PROFESSIONAL INFORMATION

SCHEDULING STATUS S2

1 NAME OF THE MEDICINE

BETADINE® VAGINAL GEL (10 % gel)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g of BETADINE® VAGINAL GEL contains 100 mg povidone-iodine equivalent to 10 mg available iodine (10 % *w/w).*

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A smooth uniform dark brown gel/ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For vaginal administration.

BETADINE® VAGINAL GEL is indicated for:

Disinfection of the vagina before and after operations.

In acute and chronic vaginal infections (colpitis, vulvovaginitis).

Mixed infections

- Unspecific infections (bacterial vaginosis; Gardnerella vag.)
- Genital herpes infections
- Fungal infections (Candida albicans), also following antibiotic or corticosteroid therapy
- Trichomonad infections, concomitant systemic treatment required, if justifiable.

4.2 Posology and method of administration

For Intra-Vaginal use. Adults and elderly.

Posology

Treatment of vaginal infections

Insert one applicator full of the vaginal gel deep into the vagina daily at bedtime. Treatment must be performed daily, including days of the menstrual cycle.

In addition, a thin film of the vaginal gel may also be applied two or three times daily on the external genital areas and 1 - 2 cm beyond, especially in cases of vulvitis.

The duration of treatment should not be longer than 5 - 10 days. If required, treatment may be prolonged upon medical instruction or the dose may be increased to twice daily application, in cases of persistent infection.

Preoperative vaginal disinfection

For preoperative vaginal disinfection, as also in the treatment of vaginitis, the gel is applied in the evening and left in the vagina overnight. The following morning before the operation, the vagina can be rinsed with BETADINE® DOUCHE.

Special populations

There is no adjustment of dose required in elderly population.

Paediatric population

Use before the first menstrual cycle is not recommended.

Method of administration

- Remove cap from tube and screw into threaded open end of applicator.
- Pull plunger back to limit.
- Fill applicator with vaginal gel by applying pressure to the bottom of tube, forcing the gel into the applicator barrel.
- Detach filled applicator from tube.
- In a reclining position, gently insert vaginal applicator high into the vagina and depress plunger to deposit vaginal gel.

BETADINE® VAGINAL GEL may also be spread thinly 1-2 cm around the external genital area two or three times a day.

To clean the applicator, disassemble by pushing the plunger out of the barrel, wash both parts in hot water, then replace plunger. A sanitary towel should be worn during the period of treatment and the vagina can be rinsed with BETADINE® DOUCHE if desired.

To avoid staining of underwear, the use of sanitary pads is recommended during treatment with BETADINE® VAGINAL GEL. Any stains can be removed from natural fabrics with soap and warm water, and from man-made fabrics with a dilute solution of ammonia.

4.3 Contraindications

- Hypersensitivity to iodine or povidone or any other of the excipients listed in section 6.1
- Hyperthyroidism or other manifest thyroid diseases
- Before and after radio iodine therapy (until treatment is concluded)
- Before radioiodine scintigraphy for thyroid testing (at least 4 weeks prior)
- Patients with nodular colloid goitre, endemic goitre, Hashimotos thyroiditis
- Use in pre-pubertal children
- Use on patients on concurrent lithium therapy

4.4 Special warnings and precautions for use

Povidone-iodine should not cover large areas of the skin for a long period (e.g. not more than 10 % of the total body surface and not for longer than 10 days) unless strictly indicated.

Even after the end of the treatment (up to 3 months) one should look for the early symptoms of possible hyperthyroidism and if necessary the thyroid function should be monitored.

Special caution is needed when regular applications to broken skin are made to patients with pre-existing renal insufficiency.

Iodine is absorbed from the vagina and following prolonged use, thyroid dysfunction may develop.

Avoid solutions containing a detergent if treating vaginal areas with povidone-iodine.

For vaginal use only.

In very rare cases BETADINE® VAGINAL GEL may produce local reactions.

In instances of local irritation on sensitivity, discontinue use.

The product may be spermicidal and should not be used when conception is desired.

Changes in the international and local antimicrobial resistance patterns should be a consideration. Principles of antibiotics stewardship should be adhered to.

4.5 Interaction with other medicines and other forms of interaction

The PVP-Iodine complex is effective at pH values of between 2,0 and 7,0. It has to be expected that the complex will react with protein and other unsaturated organic compounds, leading to impairment of its effectiveness.

The concomitant use of products containing enzymatic component, hydrogen peroxide, silver and taurolidine lead to a weakening effect of both substances.

The use of BETADINE® VAGINAL GEL together with taurolidine should be avoided, since taurolidine may metabolize to formic acid, which causes intense burning.

Simultaneous use with mercury products may lead to the formation of mercury iodine that is caustic.

Effects on diagnostic tests

The use of BETADINE® VAGINAL GEL can reduce iodine uptake by the thyroid; this can lead to problems during various tests (thyroid scintigraphy, PBI (protein-bound iodine) determination, radioiodine diagnostics), making any planned treatment of the thyroid with iodine impossible. After the end of the treatment an interval of at least 4 weeks should be allowed before a new scintigram is carried out (see section 4.3).

As a result of the oxidizing effect of povidone-iodine, several types of tests for the detection of occult blood in faeces or blood in urine may produce false-positive results.

4.6 Fertility, pregnancy and lactation

During pregnancy and lactation, the use of BETADINE® VAGINAL GEL should be strictly indicated and its use should be kept to the absolute minimum, as absorbed iodine can cross the placental barrier and can be secreted in breast milk.

Pregnancy

Povidone-iodine use may induce transient hypothyroidism in the foetus or in the newborn. Povidone-iodine should be avoided in such situations. In these cases a check of the child's thyroid function is necessary, especially in areas known for endemic low dietary iodine and tendency to goitre.

Breastfeeding

Iodine is excreted in breast milk and is present in higher concentrations in the breast milk compared to those in the serum.

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The following adverse reactions have been reported with BETADINE® VAGINAL GEL either during clinical trials or during post-marketing experience:

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) and Not known** (cannot be estimated from the available data).

Immune system disorders

Rare: Hypersensitivity

Very rare: Anaphylactic reaction

Endocrine disorders

Very rare: Hyperthyroidism (sometimes with symptoms such as tachycardia or restlessness)

Not known: Hypothyroidism

Metabolism and nutrition disorders

Not known: Electrolyte and serum osmolality disorders*, metabolic acidosis*

Skin and subcutaneous tissue disorders

Rare: Contact dermatitis (with symptoms such as erythema and swelling)

Renal and urinary disorders

Not known: Acute renal failure*

Reproductive system and breast disorders

Not known: Spermicidal (should not be used when conception is desired).

* May occur following uptake of large amounts of povidone-iodine (e.g. in the treatment of burns)

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8. Alternatively report to:

ZADrugSafety@mundipharma.co.za

4.9 Overdose

In the case of deliberate or accidental ingestion of large quantities of povidone-iodine acute iodine toxicity is manifested by abdominal symptoms, anuria, circulatory failure, oedema of glottis resulting in asphyxia, or pulmonary oedema and metabolic abnormalities.

Treatment is symptomatic and supportive with special attention to electrolyte balance and renal and thyroid function.

5 PHARMACOLOGICAL PROPERTIES

A.18.6 Vaginal preparations

5.1 Pharmacodynamic properties

Povidone-iodine is a complex of the polymer polyvinylpyrrolidone with iodine (povidone-iodine) which, after application, continues to deliver iodine over a period of time. Elemental iodine (I_2) has long been known as a highly effective microbicidal agent that rapidly kills bacteria, viruses, fungi and some protozoa *in vitro*. Two mechanisms are involved: free iodine rapidly causes microbial killing, whereas iodine bound to the polymer serves as a reservoir. As the preparation comes in contact with the skin and mucous membranes, more and more iodine dissociates from the polymer. The free iodine reacts with oxidisable –SH or –OH groups of the amino acids in the enzymes and structural proteins of microorganisms thereby inactivating and killing these enzymes and proteins. Most vegetative microorganisms are killed in less than a minute *in vitro*, with many destroyed within 15 to 30 seconds. During this process, iodine is decolourised; thus, the intensity of brown colouration serves as indicator of its effectiveness. Repeated dosing may be required upon discolouration. Resistance has not been reported.

5.2 Pharmacokinetic properties

Absorption

In normal individuals, topical application results in very little systemic iodine absorption; with vaginal administration, however, iodine absorption is rapid and serum concentrations of total iodine and inorganic iodide are increased significantly. This product is intended for topical application to the vagina.

Povidone (PVP)

Absorption, and in particular renal elimination, of povidone depend on the (mean) molecular weight (of the mixture). For molecular weights of more than 35,000 to 50,000, retention must be expected.

Iodine

The behaviour of absorbed iodine or iodide in the organisms is largely similar to that of iodine taken up by other routes. The volume of distribution corresponds to approximately 38 % of body weight in kg, biological half-life after vaginal administration has been described with approximately 2 days.

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

5.3 Preclinical safety data

Acute toxicity

In experimental animal investigations (mouse, rat, rabbit, dog), acutely toxic effects were found after systemic administration (oral, i.p., i.v.) only with excessively high doses that are of no significance for the local use of povidone-iodine.

Chronic toxicity

Subchronic and chronic tests for toxicity were carried out on rats, among other animals, in the form of the admixture of povidone-iodine (10 % available iodine) into the feed in dosages of between 75 and 750 mg povidone-iodine per day and kg body weight for up to 12 weeks. After the povidone-iodine addition was stopped, only the practically completely reversible and dose-dependent rises in PBI (protein-bound iodine) in the serum and non-specific histopathologic changes in the thyroid gland were observed. Similar changes also occurred in the control group, which received potassium iodide in iodine-equivalent amounts instead of povidone-iodine.

Mutagenic and tumour-inducing potential

No carcinogenicity studies have been conducted; no information is, therefore, available.

Reproductive toxicity

Because of the ability of iodine to pass through the placenta and the sensitivity of the foetus to pharmacologic doses of iodine, no larger amounts of iodine should be absorbed during pregnancy. The use of povidone-iodine in obstetrics may lead to a significant rise in serum iodine concentration in the mother and to transient hypofunction of the thyroid gland with elevation of TSH (thyroid-stimulating hormone) concentration in the neonate. Moreover, iodide is concentrated in the milk, as compared with the serum

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400, Macrogol 4000, Purified Water Ph Eur., Sodium Bicarbonate.

6.2 Incompatibilities

The activity of povidone-iodine is reduced in the presence of alkali, hydrogen peroxide, taurolidine, tannic acid, acetylsalicylic acid, all silver, bismuth and mercury salts.

Compatibility with barrier contraceptives has not been established. Therefore this product should not be used with such methods of contraception as their reliability may be affected.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Aluminium cylindrical tubes with an internal lacquer lining (Protaral®), with a polypropylene (PP) or heterophasic copolymer screw cap.

Pack size: 100 g.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

51/18.6/0531

Export details:

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26 May 1971 / 04 October 2022

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