SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pyodine Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each 100gm contains:
Povidone-Iodine USP 5.0g
(Equivalent to 0.5g available iodine)

3. PHARMACEUTICAL FORM

Reddish brown gel for topical application.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and elderly

"Pyodine Gel" is indicated for the treatment and prevention of following bacterial, mycotic and viral skin infections:

- Contaminated cuts, abrasions and lacerations
- Post-operative dressing
- Second and third-degree burns
- Skin infections which are secondarily infected
- All types of topical ulcers (including tuberculous and leprotic)
- Bed sores and after minor surgical procedures
- Diabetic and episiotomy wound.

4.2 Posology and method of administration

Posology

- Cover the affected area of skin with "Pyodine Gel" and apply occlusive dressing.
- Twice daily application of gel is sufficient.
- In burn and other chronic wounds thrice daily application is required.
- The product is for External use only.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Warning:

For external use only

Precautions:

If thyroid function test is desired, then during the test period “Pyodine Gel” should not be used.

4.5 Interaction with other medicinal products and other forms of interaction

Absorption of iodine from povidone iodine through either intact or damaged skin may interfere with thyroid function tests. Contamination with povidone iodine of 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

The use of Povidone-Iodine in the mother near term and during breastfeeding increases breastmilk iodine levels and can cause transient hypothyroidism in breastfed infants, especially in geographic areas that are iodine deficient. Maternal exposure to Povidone-Iodine near term can sometimes interfere with thyroid studies done as a part of newborn screening tests. Although Povidone-Iodine is minimally absorbed through intact adult skin, exposure of mothers who are or will be breastfeeding to Povidone-Iodine should be minimized by using lower concentrations of Povidone-Iodine, applying it to the smallest possible surface areas of the body, shortening contact time, and avoiding repeated applications. Iodine absorption can be extensive with vaginal use; avoid douching with povidone iodine or use of iodine-containing tampons during breastfeeding.

Effects in Breastfed Infants:

In a study in Belgium, breastfed infants had urinary iodine levels and thyroid function tests measured at 5 days of age. Infants whose mothers were not exposed to any iodine (n = 23) had urinary iodine levels of 0.144 mg/L, those whose mothers had 10% Povidone-Iodine applied to 900 square cm before epidural analgesia (n = 27) had urinary iodine levels of about 0.28 mg/L, and those whose mothers had 10% povidone iodine applied 3 times to their entire abdomen (n = 11) had urinary iodine levels of 1.84 mg/L. Both basal and thyrotropin-releasing hormone- stimulated thyrotropin (TSH) levels were higher in infants exposed to the breastmilk from mothers who received topical Povidone-Iodine. Serum thyroxine (T4) and liothyronine (T3)levels were normal in all groups.[1]

A woman began bathing almost daily with Povidone-Iodine (1% iodine) and applying Povidone- Iodine 1% ointment to her skin daily during pregnancy and for 6 weeks postpartum for furunculosis. At 6 weeks of age, her breastfed (extent not stated) infant had a low serum thyroxine level of 4 ng/L (normal 7 to 20 ng/L), a greatly elevated serum thyrotropin level of 99 units/L (normal 0.8 to 5 units/L). The infant was treated with oral levothyroxine until the age of 7 months at which time thyroid function tests and

development were normal.[6]

A woman began using Povidone-Iodine as a vaginal douche twice daily after delivery. Her breastfed infant developed hypothyroidism (low serum thyroxine and high thyrotropin) over the first 3 weeks of life. After oral levothyroxine supplementation of the infant was begun and maternal Povidone-Iodine was discontinued, the infant's thyroid function tests normalized within a week.[5]

A group of investigators in Belgium reviewed the results of infant thyrotropin levels on day 5 postpartum in 4745 newborn infants delivered over a 2-year period at their hospital. Infants were divided among those whose mothers had iodine overload (n = 3086) from topical Povidone-Iodine 10% solution during labor and delivery and those whose mothers had no iodine overload (n = 1659). Mothers had Povidone-Iodine applied either as a single application to 900 square cm for epidural anesthesia or 3 applications to the entire abdominal wall for cesarean section. Breastfed infants whose mothers had iodine overload had a greater risk for having elevated thyrotropin levels and requiring recall for retesting (3.2% with cesarean section and 2.7% with epidural anesthesia) compared to those who did not (0.1%). Bottle-fed infants were affected much less than breastfed infants.[7] After replacing Povidone-Iodine with chlorhexidine 0.5% in 70% isopropanol for disinfection for 6 months, 1178 infants that were delivered at this institution had no increased rate of elevations in thyroid function tests and a reduced rate of recalls in breastfed infants.[8]

In a study of mothers in Spain who received 10% Povidone-Iodine (n = 21) or chlorhexidine (n = 13) topically to the perineum starting immediately before the final stage of labor and daily postpartum to the episiotomy, no differences in thyrotropin, thyroxine or free thyroxine was found among their breastfed infants at day 5 to 7 postpartum.[2]

A breastfed infant whose mother was using Povidone-Iodine as a douche during pregnancy and during the first few weeks after delivery had symptoms of sinus tachycardia and increased concentrations of blood total and free thyroxine at 10 days of age and elevated thyrotropin at 1 month of age. The Povidone-Iodine was discontinued and the infant's total thyroxine normalized by 1 month of age, free thyroxine normalized by 1.5 months of age and the thyrotropin level normalized by 2.5 months of age. No other explanation for the thyroid function abnormalities could be found except maternal Povidone-Iodine use, but blood and milk iodine levels were not measured. Povidone-Iodine was the probable cause of the adverse reaction in the infant.[9]

A study in Japan randomized 80 consecutive term patients into 4 groups who received either Povidone-Iodine or benzalkoniumchlorideas a skin disinfectant before delivery and one of these for postpartum vaginal lacerations. Prepartum doses were about 7 mL and postpartum doses were about 0.5 mL of solution. Infant thyrotropin levels were elevated in the infants whose mothers received topical Povidone-Iodine pre- and postpartum compared to infants whose mothers received no Povidone-Iodine. After discontinuing the use of peripartum Povidone- Iodine, the rate of recall of infants for abnormal thyroid function tests dropped from 4.47% to 0.74%.[3]

In Switzerland, a girl born at 29 weeks of gestation with adequate size for gestational age showed negative TSH screening on day 5. Her mother had developed an abscess of the abdominal wall 1 week after her cesarian section and was treated with Povidone-Iodine tampons. The baby's TSH was elevated to 23 milliunits/L on day 23, and 288 milliunits/L on day

29. Free thyroxine (T4) levels were decreased to 2.8 ng/L and free liothyronine (T3) with 1.52 ng/L, without signs or symptoms of hypothyroidism. Iodine contents of maternal milk and of infant urine were 4.4 mg/L and 3.9 mg/L, respectively. Treatment with levothyroxine was started, breastfeeding was discontinued and disinfection with Povidone-Iodine was stopped. The infant's thyroid function tests normalized after 6 days.[10] The infant's abnormal thyroid function tests were probably caused by maternal iodine use.

4.7 Effects on ability to drive and use machines

Not reported.

4.8 Undesirable effects

Although rare, local hypersensitivity reactions have occurred. Serum PBI may increase temporarily in some patients after topical application of Povidone-Iodine

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. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

4.9 Overdose

a) Intoxication symptoms

Following inadvertent oral intake of large amounts of Povidone-Iodine, symptoms of acute iodine in-toxication can manifest such as abdominal pain and cramps, nausea, vomiting, diarrhoea, dehydration, drop in blood pressure (persistent), tendency to collapse, epiglottitis, haemorrhagic diathesis (mucosal membranes and kidneys), cyanosis, renal damage (acute tubular necroses up to anuria [after1-3 days]), parathesias, fever and pulmonary oedemas. Following long-term excessive intake of iodine, hyperthyroidism, tachycardia, restlessness, tremor and headache can occur as symptoms.

In the literature, symptoms of intoxication after the intake of more than 10g Povidone-Iodine were reported.

b) Therapeutic measures to treat cases of intoxication

Immediate administration of foodstuffs containing starch and protein, e.g., corn flour stirred into milk or water, or gastric lavage with 5% sodium thiosulphate solution or starch suspension.

After absorption has already taken place toxic serum iodine concentrations can be reduced effectively by peritoneal dialysis or haemodialysis.

Thyroid function must be monitored carefully clinically to rule out or identify at any early stage any possible iodine-induced hyperthyroidism.

Further therapy is carried out as required to manage other possible existing symptoms such as metabolic acidosis and renal dysfunction, for example.

c) Treatment of iodine-induced hyperthyroidism

The treatment of iodine-induced hyperthyroidism (possible side effect in predisposed patients, see also 4.3 “Contraindications”) is conducted as clinically indicated. Mild forms may require no treatment, pronounced forms may require anti-thyroid medical therapy (which is, however, effective only after a delay). In the most severe cases (thyrotoxic crisis), intensive therapy, plasmapheresis or thyroidectomy may be required.

Excess iodine can produce goitre and hypothyroidism or hyperthyroidism. Systemic absorption of iodine after repeated application of povidone iodine to large areas of wounds or burns may lead to a number of adverse effects: metallic taste in mouth, irritation and swelling of the eyes, pulmonary oedema, skin reactions, gastrointestinal upset and diarrhoea, metabolic acidosis, hypernatraemia and impairment of renal function. In the case of accidental ingestion of large quantities of Betadine, symptomatic and supportive treatment should be provided with special attention to electrolyte balance and renal and thyroid function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Broad-spectrum antiseptic, bactericidal, virucidal and fungicide.

Mechanism of action:

Povidone iodine is an iodophore that has an established use as a broad-spectrum antiseptic, mainly for the treatment of contaminated wounds and for the preoperative preparation of the skin, mucous membranes and the ocular surface. The organic complex contains approximately 10% of active available iodine.

Its spectrum of activity is iodine which gradually and slowly released exerts:

- bactericidal effect in less than 5 minutes in vitro, for all bacteria,

- fungicide effect for yeasts and filamentous fungi.

Solutions of povidone iodine gradually release iodine to exert an antimicrobial effect against bacteria, fungi, viruses, and spores. Although povidone iodine is less potent than preparations containing free iodine, it is also less toxic.

Organic materials (proteins, serum and blood) reduce the activity of free iodine, the active form of the medicinal product. Iodophor**e**s are unstable at alkaline pH.

Elemental iodine has a very broad antimicrobial spectrum: bacteria, viruses, bacterial endospores, fungi and protozoas are destroyed through oxidative interaction and direct iodination of biological macromolecules. However, there have been reports of certain resistant germs. Povidone-Iodine (synonym: PVP iodine) is an iodophor, i.e., it is a labile complex of iodine with the polyvinylpyrrolidone polymer, from which iodine is continually delivered. Only this free iodine has antimicrobial activity. In iodophors there is a complex relationship between the concentration of the solution and the concentration of free iodine, so that e.g. through the dilution of a 10% solution with a rate of 1:10 *more* free iodine is released from the complex and the antimicrobial activity is increased.

The active ingredient, povidone iodine, slowly liberates iodine when in contact with skin and mucous membranes. The activity of 'iodine' as a microbicide is then governed by a series of dissociations: $I_2 \leftrightarrow I^+ + I^-$; $I_2 + H_2O \leftrightarrow H_2O\ I^+ + I^-$; $I_2 + I^- \leftrightarrow I_3^-$. The microbicidal species $H_2O\ I^+$ preferentially displaces oxygen as the end electron acceptor in the microorganism's respiratory cycle. $H_2O\ I^+$ similarly interacts within the electron transport chain and reacts with the amino acids of the microbial cell membrane.

5.2 Pharmacokinetic properties

After applying Povidone-Iodine the possibility of iodine absorption must be considered. This depends upon the nature and duration of treatment as well as the amount applied. Following application to the intact skin only very small amounts of iodine are absorbed. Marked absorption of iodine can occur after long-term application of Povidone-Iodine-containing medication to mucosal membranes, extensive skin, wound or burn surfaces and especially after irrigation of body orifices. An elevated iodine concentration in the blood as a result of this is generally transient. In people with a healthy thyroid gland, the increased availability of iodine does not lead to clinically relevant changes in thyroid hormone status. If iodine metabolism is normal, iodine elimination via the kidneys is enhanced.

The absorption of povidone and, to a greater extent, the renal elimination of povidone is dependent on the average molecular weight of the mixture. Above a molecular weight of 35,000 to 50,000 retention within the reticulohistiocytic system is to be expected. The accumulation of povidone in the body and other changes which may be seen following intravenous or subcutaneous administration of povidone-containing medicaments do not occur after topical application of Povidone-Iodine.

5.3 Preclinical safety data

Povidone-Iodine had a low acute toxicity in both dogs and cats following either oral or intraperitoneal administration. Absorption of iodine through intact skin is low following the application of solutions of Povidone-Iodine although systemic absorption of iodine is greatly increased if the solutions are applied to broken skin, mucous membranes or are introduced into cavities of the body. At subcutaneous dose levels of up to 75mg/Kg/day, Povidone-Iodine was non-teratogenic in rabbits following administration to pregnant animals during the period of organogenesis.

Some early *in vitro* studies indicated a possible mutagenic action for Povidone-Iodine. However, a number of later studies, using *in vitro* and *in vivo* test systems, do not indicate a significant level of mutagenic/genotoxic activity for Povidone-Iodine. Although conflicting data have been published, there is no convincing evidence to suggest that Povidone-Iodine adversely affects wound healing. Concentration of 0.05 and 0.5% Povidone-Iodine did not cause significant ocular damage when administered into the vitreous cavities of rabbits' eyes. There is some evidence to suggest that Povidone-Iodine-containing solutions applied to the round window of the chinchilla ear could result in high frequency hearing loss.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene Glycol 400 Liquid

Polyethylene Glycol 4000 (Flakes)

Sodium Hydroxide

D.I. Water (Purified water)

6.2 Incompatibilities

Povidone-Iodine is incompatible with reducing agents, alkaloid salts, tannic acid, salicylic acid, silver, mercury and bismuth salts, taurolidine and hydrogen peroxide.

6.3 Shelf life

3 years (36 months)

6.4 Special precautions for storage

Store at temperature below 30^{o}C away from light and moisture.

6.5 Nature and contents of container

Packed in 20gm aluminium tube, sealed with plastic cap, further packed in carton with insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Brookes Pharma Private Limited.
58 & 59, Sector No15, Korangi Industrial Area
Karachi –74900
Pakistan

8. MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0442

9. DATE OF RENEWAL OF THE AUTHORIZATION

07th October, 2022

10. DATE OF REVISION OF THE TEXT