The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in March 2018

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Betadine Gargle
Concentrated Solution
Gargle and Mouthwash

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betadine Gargle contains 7.5% povidone-iodine (0.75% available iodine).
For the a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Concentrated Solution
Gargle and Mouthwash

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- For the treatment of infectious-inflammatory diseases of the mucous membranes in the mouth, throat and the gingiva caused by fungi, viruses and bacteria (e. g. thrush, aphthae, superinfected and herpetic ulcers, gingivitis, stomatitis, pharyngitis, supporting treatment in the case of tonsillitis).
- For the treatment of injuries in the mouth and throat region.
- For antiseptic treatment of the oral mucous membrane (e. g. prior to surgery), especially in patients with immunodeficiency and patients at risk for endocarditis (prevention of bacteremia).
- Prevention of radiation-induced mucositis in patients undergoing radiotherapy or radio-chemotherapy.

Betadine Gargle may be used in adults, infants, toddlers, children and adolescents.

4.2 Posology and method of administration

Betadine Gargle is used undiluted or diluted with lukewarm water. The screw cap may be used for dosing. The screw cap has a volume of 5 ml.

Dosage:
For infectious inflammatory diseases and injuries in the mouth and throat region
A dilution of 1:8 to 1:16 (approx. 2-4 caps in 125 ml water) is recommended. Rinse mouth and/or gargle for at least 30 seconds every 1-4 hours until the disease subsides.

Antisepsis prior to surgery

Apply Betadine Gargle undiluted to the area of the planned surgery for at least 30 seconds.

Prevention of radiation-induced mucositis
A dilution of 1:8 (approx. 4 caps in 125 ml water) is recommended. The treatment should be repeated several times daily after meals. The solution should remain in the mouth for at least 3 minutes. Do not rinse.

Betadine Gargle should only be used in toddlers, if proper use is ensured. (The solution should not be swallowed.)

Type of use
For use in the mouth and throat region.
Betadine Gargle is intended for rinsing the mouth and throat region and for gargling, solely in the dilutions specified in the instructions. The dilution should be prepared just prior to use.
The solution is not intended for oral intake.
Dentures, braces and similar medical devices should be temporarily removed prior to the use of Betadine Gargle, to allow better accessibility to the gingiva and oral mucous membranes and to prevent discoloration of the material.

Duration of use
Duration of the use of Betadine Gargle depends on the respective area of application.
Betadine Gargle should be used as long as signs of infection or a significant risk of infection are present.
Betadine Gargle should not be used together with other gargles.

4.3. Contraindications

- Hypersensitivity to the active ingredient or one of the other excipients listed in section 6.1.
- Hyperthyroidism or other apparent thyroid diseases.
- Dermatitis herpetiformis (Duhring disease).
- Prior to or after radioactive iodine therapy (until conclusion of treatment).

4.4. Special warnings and precautions for use

In the event of latent thyrotoxicosis (especially in older patients) and in patients with goiter or thyroid nodules povidone-iodine should be applied for prolonged periods (more than 14 days) or on large areas (more than 10 % of the body surface) only after a careful assessment of the benefits and risks, as subsequent hyperthyroidism may not be completely ruled out. After discontinuation of the treatment (up to 3 months) these patients should be monitored for early symptoms of hyperthyroidism and thyroid function should be tested, if necessary.

The product must not be used prior to or after radioiodine scintigraphy or radioiodine treatment for thyroid cancer.

Aspiration should be avoided when using Betadine Gargle in the pharyngeal area, since this may cause respiratory problems and even pneumonia. This can happen especially in intubated patients.

Children, newborns and babies

Due to the skin texture and sensitivity to povidone-iodine of newborns and babies up to 6 months of age, povidone-iodine should be used only if an indication is carefully established. If necessary, thyroid function (e. g. T_4 and TSH levels) should be monitored (see also section 4.6, Fertility, Pregnancy and Lactation).
In children, especially in toddlers, Betadine Gargle should only be used, if proper use can be ensured, so that the solution is not swallowed.
Any oral intake of povidone-iodine in newborns, babies and toddlers must be prevented.

The oxidative properties of povidone-iodine may cause corrosion of metals (braces and dentures). Plastic materials are generally inert to povidone-iodine. In some instances, reversible discoloration may occur.

Betadine Gargle contains about 30% ethanol.

4.5 Interactions with other medicinal products and other forms of interaction

Concurrent use of povidone-iodine and hydrogen peroxide, enzymatic or silver- and taurolidine-containing wound healing agents or antiseptics leads to reduced effectiveness of both.

Using Betadine Gargle together with taurolidine should be avoided, as taurolidine may be converted to formic acid which causes painful burning.

Povidone-iodine must not be used in combination with mercury-containing preparations, since this may lead to the formation of corrosive mercury iodide.

Povidone-iodine must not be used in combination with octenidine-based antiseptics, as this may lead to temporary dark discolorations.

The povidone-iodine-complex is effective at a pH between 2.0 and 7.0. It can be expected that povidone-iodine will react with proteins and various other organic substances, such as components of the blood or pus, which would reduce efficacy. This may be compensated for with a higher povidone-iodine dose.

Long-term use and especially use on large areas should be avoided in patients on lithium therapy, as high amounts of iodine could be resorbed. In exceptional cases this may induce (temporary) hypothyroidism. In such specific situations, a synergistic effect with the similar potential adverse effect of lithium may occur.

Effect on diagnostic tests:
Use of povidone-iodine may reduce iodine uptake of the thyroid. This may lead to errors in various assays (thyroid scintigraphy, PBI (protein-bound iodine) determination, radioiodine diagnostics) and may prevent any planned radioiodine therapy of the thyroid.
A waiting period of 1-2 weeks after discontinuation of the treatment with povidone-iodine should be observed.

Various diagnostic tools may provide false positive results due to the oxidizing effect of povidone-iodine (among others, toluidine and guaiac resin for the determination of hemoglobin and glucose in stool and urine).

4.6. Fertility, pregnancy and lactation

Povidone-iodine is not a teratogen.

Povidone-iodine should be used in pregnant and lactating women after careful diagnosis and in strictly limited quantity only. Thyroid function should be monitored in pregnant women after the completion of the first trimester as well as in lactating women and their babies. Povidone-iodine may induce temporary hypothyroidism (increased TSH levels).

Iodine passes the placental barrier and penetrates into breast milk. In addition, concentrations of iodine are higher in breast milk than in serum.

4.7. Effects on the ability to drive and operate machines

Betadine Gargle has no or only a negligible impact on the ability to drive and operate machines.

4.8. Adverse effects

The following definitions for the frequency of adverse drug reactions were used:

Rare (≥ 1/10,000, < 1/1,000)
Very rare (≤ 1/10,000)
Unknown (the frequency cannot be estimated based on the available data)

Diseases of the immune systems
Rare: Hypersensitivity
Very rare: Anaphylactic reactions often associated with blood pressure drop, dizziness, nausea and possible respiratory distress

Endocrine diseases
Very rare: Iodine-induced hyperthyroidism in predisposed persons (sometimes with symptoms of tachycardia or restlessness, see section 4.3, Contraindications, and section 4.9, Overdose)[1]
Unknown: Hypothyroidism[2]

Metabolic and nutrition disorders
Unknown: Electrolyte imbalance[3], metabolic acidosis[3]

Diseases of the respiratory tract, the thorax and mediastinum
Unknown: Pneumonitis[4]

Diseases of the skin and subcutaneous tissue
Rare: Hypersensitivity reactions of the skin (e. g. delayed contact allergic reactions manifested as pruritus, erythema, blisters or similar conditions)
Very rare: Angioedema

Diseases of the kidneys and urinary tract
Unknown: Acute kidney failure[3], abnormal osmolarity of the blood[3]

1) In patients with a history of thyroid dysfunction (see Special warnings and precautions for use) after uptake of a larger quantity of iodine, for example in the

use of povidone-iodine on large areas in the treatment of wounds and burns over an extended period of time

2) Hypothyroidism after long-term or excessive use of povidone-iodine
3) Can occur after uptake of a larger quantity of povidone-iodine (for example, in the treatment of combustion)
4) Complications due to aspiration - see section 4.4

A considerable uptake of iodine may occur with long-term use of Betadine Gargle.

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

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9. Overdose

Povidone-iodine There are reports in the literature regarding symptoms of intoxication due to oral administration of more than 10 g of povidone-iodine.
These symptoms are: abdominal pain and cramping, nausea, vomiting, diarrhea, dehydration, hypotension with tendency to collapse, edema of the glottis, tendency to bleed (mucous membranes, kidneys), cyanosis, kidney damage including anuria, paresthesia, fever and pulmonary edema.
Long-term excessive intake of iodine may lead to symptoms of hyperthyroidism, tachycardia, restlessness, tremor and headaches.

Ethanol:
Oral administration of the concentrated solution may lead to symptoms of ethanol intoxication due to the ethanol content.

Treatment in case of overdose:
Povidone-iodine
Immediate administration of food rich in starch and protein (such as corn starch in water or milk). If necessary, gastric lavage with 5 % sodium thiosulfate solution (or 10 ml sodium thiosulfate I.V) every three hours.
Toxic iodine levels after resorption in the serum may be reduced efficiently using peritoneal dialysis or hemodialysis.
Thyroid function should be monitored closely, especially in high-risk groups, to rule out possible iodine-induced hyperthyroidism or aimed at an early detection.

Additional treatments depend on other symptoms, which may occur, such as metabolic acidosis and renal dysfunction.

Ethanol: Therapy for ethanol intoxication follows known clinical rules.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Pharyngeal preparations, antiseptics
ATC code: R02AA15

Povidone-iodine is a complex of the polymer polyvinyl-pyrrolidone with iodine (povidone-iodine). The microbicidal effect is based on the content of free, non-complexed iodine released by the povidone-iodine complex during an equilibrium reaction. Thus, the povidone-iodine complex is an iodine depot slowly releasing elemental iodine over a prolonged period of time and maintaining a constant concentration of active free iodine.
Binding of iodine to the povidone complex largely reduces local irritating properties of alcoholic iodine preparations and is well tolerated by skin, mucous membranes and wounds.
Free iodine reacts with oxidizable SH- or OH-groups of amino acids in enzymes and structural proteins of microorganisms, which are thereby inactivated and killed. This process decolors the iodine. Therefore, the intensity of the brown color is an indicator for its efficacy. Decoloration requires an additional dosage. This relatively unspecific mode of action is the reason for the comprehensive efficacy of povidone-iodine against a wide spectrum of human pathogens: gram-positive, gram-negative, bacteria, Gardnerella vag., Mycoplasma, Treponema pallidum, Chlamydia, fungi (e. g. candida), viruses (including herpes and HIV), protozoa (e. g. trichomonas) as well as spores.
Resistance or development of secondary resistance with long-term use is not expected due to the mode of action.
Betadine Gargle is a therapeutic anti-infectious mouth rinse, which tastes good and prevents bad breath. Betadine Gargle is water-soluble and easy to rinse off.

5.2. Pharmacokinetic properties

After use of Betadine Gargle the possibility of iodine resorption must be considered depending on the duration of use and the applied amount.
A significant amount of iodine may be absorbed with long-term use of Betadine Gargle on large wounds and burned areas as well as mucous membranes. The resulting increase in iodine levels in the blood is generally temporary (normalization within 7 to 14 days after discontinuation of the treatment).
In a healthy thyroid, the increased iodine levels do not lead to any clinical relevant changes in the hormone status of the thyroid.

Povidone:
Resorption and renal elimination of povidone depends on the (average) molecular weight (of the mixture). Retention mainly in the reticulo-endothelial system is expected above a molecular weight of 35,000 to 50,000 Dalton. However thesaurismosis and other changes observed after intravenous or subcutaneous administration of other povidone-containing medications were not observed for povidone-iodine.
Iodine:
The behavior of resorbed iodine or iodide in the organism corresponds to a great extent to that of otherwise absorbed iodine. The volume of distribution corresponds to about 38 % of the body weight in kg. The biological half life after vaginal administration was reported to be about 2 days. The normal value of total iodine in the serum is 3.8 to 6.0 µg/dl and of inorganic iodine 0.01 to 0.5 µg/dl.
Elimination occurs almost exclusively renally with a clearance rate of 15 to 60 ml plasma/min depending on the iodine level in serum and creatinine clearance (normal value: 100 - 300 µg iodide per 1 g of creatinine).

5.3. Preclinical safety data

Data from preclinical studies on safety pharmacology, toxicity with repeated administration, genotoxicity or carcinogenic potential showed no indications of risks for the use in humans. Due to the extensive clinical experience with iodine, no long-term carcinogenicity studies in animals were performed. Studies in animals showed no teratogenic effects.

Sub-chronic and chronic toxicity studies, among others in rats, showed mainly reversible and dose dependent increase of PBI (protein-bound iodine) and nonspecific, histopathological changes of the thyroid after discontinuation of povidone-iodine administration.
Iodine crosses the placental barrier and the thyroid of fetuses is sensitive to pharmacological iodine doses. Therefore, no large amounts of iodine should be resorbed during pregnancy. Additionally, there in increased accumulation of iodine in milk compared to serum (see section 4.6, Fertility, Pregnancy and Lactation).
The toxicological properties of ethanol are known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ethanol 96%, glycerol, disodium phosphate, saccharin sodium, methyl salicylate, citric acid, sodium hydroxide, Levomenthol, purified water.

6.2. Incompatibilities

Povidone-iodine is incompatible with reducing substances, alkaloidal salts, tannic acid, salicylic acid, salts of silver, mercury and bismuth, hydrogen peroxide, octenidine (see also section 4.5 Interaction 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.
Shelf life after first opening: may be used within 12 months, but no later than the expiry date marked on the package.

6.4. Special precautions for storage

Store below 25ºC.

6.5. Nature and contents of container

Plastic polyethylene bottle with LDPE dropper and polypropylene screw cap containing of 100 ml or 120 ml.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Betadine Gargle may be removed from textiles and other materials with soap and warm water. In more stubborn cases, ammonia or fixing salt (sodium thiosulfate) may be used.
Unused medication or waste material should be disposed of in accordance with national regulations.

7. REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.
Registration number:
Manufacturer: Mundipharma GmbH, Germany

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