</td>
</tr>
<tr>
<td>Wound rinsing in cases of inflammation and after extractions</td>
<td>1:10**</td>
</tr>
</tbody>
</table>

* In general, care must be taken to ensure that in pre-operative skin and mucous membrane antisepsis no amounts of liquid accumulate under the patient (pools oring). Otherwise when high-frequency devices are used and/or in cases of occlusion of Braunol® burns or skin irritations can occur.

** Dilution with NaCl or Ringer’s solution

*** Dilution with BSS-Buffer
Interval antisepsis with Braunol®/Prontosan®

Initial cleansing of the wound
- In cases of obvious infection or heavy contamination with an increased risk of infection ➔ antiseptic treatment with Braunol® (wound dressing with e.g. Prontosan® Wound Gel and/or Askina® products)
- With no signs of infection and in cases of (moderate) contamination ➔ cleansing and conditioning of the wound by irrigating with Prontosan® Wound Irrigation Solution (wound dressing with e.g. Prontosan® Wound Gel and/or Askina® products)

Treatment of the wound after the 1st dressing change
- In cases of persistent or progressive infection ➔ antiseptic treatment with Braunol® (wound dressing with e.g. Prontosan® Wound Gel and/or Askina® products)
- With no signs of infection ➔ cleaning and conditioning of the wound by irrigating with Prontosan® Wound Irrigation Solution (wound dressing with e.g. Prontosan® Wound Gel and/or Askina® products)
- In general the following applies: wound inspection daily in cases of persisting signs of infection!

Continuation of the wound treatment in cases of regressive infection
1st day: Antiseptic treatment of the wound with Braunol® and wound dressing with Prontosan® Wound Gel
2nd–3rd day: Cleansing of the wound by irrigating with Prontosan® Wound Irrigation Solution, wound dressing with Prontosan® Wound Gel
4th day: Antiseptic treatment of the wound with Braunol® in cases of residual signs of infection (wound dressing with Prontosan® Wound Gel)

Subsequent days: When the infection has completely settled down: cleaning with Prontosan® Wound Irrigation Solution. Further applications of Braunol® only in cases of residual signs of infection (every 3 days).

It must be noted that a wound infection must be treated with antibiotics as soon as there is the danger of a systemic infection, e.g. bacteraemia. This is particularly advisable in cases of deep acute wounds, third-degree burns, and as standard therapy following surgical interventions. The topical use of antiseptic solutions is an important supportive measure in the treatment of an infected wound, and is crucial for optimal healing.

Due to a potential tissue toxicity, the use of Braunol® should be restricted to the treatment period during which there are clinically manifest signs of infection.
The role of povidone-iodine in wound healing

There are many criteria showing that povidone-iodine-products like Braunol® are «The Gold Standard» antiseptic for wound treatment:

Antiseptic properties
- There is almost a universal agreement in literature that the overall antibacterial activity of povidone-iodine is superior to compared to other antiseptics (Selvaggi 2003)
- Povidone-iodine can show high antibacterial activity in only 30 or even 15 seconds after application (Kunisada 1997)
- In current studies aqueous povidone-iodine-solutions achieved a total eradication aqeous against MRSA strains compared to chlorhexidine achieving only 9% of eradication success (McLure 1992)

Effect on the wound healing
- Recent studies revealed that time to healing was significantly reduced by 2-9 weeks in povidone-iodine-treated ulcers but it only showed a trend of reduction without reaching significance in the silver-sulfadiazine and chlorhexidine-digluconate-treated ulcers due to following factors (e.g. Fumal 2002):
  - Stimulation of macrophages and cytokines
  - Growth factor stimulation results in collagen synthesis
  - Enhancement of angiogenesis
  - Beneficial toxicity since ulcer beds contain too many vessels, senescent fibroblasts, macrophages, moderate cytotoxicity might somewhat regulate such an excess
- In addition it was shown that povidone-iodine-products inhibit the excessive levels of matrix metalloproteases accumulation in chronic wounds (Eming 2006)

Resistance
- Absence of acquired resistance after a long-term use of povidone-iodine is already confirmed (Lanker Klossner 1997)
- A few works report the resistance of MRSA to iodine formulations, but these studies considered very specific situations such as very long conservation period and unusual storage temperature, no in-vivo test was used (e.g. Shirashi 1997)

Conclusion
- Newer formulations of iodine such as Braunol® with povidone-iodine show the same clinical efficacy with avoiding the problem of toxicity
- In most of the studies, it proved to be superior to other antiseptics in assessments of antimicrobial performance against MRSA, fungi and viruses, being the favourite antiseptic to eradicate spores
When conjunctivitis occurs in babies younger than 4 weeks old, it is called neonatal conjunctivitis or ophthalmia neonatorum. Newborns are also susceptible to infectious conjunctivitis, which can be serious. The sexually transmitted bacteria Chlamydia trachomatis and Neisseria gonorrhoeae can pass from an infected mother’s birth canal into her baby’s eyes during delivery. These bacteria can cause symptoms of conjunctivitis in babies within the first 2 weeks of life, and can lead to serious eye damage. Less commonly, the viruses that cause genital and oral herpes can similarly be passed to an infant at the time of delivery and may also damage the eyes.

In 1881 the German gynaecologist Karl Sigmund Franz Credé introduced the use of 2% silver nitrate eye drops for the prophylaxis of ophthalmia neonatorum, so-called Credé’s prophylaxis. Because of the high success, this procedure became mandatory in many countries. However, because of the potential of silver nitrate to cause chemical conjunctivitis – even at a concentration of a 1% solution – and also having no effect on Chlamydia trachomatis, the use of silver nitrate in the prevention of ophthalmia neonatorum has been questionable.

Several countries experienced a rise in the incidence of ophthalmia neonatorum when the prophylaxis was discontinued. Therefore prevention is still recommended.

Many studies have been conducted to find a replacement for silver nitrate. Isenberg et al. (1995) conducted a study in Kenya comparing silver nitrate, erythromycin and povidone-iodine (2.5%). The study demonstrated that with the application of povidone-iodine (13.1%) the incidence of infectious conjunctivitis has been lower than with the administration of erythromycin (15.2%) or silver nitrate (17.5%). The study investigators also compared the incidence of non-infectious conjunctivitis resulting as a toxic reaction from the application of the agents used. Silver nitrate showed the highest rate of incidence (13.9%), followed by erythromycin (13.3%). Povidone-iodine demonstrated a significantly lower incidence of non-infectious conjunctivitis (9%).

The increasing development of resistance to antibiotics hindered the worldwide introduction of antibiotic prophylaxis. Due to this fact, antiseptics are the preferred agents in the prevention of ophthalmia neonatorum. However, chlorhexidine is contraindicated since it may cause irreversible damage to the cornea. Polihexanide is well tolerated but it needs at least 5 minutes to take effect. Since povidone-iodine shows efficacy against bacteria, C. trachomatis, and viruses within 30 s and is well tolerated in the eye without the risk of inducing drug resistance, 1.25% povidone-iodine can be considered as the treatment of choice for Credé’s prophylaxis (Assadian et al. 2002).

In a different study, Kramer et al. (2006) have shown that no influence of povidone-iodine on thyroid function of newborns was observed. After application of 1.25% povidone-iodine eye drops, both urinary iodine excretion and TSH (Thyroid Stimulating Hormone) in newborns remained in the physiological range.

The safe use was confirmed in a further investigation on 50 newborns who were treated with 2.5% povidone-iodine eye drops for Crede’s prophylaxis. No significant differences (p = 0.09) in TSH were found compared to controls (Zbojan et al. 2004).
Preoperative eye disinfection with the use of povidone-iodine
Numerous agents are used as a disinfectant in ocular surgery. Due to its ocular tolerance as well as high antimicrobial efficacy, povidone-iodine is established as the standard for preoperative eye antisepsis (Kramer et al. 2006). Povidone-iodine reduces the incidence of postoperative endophthalmitis when used as a topical antiseptic e.g. in cataract surgery, corneal transplant surgery or glaucoma surgery. It is clearly more effective and efficient than local antibiotics or silver nitrate. As mentioned above, povidone-iodine has a broad antimicrobial spectrum without the risk of the development of resistance. At concentrations of 1.25 % and 2.5 % it is well tolerated and does not show any systemic resorption.

Povidone-iodine: treatment of septic arthritis
Bacteria may invade joints, trigger an inflammatory response and thus cause septic arthritis. The most common route of the spread of bacteria causing septic arthritis is haematogenous. Other routes include trauma or inoculation such as during injections. The knee is the most commonly involved joint, accounting for about 50% of the cases.

The acute form of septic arthritis is usually caused by bacteria, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, group B *Streptococci*, or *Gonococci* (which cause gonorrhoea). Sometimes the micro-organisms that cause AIDS, hepatitis B, mumps, or rubella can move into and infect a joint. Chronic septic arthritis is more rare and tends to be caused by micro-organisms such as *Mycobacterium tuberculosis* and *Candida albicans*.

On entering the joint space, the bacteria initially deposit in the synovial membrane and produce an inflammatory reaction, usually with synovial cells, which readily spill into the synovial fluid. Synovial membrane hyperplasia develops in 5 to 7 days, and the release of cytokines leads to hydrolysis of proteoglycans and collagen, cartilage destruction, and eventually bone loss. To prevent contamination after trauma or for treatment of bacterial joint infection both drainage of the joint and application of antimicrobial drugs topically and systemically should be carried out as early as possible.

However, the adverse effect of topically applied antiseptics should be taken into consideration.

Müller and Kramer (2005, and according to Kramer et al. 2002) conducted an in-vitro study to determine the effective concentration of antiseptics required for killing the bacteria in the presence of articular cartilage and to assess the biochemical response of chondrocytes to this treatment. Bovine sesamoid bones from the metacarpophalangeal joint have been used for this investigation to demonstrate the effect of various antiseptics (povidone-iodine, octenidine, PHMB) on the metabolism of chondrocytes.

It was determined that 0.5% povidone-iodine, 0.005% PHMB and 0.005% octenidine were effective in killing the bacteria *Staphylococcus aureus*, and *Escherichia coli* in the presence of articular cartilage.

The inhibiting and stimulating effects of the tested antiseptics on cartilage metabolism were determined by $^{35}$S-sulphate incorporation newly synthesised proteoglycans.

Under the influence of octenidine and PHMB, the $^{35}$S-sulphate incorporation was reduced, showing the inhibition of proteoglycan synthesis. The incorporation rate of $^{35}$S-sulphate in cartilage after octenidine application was reduced more strongly than for PHMB.

In contrast, this study showed that povidone-iodine (dilution 1:10, 1:20) did not produce any negative effect in cartilage. Moreover, there was a stimulation of $^{35}$S-sulphate incorporation by 10-20%, which reflects a stimulation of proteoglycan synthesis. An additional study investigating authentic Braunol® using the same approach revealed comparable results for Braunol® alike, i.e. 1:10 and 1:20 dilution (Müller and Kramer 2007, unpublished).

Povidone-iodine is an excellent alternative for the antiseptic treatment of septic arthritis. Low concentrations of povidone-iodine (< 1 %) and short incubation times (< 30 min) have no damaging influence on chondrocytes.
1. Why are only 50% propan-2-ol in Braunoderm® as competitor are using 70% ethanol. Is not 70% in the minimum concentration to have an antimicrobial effect? Why does Braunoderm® contains only 1% povidone-iodine?

The efficacy of Braunoderm® is proven by independent expert reports in line with harmonized European test methods or standard test methods of the German Society of Hygiene and Microbiology.

The optimum working concentration for alcohols against bacteria are (source: Kramer et al. Krankenhaus- und Praxis-hygiene, Urban & Fischer Verlag 2001, page 222):

- 42% (v/v) propan-1-ol
- 60% (v/v) propan-2-ol = 52,3% (w/w)
- 77% (v/v) ethanol

The efficacy against bacteria is decreasing from top to down. The activity against viruses of ethanol 80% is superior to the one of propan-2-ol 60%. However, since Braunoderm® is a special galenic formulation which was targeted towards a synergistic combination of both active ingredients, povidone–iodine AND propan-2-ol, its purpose was to fulfill the demands of the clinical user:

- Full antimicrobial activity against bacteria, fungi, viruses, spores at a very short exposure time
- Reduced amount of alcohol (occupational health and safety)
- Optimised dermal tolerability of alcohol

Dermal tolerability of propan-2-ol is known to be better than that of ethanol. Therefore it is commonly used in cosmetics. Furthermore, the fact that propan-2-ol is less effective against viruses than ethanol is fully compensated by the addition of povidone-iodine which extends the efficacy spectrum against viruses.

Braunoderm® is a product with a synergistic effect of the active ingredients propan-2-ol, and povidone-iodine. Therefore, a lower alcohol, and povidone-iodine content is needed to reach the efficacy which are presented in our expert reports.

2. How can Braunol® be diluted for preoperative ocular antisepsis?

Braunol® can be used for preoperative ocular antisepsis (e.g. cataracts) in a BSS buffer in 1:3 – or 1:6 – dilution (1:3 means 1 part Braunol® plus 2 parts of BSS – buffer / 1:6 means 1 part of Braunol® plus 5 parts of BSS – buffer).

3. For how long can a diluted Braunol® solution be used?

Braunol® has been studied in dilutions with a 0.9% NaCl-solution of 1:2 to 1:100 regarding its stability, and a shelf-life of up to 4 weeks has been noted after the preparation of the respective dilution (stability parameters: iodine content and pH value, at normal room temperature).

4. Does an incompatibility exist between povidone–iodine products and hydrocolloids?

B. Braun’s povidone–iodine containing products are medicinal products (registered drugs). For that reason they shall only be used for the registered indications given on the instructions for use. The typical indication for the use of povidone-iodine medicinal products (especially povidone-iodine ointments) in wound treatment is an infected wound.

Hydrocolloids are a type of dressing containing gel-forming agents, such as sodium carboxymethylcellulose (NaCMC) and gelatine combined usually with a polyurethane film.

Because they are occlusive, hydrocolloid dressings do not allow oxygen into the wound therefore such dressings are not suitable in the treatment of infected wounds.

If povidone–iodine containing medicinal products are in use, the frequency of changing the wound dressing should be per minimum once daily whereas hydrocolloid dressings can be left on the wound for up to 4-5 days.

In conclusion, both products are normally not used at the same time because hydrocolloids are not suitable for infected wounds and too expensive for a daily renewal of the wound dressing.
In case if aqueous povidone-iodine solutions are used for wound irrigation prior to the application of a hydrocolloid we expect no reaction but in lack of clinical data we avoid giving recommendations.

5. What is the difference between Braunol® with 7.5% povidone-iodine compared to that with 10% povidone-iodine? Why is Braunol® at least as good in general as the 10% povidone-iodine formulation?

The terminus «standardised aqueous povidone-iodine-solution» describes the special galenic profile of this formulation which means that it assures a consistently released free iodine level over the whole time of the given shelf life - therefore also guaranteeing in parallel that a potentially conceivable exogeneous contamination in the hospital (after the first opening of the container) could be adequately counter-acted by a sufficient level of the active principle «free iodine». From the eighties and nineties several publications are available describing «non-standardised» povidone-iodine preparations in the US that led, by accidental exogenous contamination with a certain type of Pseudomonas (Ps. cepacia), to either false-positive laboratory results by contaminating screening tools or by actually infecting patients by these germs - an analysis performed afterwards showed that free iodine levels in these preparations to be only around 1 ppm (Berkelman et al. 1981).

The key message in the publication by Atemnkeng et al. (2006) is that Braunol® meets all the criteria given for a safe and efficacious formulation with consistently high quality performance over the time of shelf life.

This has been proven by two different and independent approaches:

- by a physico-chemical approach (work of Prof. Jacqueline Plaizier-Vercammen, Free University of Brussels): the free iodine level is highest for Braunol® followed in ranking by the standardised Betadine® and the non-standardised Betadine® the latter with the lowest values;

- by a microbiological approach (Prof. Anette Schuermans, Catholic University of Leuven): it could be shown that the above physico-chemical observation can readily be «translated» into a microbiologically quantifiable behaviour of the three tested povidone-iodine solutions as to their microbicidal activity on the germ S. aureus which was unexpected:

Braunol® reveals a very rapid onset in action after already 15 sec., whereas the two other formulations do develop their activity (log reduction factors in table 1, page 11) «only» after 60 sec. and even then the un-standardised formulation achieved log. red. factors only below 5.

Although these results might be considered as being of «relative» relevance to the clinical practise they clearly show that Braunol® is absolutely at least comparable to our competitors’ products and even show in the given context additional advantages concerning efficacy and safety of its use.

6. Are figures available on the allergy rate of Braunol® and povidone-iodine?

No, because povidone-iodine has an extremely low if any allergenic potential, which is based on the chemical reactivity and the redox potential of iodine; the reductive degradation is rapid. Povidone as such, the iodine carrier, does not display any allergenic properties according to our knowledge.

7. How long after first opening Braunol® can be used?

Braunol® is usable up to the expiration date printed on the label, if the bottle is immediately closed after application of solution, is stored at ambient temperature, and handled under controlled hygienic conditions.
Decolourisation of stains

As part of its application technology service, B. Braun answers questions about avoiding stains on clothing, bed-linen and floor coverings caused by drops of iodine-containing skin and mucous membrane antiseptics. Iodine stains on clothing and bed-linen are removed without trace after a single wash in a household washing machine using a standard washing program including a cold pre-rinse.

Coloured skin antiseptics are indispensable for marking the operating field. Coloured alcoholic skin disinfectants spilled on the floor must be cleaned up immediately, otherwise the colouring agent can penetrate into plastic floor coverings and then cannot be removed.

The povidone-iodine stain remover contains sodium thiosulphate, which in a chemical redox-reaction converts brown elemental iodine into colourless iodide.

This reaction can only guarantee complete decolourisation on fresh, still damp patches. If the elemental iodine has migrated into the material (floor covering or medical inventory), the thiosulphate cannot reach it and a visible stain will remain, although it may slowly bleach as a result of e.g. strong sunlight.

Therefore, after the soiling of e.g. floors or medical inventory with the povidone-iodine products, the stains should be decoloured immediately with the povidone stain remover.
Maintenance of surgical instruments

Surgical instruments, bowls, and kidney dishes that come into contact with povidone-iodine-containing solutions during the operation or on the ward must be wiped with e.g. a cotton-wool swab before being put aside, i.e. before being sent for reprocessing. Otherwise, if the solutions dry on, the iodine may corrode even high-quality surgical steel. The feared pitting occurs.

The measures described above for the maintenance of surgical instruments also apply for infusion and irrigation solutions containing chloride, such as e.g. physiological saline solution or Ringer’s solution. Body fluids such as blood can also be a source of chloride.

Epicutaneous test kits

Allergic reactions caused by the use of antiseptics can never be completely excluded. In cases of suspicion that the used B. Braun antiseptic may have led to a toxic-irritative or allergic reaction, the company offers a epicutaneous test kit. This test kit is provided to dermatologists/allergologists. It contains all components of the antiseptic in dermatologically appropriate concentration for a patch test to give evidence if the suspicion is confirmed or not.


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Braunol®

Wirkstoff: Povidon-Iod

Zusammensetzung:
100 g Lösung enthalten:
7,5 g Povidon-Iod, mittleres Molekulargewicht 40 000,
mit einem Gehalt von 10% verfügbarem Iod.
Sonstige Bestandteile:
Natriumdihydrogenphosphat-Dihydrat, Natriumiodat, Macrogollaureth 9 EO
(Ph. Eur.), Natriumhydroxid, gereinigtes Wasser.

Anwendungsgebiete:
Zur einmaligen Anwendung:
Desinfektion der intakten äußeren Haut oder Antiseptik der Schleimhaut wie
z. B. vor Operationen, Biopsien, Injektionen, Punktionen, Blutentnahmen und
Blasenkatheterisierungen.

Zur wiederholten, zeitlich begrenzten Anwendung:
Antiseptische Wundbehandlung (z. B. Druckgeschwüre, Unterschenkelgeschwüre),
Verbrennungen, infizierte und superinfizierte Hauterkrankungen.

Hygienische und chirurgische Händedesinfektion.

Gegenanzeigen:
Braunol® darf nicht angewendet werden bei:
- Überempfindlichkeit gegenüber Iod oder einen anderen Bestandteil des Arznei-
mittels.
- Hyperthyreose oder einer anderen manifesten Schilddrüsenerkrankung,
- Dermatitis herpetiformis Duhring,
- Planung oder Durchführung einer Radioiodtherapie (bis zum Abschluss der
Behandlung),

Nebenwirkungen
In sehr seltenen Fällen können Überempfindlichkeitsreaktionen der Haut auftre-
ten, z. B. kontaktallergische Reaktionen vom Spättyp, die sich in Form von Jucken,
Rötung, Bläschen o. ä. äußern können. Sehr selten wurde über eine Beteiligung
anderer Organe berichtet.
Eine nennenswerte Iodaufnahme kann bei längerfristiger Anwendung von
Braunol® auf ausgedehnten Wund- und Verbranungsflächen erfolgen. Sehr
selten können Patienten mit Schilddrüsenerkrankungen in der Vorgeschichte eine
Schilddrüsenüberfunktion (iodinduzierte Hyperthyreose), zum Teil mit Symptomen
wie z. B. Pulbeschleunigung oder innere Unruhe, entwickeln.
Nach Anwendung größerer Mengen von Povidon-Iod-haltigen Arzneimitteln
(z. B. bei der Verbranungsbehandlung) ist das Auftreten von (zusätzlichen)
Elektrolyt- und Serumosmolaritäts-Störungen, einer Beeinträchtigung der
Nierenfunktion sowie Übersäuerung des Blutes (metabolische Azidose) beschrie-
ben worden.

Stand der Information:
Oktober 2009

Pharmazeutischer Unternehmer:
B. Braun Melsungen AG
34209 Melsungen
Braunoderm® / Braunoderm® nachgefärbt

Zusammensetzung:
100 g Lösung enthalten:

Wirkstoffe:
2-Propanol (Ph. Eur.) 50,0 g, Povidon-Iod mit 10% verfügbarem Iod (mittleres Molekulargewicht von Povidon etwa 40.000) 1,0 g

Sonstige Bestandteile:
Gereinigtes Wasser, Kaliumiodid (0,4 g, Stabilisator), Natriumdihydrogenphosphat (Braunoderm® nachgefärbt zusätzlich: Farbstoffe E 110, E 124, E 151)

Anwendungsgebiete:
Zur Desinfektion der Haut vor operativen Eingriffen, Injektionen, Punktionen, Katheterisierungen, Blutentnahmen, Impfungen.

Gegenanzeigen:
- Hyperthyreose oder eine andere manifeste Schilddrüsenerkrankung,
- Dermatitis herpetiformis Duhring,
- Planung oder Durchführung einer Radioiodtherapie (bis zum Abschluss der Behandlung),
- Überempfindlichkeit gegenüber Iod, 2-Propanol oder einen anderen Bestandteil des Arzneimittels.

Warnhinweise:
Entzündlich.
Behälter dicht geschlossen halten.
Von Zündquellen fernhalten. - Nicht rauchen!
Nicht in die Augen bringen. Nicht auf verletzter Haut oder auf Schleimhäuten anwenden.
Nur zur äußerlichen Anwendung.
21-22 °C Flammpunkt nach DIN 51755.

Nebenwirkungen:
Sehr selten können Überempfindlichkeitsreaktionen der Haut, z.B. kontaktallergische Reaktionen vom Spättyp auftreten, die sich in Form von Jucken, Rötung, Bläschen o.ä. äußern können. In Einzelfällen wurde über eine Beteiligung anderer Organe berichtet.
Gelegentlich können lokale, alkoholbedingte Austrocknungs- und Reizerscheinungen der Haut (Rötung, Spannung, Juckreiz) auftreten.

Stand der Information:
Oktober 2008

Pharmazeutischer Unternehmer:
B. Braun Melsungen AG
D-34209 Melsungen
Braunovidon® Salbe

**Wirkstoff:** Povidon-Iod

**Zusammensetzung:**
100 g Salbe enthalten:
10 g Povidon-Iod mit 10% verfügbarem Iod (PVP mittl. Mw 40 000)
Sonstige Bestandteile:
Macrogol 400, Macrogol 4000, gereinigtes Wasser, Natriumhydrogencarbonat

**Anwendungsgebiete:**
Zur wiederholten, zeitlich begrenzten Anwendung als Antiseptikum bei geschädigter Haut, wie z.B. Decubitus (Druckgeschwür), Ulcus cruris (Unterschenkelgeschwür), oberflächlichen Wunden und Verbrennungen, infizierten und superinfizierten Dermatosen (Hauterkrankungen).

**Gegenanzeigen:**
Braunovidon® Salbe darf nicht angewendet werden
- bei Schilddrüserkrankungen
- bei Überempfindlichkeit gegen Iod (Iodallergie) oder andere Inhaltsstoffe
- bei Dermatitis herpetiformis Duhring (seltene Hauterkrankung mit Brennen, Juckreiz und verschiedenartigen Hauterscheinungen, vor allem an Armen, Beinen, Schultern und Gesäß)
- bei einer Behandlung mit radioaktivem Iod (Radioiodtherapie)
- bei Neugeborenen und Säuglingen bis zum Alter von 6 Monaten


**Nebenwirkungen**
Bei längerer Behandlung kann eine Störung der Wundheilung sowie vorübergehend Schmerzen, Brennen und Wärmegefühl auftreten.
In Einzelfällen kann es zu Überempfindlichkeitsreaktionen gegen Iod (Iodallergie) kommen.
Bei Patienten mit Schilddrüserkrankungen soll regelmäßig eine Überwachung der Schilddrüsenfunktion erfolgen, wenn Braunovidon® Salbe grossflächig oder oft, besonders auf geschädigter Haut, angewendet wird.

**Stand der Information:**
November 2009

**Pharmazeutischer Unternehmer:**
B. Braun Melsungen AG
34209 Melsungen
Braunovidon® Salbengaze

Wirkstoff: Povidon-Iod

Zusammensetzung:
1 Abschnitt Salbengaze enthält:
Arzneilich wirksame Bestandteile:

<table>
<thead>
<tr>
<th>Abmessung</th>
<th>Menge aufgetragener Salbe</th>
<th>Povidon-Iod mit 10% verfügbarem Iod (PVP mittl. Mw 40 000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7,5 x 10 cm</td>
<td>10,5 g</td>
<td>1,05 g</td>
</tr>
<tr>
<td>10 x 20 cm</td>
<td>28,0 g</td>
<td>2,8 g</td>
</tr>
</tbody>
</table>

Sonstige Bestandteile:
Macrogol 400, Macrogol 4000, gereinigtes Wasser, Natriumhydrogencarbonat, Baumwollgewirke, Weißes Vaselin

Anwendungsgebiete:
Zur wiederholten, zeitlich begrenzten Anwendung als Antiseptikum bei geschädigter Haut, wie z.B. Decubitus (Druckgeschwür), Ulcus cruris (Unterschenkelgeschwür), oberflächlichen Wunden und Ver-brennungen, infizierten und superinfizierten Hauterkrankungen.

Gegenanzeigen:
Braunovidon® Salbengaze darf nicht angewendet werden
- bei Schilddrüsenerkrankungen
- bei Überempfindlichkeit gegen Iod (Iodallergie) oder andere Inhaltsstoffe
- bei Dermatitis herpetiformis Duhring (seltene Hauterkrankung mit Brennen, Juckreiz und verschiedenartigen Hauterscheinungen, vor allem an Armen, Beinen, Schultern und Gesäß)
- bei einer Behandlung mit radioaktivem Iod (Radioiodtherapie)
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Nebenwirkungen:
Bei längerer Behandlung kann eine Störung der Wundheilung sowie vorübergehend Schmerzen, Brennen und Wärmegefühl auftreten.
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Bei Patienten mit Schilddrüsenerkrankungen soll regelmässig eine Überwachung der Schilddrüsen-funktion erfolgen, wenn Braunovidon® Salbengaze großflächig oder oft, besonders auf geschädigter Haut, angewendet wird.

Stand der Information:
September 2008

Pharmazeutischer Unternehmer:
B. Braun Melsungen AG
D-34209 Melsungen