SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Betadine Topical Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Povidone-iodine 2.5 %

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dry Powder Spray

Spray for application on skin.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

As antiseptic for prevention and treatment of infections associated with burns, cuts, and scrapes, and for preventive treatment of wounds at risk of infection, e.g., after placement of a suture for wound treatment or after surgery.

4.2. Posology and Method of Administration

Posology

Dosage will depend on the size of the site to be treated.
Apply spray once to several times daily to site to be treated until it is visibly covered with the golden-brown PVP iodine powder.
Upon discoloration of the Betadine Topical Spray an additional dose is required.

Method of Administration

- Betadine Topical Spray is intended for external use (use on the skin and application on the wound).

Betadine Topical Spray forms a dry film on the treated area and can be easily washed off.

Shake spray can vigorously before use, hold upright when using and spray on site to be treated at a distance of 15 cm. The propellant gas will vanish immediately, and the cold sensation experienced upon application will disappear rapidly.

If needed, the treated area may be bandaged.

Duration of Use
The use of Betadine Topical Spray is to be continued for as long as signs of infection or a substantial risk of infection persist. If the infection recurs after treatment with Betadine Topical Spray has been stopped, treatment can be resumed again at any time.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Thyroid dysfunction.
- Duhring's dermatitis herpetiformis.
- Before and after radioiodine therapy (until treatment has been completed).
- Before or during radioiodine scintigraphy or radioiodine therapy of thyroid carcinoma due to the competitive uptake of iodine. After radioiodine scintigraphy or radioiodine therapy an appropriate interval of at least 1-2 weeks should be observed between the last povidone-iodine exposure and the treatments (see section 4.5).

- Mercury-containing preparations must not be used concomitantly with povidone-iodine containing medicinal products as this may result in the formation of a skin-damaging substance. (see section 4.5).
- Children younger than 1 year of age.

4.4. Special Warnings and Precautions for Use

The occurrence of electrolyte and serum osmolality disturbances and the associated impairment of renal function or metabolic acidosis may be favored during large-scale burn treatment with povidone-iodine (see section 4.8).

Special caution is indicated in pregnant and breast-feeding patients. In such cases an appropriate risk-benefit assessment should be done and povidone-iodine should only be administered, if definitely needed (see section 4.6).

Because of the risk of subsequent hyperthyroidism prolonged use of Betadine Topical Spray (for more than 14 days) or extensive use on large surfaces (more than 10% of body surface) in patients with latent thyroid function disorders (especially elderly patients), those with goiter or thyroid nodules and patients following thyroid disorders should only be considered after carefully weighing the expected benefits against the potential risks. Even after the end of treatment (up to 3 months) these patients are to be appropriately monitored for early symptoms of possible hyperthyroidism and thyroid function should be monitored as needed.

Flammable! Keep away from heat, hot surfaces, sparks, and open fire.

Caution, do not inhale the spray and do not spray into eyes or on areas around eyes. The propellant gases are combustible. As the spray mist is inflammable,

caution is required for use in the vicinity of open fire. Electrocautery should only be used after spray mist has completely vanished.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Use of Betadine Topical Spray together with taurolidine should be avoided, as taurolidine may be converted to formic acid, which causes intensive burning.

Preparations containing mercury should not be used concomitantly with povidone-iodine-containing medications because of the risk of formation of a potentially skin-damaging substance (see section 4.3).

The povidone-iodine complex is effective at a pH between 2 and 7. It is to be expected that povidone-iodine will react with protein and various other unsaturated organic compounds, which may impair its efficacy. This may be compensated by a higher povidone-iodine dose.

The concomitant use of wound treatments containing enzymatic components will result in a decrease of the effects of both substances. Preparations containing silver, hydrogen peroxide or taurolidine, or antiseptics may react with povidone-iodine and result in a mutual reduction of effects.

Povidone-iodine products may cause temporary dark discolorations at the site of application before or after application of octenidine-containing products.

Prolonged use, especially on extensive surfaces should be avoided in patients undergoing lithium therapy, as larger amounts of iodine may be absorbed.

Effects on Diagnostic tests
The iodine absorption from povidone-iodine products may reduce thyroid iodine absorption. This may result in disturbances in various tests (thyroid scintigraphy, determination of protein-bound iodine (PBI), radioiodine diagnostics), and make a planned radioiodine therapy impossible (see section 4.3).

Because of the oxidizing effect of povidone-iodine, various diagnostics may yield false-positive results (e.g., toluidine and guaiac gum for hemoglobin and glucose determination in stool or urine).

4.6. Fertility, Pregnancy and Lactation

Pregnancy and lactation
Generally, the use of povidone-iodine should be ~~strictly~~ avoided, unless the potential benefit for the mother justifies the potential risk for the fetus and the newborn, if no safe alternative is available.

Use during pregnancy and during lactation requires strict assessment of indication and application of povidone-iodine should be strictly limited. When

used in pregnant women or during lactation, adequate monitoring of thyroid function of mother and infant respectively is indicated. Povidone-iodine may induce transient hypothyroidism (elevated TSH), including hereditary hypothyroidism in offspring.

Iodine crosses the placenta barrier and passes into breast milk. Moreover, iodine will be present in breast milk at higher concentrations as compared to serum.

Accidental oral absorption of Betadine Topical Spray by the breast-fed infant as a result of contact with the treated body areas of the breastfeeding mother must be avoided.

Fertility
No clinical and preclinical data on effects on fertility are available.
Povidone-iodine is non-teratogenic.

4.7. Effects on Ability to Drive and Use Machines

Betadine Topical Spray has no impact on the ability to drive and operate machines.

4.8. Undesirable Effects

Evaluation of adverse effects has been based on the following frequency categories:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000, <1/1,000)
Very rare (≤1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping adverse effects are listed in the sequence of decreasing severity.

Immune System Disorders
Rare: hypersensitivity
Very rare: anaphylactic reactions frequently accompanied by blood pressure drop, dizziness, nausea and possibly dyspnea.

Endocrine Disorders
Very rare: iodine-induced hyperthyroidism in predisposed persons (sometimes with symptoms of tachycardia or restlessness; see sections 4.3 and 4.9)[1)]
Not known: hypothyroidism[2)]

Metabolism and Nutrition Disorders
Not known: electrolyte imbalance[3)], metabolic acidosis[3)]

Skin and Subcutaneous Tissue disorders
Rare: contact dermatitis (with symptoms like erythema, blistering and itching)
Very rare: angioedema

Renal and Urinary Disorders
Not known: acute renal failure[3)], abnormal osmolarity of blood[3)]

1) In patients with a history of thyroid dysfunction upon absorption of larger volumes of iodine e.g., in the course of large-scale use of povidone-iodine in the treatment of wounds and burns for a prolonged period

2) Hypothyroidism upon prolonged or excessive use of povidone-iodine

3) May occur upon absorption of larger volumes of povidone-iodine (e.g., treatment of burns).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.

https://sideeffects.health.gov.il/

4.9. Overdose

Symptoms of Overdose
Literature describes symptoms of intoxication upon absorption of more than 10 g of povidone-iodine.

Acute iodine toxicity is manifested by abdominal symptoms like nausea, vomiting, diarrhea, dehydration, blood pressure drop, bleeding tendency (mucous membranes, kidneys), cyanosis, anuria, circulatory collapse, pulmonary edema and metabolic disorders.

Upon prolonged excessive exposure with iodine, symptoms of hyperthyroidism, tachycardia, unrest, tremor and headache may occur.

Systemic toxicity may result in renal dysfunction (including anuria), paresthesia, tachycardia, hypotension, circulatory failure, glottis edema causing asphyxia or pulmonary edema, seizures, fever and metabolic acidosis. Hyperthyroidism or hypothyroidism may also develop.

Management of Overdose:
Treatment is symptomatic and supportive.

In case of severe hypotension intravenous fluid is to be administered and additional vasopressors should be administered if needed.

Endotracheal intubation may be required, if a caustic injury of the upper airways causes significant swelling and edema.

Vomiting should not be induced. The patient is to be kept in a position keeping the airways patent and preventing aspiration (in the case of vomiting).

If the patient does not vomit and oral nutrition is possible, the intake of starchy foodstuffs (e.g., potatoes, flour, bread) may support the conversion of iodine to the less toxic iodide. If no signs of intestinal perforation are seen gastric lavage with starch solution (5% sodium thiosulfate solution (or 10 ml sodium thiosulfate IV) at intervals of 3-hours) may be given via a nasogastric probe (the gastric discharge will show a dark-blue/purple discoloration which may be used as an indication, when the lavage may be terminated).

Haemodialysis will effectively flush out iodine and should be used in severe cases of iodine intoxication, especially in the presence of renal failure. Continuous venovenous hemodiafiltration will be less effective than hemodialysis.

In the case of a thyroid dysfunction treatment with povidone-iodine should be discontinued

Moreover, close clinical monitoring of thyroid function is indicated to allow exclusion or early diagnosis of potential hyperthyroidism.

Further management will depend on the presence of any other potential symptoms such as metabolic acidosis and renal dysfunction.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Antiseptics and disinfectants, iodine products, povidone-iodine ATC code: D08AG02

Povidone-iodine is a complex of the polymer polyvinylpyrrolidone with iodine (povidone-iodine). The microbicidal effect of povidone-iodine is based on its share of free iodine without complex binding, which is being released from the povidone-iodine complex by an equilibrium reaction. Hence, the povidone-iodine complex represents an iodine depository providing for the sustained release of elementary iodine and ensuring a constant concentration of active free iodine.

By its binding to the povidone-iodine complex, iodine largely loses the local irritant properties being characteristic of alcoholic iodine preparations and thus shows good tolerability for skin, mucous membranes and wounds.

The free iodine reacts with oxidizable SH or OH groups of the amino acids in enzymes and structural proteins of microorganisms thereby inactivating and killing these enzymes and proteins. During this process iodine is discolored; thus, the intensity of brown coloration serves as indicator of its effectiveness. Redosing is required upon discoloration.

This rather unspecific mechanism of action explains the extensive activity of povidone-iodine against a broad spectrum of human pathogens:

gram-positive and gram-negative bacteria, Gardnerella vaginalis, mycoplasmas, Treponema pallidum, chlamydiae; fungi (e.g. Candida), viruses (including Herpes and HIV); protozoae (e.g. trichomonads) and spores.

Because of this mechanism of action resistances, including secondary resistance upon prolonged use, are not to be expected.

5.2. Pharmacokinetic Properties

After use of Betadine Topical Spray, the possibility of iodine absorption must be considered; this absorption will depend on the kind and duration of use and on the amount applied.

Prolonged application of Betadine Topical Spray on extensive wounds and burns or on mucous membranes may result in substantial iodine uptake. In general, the resultant increase of iodine level in blood is only transient (restitution within 7-14 days after discontinuation of treatment).

In patients with normal thyroid function, the increased iodine supply does not cause any clinically significant ~~relevant~~ changes in thyroid hormone status.

Povidone:

Absorption and, in particular, renal elimination of povidone is dependent on the (mean) molecular weight (of the mixture). For a molecular weight of more than 35,000 to 50,000 dalton, retention, must be anticipated, especially in the reticulohistiocytic system. However, the saurismosis and other changes as seen after intravenous or subcutaneous administration of other povidone containing drugs are not seen for povidone-iodine.

Iodine:

Absorption after topical application to the skin: After short exposure, absorption is limited on intact skin. The application to damaged skin, e.g., wounds or burns, results in increased absorption.
The behavior of absorbed iodine or iodide in the organism is largely similar to that of iodine taken up by other routes. The volume of distribution is about 38% of body weight in kg; a biological half-life of approx. 2 days has been described

after vaginal administration. The normal value for total iodine in serum is about 3.8 to 6,0 µg/dl, and about 0.01 to 0.5 µg/dl for inorganic iodine.
Elimination is almost exclusively by renal route with a clearance of 15 to 60 ml plasma/min depending on serum-iodine level and creatinine clearance (normal value: 100-300 µg iodide per g creatinine).

5.3. Preclinical Safety Data

Acute, subchronic and chronic toxicity studies with povidone-iodine demonstrated toxicity when administered systemically at relatively high doses, but this is not relevant for the clinical use of Betadine Topical Spray.

In mice, embryotoxicity was demonstrated when povidone-iodine was administered into the vaginal opening. Developmental toxicity studies in rabbits showed that a low molecular weight povidone-iodine complex (16-75 mg/kg/day) resulted in decreased maternal weight gain in a dose-dependent manner. Furthermore, the average embryo and placental weight was lower than in control animals. Because of the placental permeability of iodine and the sensitivity of the fetus to pharmacological doses of iodine, povidone-iodine should be used in pregnant women only after careful medical evaluation.

While several in vitro genotoxicity studies indicate a mutagenic capacity of povidone-iodine, other studies, including in vivo studies, yielded negative results. Considering the toxicity of povidone-iodine in in vitro test systems, the present results indicate that povidone-iodine is not genotoxic. No long-term carcinogenicity studies have been performed in animals.

Data from preclinical studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential reveal no evidence of any special hazards of use for humans. Animal studies revealed no teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of the Other Excipients

Isopropyl myristate, n-pentane, gas propellant (mixture of propane, butane and isobutane).

6.2. Incompatibilities

Povidone-iodine is incompatible with reducing agents, alkaloid salts, tannic acid, salicylic acid, silver, mercury and bismuth salts, taurolidine, hydrogen peroxide, and octenidine (see also section 4.5 Interactions with other medicinal products and other forms of interaction).

6.3. Shelf Life

The expiry date of the product is indicated on the packaging materials.

6.4. Special Precautions for Storage

Easily flammable. Store below 25ºC.
Do not expose to temperatures above 50°C.
Keep away from potential sources of inflammation.

6.5. Nature and Contents of The Container

Pressurized aerosol aluminium can with inside lacquer, spray valve and spray head, weighing 30 g or 80 g.
Not all pack sizes may be marketed.

6.6. Special Precautions for Disposal and Other Advice on Handling

Shake the spray can well before use, hold upright and spray from a distance of 15 cm on the area to be treated. (See 4.2 Posology and route of administration).

Due to the oxidative effect of the povidone-iodine, metals may become corroded; plastics are generally resistant to povidone-iodine. In some cases, mostly reversible discolouration may occur.

Betadine Topical Spray can be easily removed from textiles and other materials with warm water and soap, and, in stubborn cases, by using ammonia (ammonia solution) or sodium thiosulphate (fixing salt).

Unused medicinal product or waste material must be disposed of in accordance with national requirements.

7. REGISTRATION HOLDER

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Registration number: 160-94-35157

Manufacturer: Mundipharma Ltd. Nicosia Cyprus.

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