SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

BETADINE® 200 mg vaginal suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal suppository contains 200 mg of povidone-iodine, equivalent to 20 mg of available iodine.

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- vaginal suppository

Dark brown to red, bullet-shaped pessary.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Betadine vaginal suppositories are indicated for acute and chronic vaginal infections (vaginitis) caused by mixed infections, non-specific infections, Trichomonas vaginalis infections and mycotic (Candida albicans) infections, especially after antibiotic or steroid therapy.

4.2. Posology and method of administration

Once a day, at bedtime, in lying position, insert previously water-wetted vaginal pessary deeply into the vagina.
Unless the doctor prescribes otherwise, usual therapy lasts 14 days, in any time of the menstrual cycle, including the days of menstrual bleedings.
Since leaking of the medicine out of the vagina can not always be prevented, sanitary pads, but not tampons are recommended.
This medicine is not intended for use in pre-pubertal children.

4.3. Contraindication

Betadine vaginal suppositories are contraindicated in:
- known hypersensitivity to iodine;
- hyperthyroidism;
- dermatitis herpetiformis;
- before and after radioiodotherapy.

4.4. Special warnings and special precautions for use

Regular or prolonged use of povidone-iodine should be avoided in patients on lithium therapy, renal failure and thyroid disease.
Povidone-iodine is not recommended for use in patients with renal failure due to the potential for metabolic acidosis and nephrotoxicity.
Povidone-iodine is also not recommended for use in patients with hepatic failure.
Betadine vaginal suppositories are for vaginal use only.
If signs of local intolerance occur (irritation, hypersensitivity), the therapy should be discontinued and a physician should be consulted if needed.

Special warning
Brown coloration of povidone-iodine indicates the efficacy of the preparation. Decoloration of the preparation signifies diminishing of its activity.
Concomitant administration of povidone-iodine may perturb thyroid scintigraphy. A period of 1-2 weeks without povidone-iodine treatment is necessary before thyroid scintigraphy is conducted.
The product may be spermicidal and should not be used when conception is desired.

4.5. Interaction with other medicaments and other forms of interaction

Povidone-iodine vaginal suppositories should not be used with preparations containing chlorhexidine, hydrogen-peroxide, taurolidine, Ag-sulfadiazine, alkalis and mercury, because partial inactivation may occur.

Povidone-iodine products when used concomitantly or immediately after application of octenidine containing antiseptics in the same or adjacent sites may lead to transient dark decolorations in the areas involved.

Due to the oxidative effect of povidone-iodine preparations various diagnostic agents can show false-positive lab results (e.g., tests with toluidine or gum guaiac for the determination of hemoglobin or glucose in the stool or the urine).

In patients treated with lithium concomitant administration of povidone-iodine, exhibits synergistic hypothireotic effect.

4.6. Pregnancy and lactation

During pregnancy and lactation, povidone-iodine solution should only be used if strictly indicated and its use should be kept to the absolute minimum.
Because of the ability of iodine to pass through the placenta and be secreted in breast milk, and because of the increased sensitivity of the fetus and newborn to iodine, no large amounts of povidone-iodine should be administered during pregnancy and lactation.
Iodine concentration in the breast milk is comparable with the serum concentration. Povidone-iodine use may induce transient hypothyroidism with elevation of TSH (thyroid

stimulating hormone) in the fetus or in the newborn.
A check of the child's thyroid function may be necessary.
Any possible oral ingestion of the solution by the infant must be absolutely avoided.

4.7. Effects on ability to drive and use machines

Betadine vaginal suppositories does not affect driving ability or operating machinery.

4.8. Undesirable effects

Undesirable effects are classified according to the following frequencies:

- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1,000 to <1/100)
- rare (≥ 1/10,000 to < 1/1,000)
- very rare (<1/10,000)
- 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 imbalance **, metabolic acidosis **

Skin and subcutaneous tissue disorders
Rare: contact dermatitis (with symptoms such as erythema, small blisters and pruritus)
Very rare: angioedema

Renal and urinary disorders
Not known: acute renal failure **, blood osmolarity abnormal **

Injury, poisoning and other complications
Not known: chemical burn of skin ***

* In patients with a history of thyroid disease following a notable uptake of iodine e.g. following long-term use of povidone-iodine solution for the treatment of wounds and burns over extensive areas of the skin.
** May occur following uptake of large amounts of povidone-iodine (e.g. in the treatment of burns)
*** May occur due to "pooling" beneath the patient in pre-operative preparation
**** Hypothyroidism following prolonged or extensive use of povidone-iodine.

4.9. Overdose

Overdosage is manifested with symptoms associated with iodine toxicity (fever, diarrhea,

metabolic acidosis and abnormal thyroid function).
In case of manifest iodine-induced hyperthyroidism due to iodine therapy, thyreostatic therapy, plasmapheresis or thyroidectomy may be necessary.

5. PHARMACOLOGICAL PROPERTIES

Pharmaco-therapeutical group: Gynecological antiinfectives and antiseptics
ATC code: G01AX11

5.1. Pharmacodynamic properties

Povidone-iodine is known to be a powerful broad-spectrum germicidal agent effective against a wide range of bacteria, viruses, fungi, protozoa, and spores.
Povidone-iodine acts against bacteria (Gram positive and Gram negative) including Eschericia coli, Proteus spp., Salmonella typhimurium, Staphylococcus aureus, Staphylococcus albus, Shigella sonnei, Streptococcus haemolythicus (A, B, C, D), Clostridium spp, Bacillus subtillis etc, as well as bacterial spores (Bacillus spp. and Clostridium spp.). Povidone-iodine acts against Aspergilus flavus, Aspergilus niger, Candida albicans and Penicillium spp., as well as their spores. Povidone-iodine is effective against protozoa Trichomonas vaginalis and viruses Herpes simplex, Rubeolla, Vaccinia, Poliovirus, Rabbies and Mixoma viruses and Trachoma.
Povidone-iodine is superior to chlorhexidine gluconate, alkyldiaminoethylglycine hydrochloride, and benzalkonium chloride for killing organisms responsible for nosocomial infections (methicillin resistant Staphylococcus aureus, Serratia marcescens, Pseudomonas aeruginosa, and Burkholderia cepacia). Povidone-iodine is also effective against strains known to be resistant to antiseptics. Most organisms do not develop resistance to elemental iodine.
An iodophor, povidone-iodine is a combination of a complex of iodine with a solubilizing agent or carrier that liberates free iodine in solution. Povidone-iodine is a complex of iodine with polyvinylpyrrolidone. Iodophors are widely used at the present time for the purpose of sanitization.
Free iodine with its oxidative property reacts with -SH or -OH amino acid radicals in microorganism's enzymes and structure proteins, which is its mechanism of action. This non-specific mechanism of action explains the efficacy of povidone-iodine against broad spectrum of microorganisms (bacteria, fungi, viruses, protozoa).
Different organic substances (blood, pus, etc) decrease the efficacy of iodine.

5.2. Pharmacokinetic properties

Povidone-iodine is a flexible molecule with rigid tridimensional configuration. It has hydrophilic and lipophobic properties and the transmembranic pass is possible via pores or pinocytosis.
Resorption of povidone-iodine depends of molecular weight. After oral or intraduodenal application of povidone-iodine having molecular weight of 40,000, negligible quantities are detected in the blood, urine and bile. The marked povidone-iodine^{131} having a molecular weight of 40,000 is being slightly absorbed from skin.
Absorption of iodine from povidone-iodine solution is possible after a long-term treatment, application on large areas, open wounds and frequent application. The absorption of iodine results with an elevated blood iodine concentration, thyroid dysfunction, nephrotoxicity, metabolic acidosis and elevated iodine excretion in urine.

Povidone-iodine has complex elimination kinetics. It is mainly eliminated via kidneys and the renal passage limit of povidone-iodine is a molecular weight higher than 35,000-40,000. The elimination half-life in healthy volunteers for povidone-iodine^{131} is 11-15 hours.

5.3. Preclinical safety data

Subchronic and chronic toxicity studies in rats had shown reversible and dose dependent elevations of PBI (protein binding iodine) in serum and nonspecific hystopathological changes in thyroid gland. Preclinical safety data concerning mutagenicity, teratogenicity and embriotoxicity exclude povidone-iodine toxicity. Cancerogenic potential could not be excluded, because long-term carcinogenic studies are not carried out.
Iodine is susceptible to modify fetal thyroid function, because of possible placental distribution.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Macrogol 1000

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Four (4) years.
Not to be used after the expiry date.

6.4. Special precautions for storage

To be stored at a temperature below 25^0C.

6.5. Nature and contents of container

PVC/PE strip (alveolus shape), each contains 7 vaginal suppositories.
The carton box containing 14 vaginal suppositories (2-two strips) and a patient information leaflet inside.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT