stedman PHARMACEUTICALS PRIVATE LTD.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

DREZ Solution (Iodinated Povidone and Metronidazole Solution)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Iodinated-Povidone BP 5.0% w/v

(0.5% w/v available Iodine)

Metronidazole BP 1.0% w/v

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM:

Topical Solution

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications

Drez Solution is a topical dressing medicament for cleaning of wounds. It is also for Pre operative irrigation of the operative site, Postoperative irrigation of the operated site, Irrigation of wounds.

4.2 Posology and method of administration

Adults

DREZ Solution is for external use only. Should be applied in full strength. Sufficient quantity of solution should be used to irrigate wounds or for pre and post operative irrigation of the operated site as often as required (or) as directed by the physician.

Children

Dosage recommendations and indications for the use of DREZ Solution in children have not been established.

Geriatric Use

No overall differences in efficacy and safety were observed in elderly patients compared to younger patients.

4.3 Contraindications

DREZ Solution is contraindicated in those patients who are hypersensitive to iodine or other ingredients of the preparation. Povidone iodine is not recommended for regular use in neonates and contraindicated in very low birth weight infants (Below 1500 grams). Regular use is contraindicated in patients or users with thyroid disorders.

4.4 Special warnings and precautions for use

Application of Drez Solution to large areas of the body is to be done under medical supervision. Hypothyroidism may occur following ingestion of large quantities of Drez Solution.

This medicine is not ophthalmic use. Use this medicine as directed by the Physician. Do not use expired medicines. Do not exceed maximum recommended period of use.

4.5 Interaction with other medicinal products and other forms of Interactions

Can interact with lithium therapy Absorption of iodine from Iodinated Povidone may interfere with thyroid function tests. Contamination with Iodinated Povidone of several types of tests for the detection of occult blood in faeces or blood in urine may produce false positive results.

4.6 Pregnancy and lactation

Hypothyroidism can occur in neonates both as a result of absorption iodine from Povidone-iodine applied to the neonate and also to the mother during pregnancy or breast-feeding.

Topical Iodine containing antiseptics may induce hypothyroidism in very low-birth weight infants, (Smerdely et al., 1989). Multiple applications of Povidone Iodine in pregnancy, and lactation caused transient congenital Hypothyroidism in a 6 week old girl, (Danziger et al., 1987). Regular use of Povidone Iodine containing products should be avoided in pregnant and lactating woman.

There are no controlled data in human pregnancies. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral Metronidazole in rats or mice. Because animal reproduction studies are not

always predictive of human response, Metronidazole should only be given during pregnancy when benefit outweighs risk and when alternative treatments have been ineffective.

Regular use of Povidone Iodine containing products should be avoided in lactating woman. After oral administration, Metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels of Metronidazole via topical route is significantly lower than those achieved after oral Metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

Occasionally local side effects such as skin rash, itching and redness may be associated with the use of Drez Solution.

4.9 Overdose

Ingestion of iodine may cause corrosive effects such as oedema of the glottis, with asphyxia, aspiration pneumonia, pulmonary oedema and shock, vomiting and bloody diarrhoea.

The CNS, cardiovascular and renal toxicity following acute iodine ingestion appears to be due to the corrosive gastroenteritis and resultant shock. Vomiting, hypotension and circulatory collapse may be noted following severe intoxication.

Skin exposure: Skin contact with iodine may give rise to hypersensitivity reaction, fever and skin eruption. Death following skin contact covering one third of body surface is reported to have occurred, (Gosselin et al., 1984).

Intact skin: Irritant contact dermatitis caused by povidone-iodine has been reported, Okano, 1989).

Liberal application of the tincture or povidone-iodine to the skin resulted in significant plasma and urine iodine levels and may cause systemic iodine toxicity (Luckhardt et al., 1920; Smerdely et al., 1989; Pyati et al., 1977; Chabrolle & Rossier, 1978;

Coakley et al., 1989; L'Allemand et al., 1987; Dantzigen et al., 1987; Schoenberger & Grim, 1982).

Injured skin: Continuous postoperative wound irrigation with povidone-iodine resulted in death of a patient. Toxic manifestations of systemic iodine absorption appeared to cause the death, (D'Auria et al., 1990; Glick et al., 1985).

Application of povidone-iodine on skin burns may cause systemic iodine toxicity (Lavelle et al., 1975; Peitsch & Meakins, 1976).

Iodism effects

A mild toxic syndrome called iodism results from repeated administration of small amount of iodine. Iodism is characterised by hyper-salivation, coryza, sneezing, conjunctivitis, headache, laryngitis, bronchitis, stomatitis, parotitis, enlargement of the submaxillary glands, skin rashes and gastric upsets, (Reynolds, 1989, Gosselin et al, 1984). In rare cases jaundice, bleeding from mucous membranes and bronchospasm may occur. Inflammatory states may be aggravated by these adverse reactions, (Bouillon, Do not induce vomiting nor do gastric lavage. Treatment is symptomatic. In symptomatic patients, early endoscopy is indicated in order to provide an early evaluation of the corrosive lesions in the oesophagus and the stomach.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Halogens such as Iodine are rapidly bactericidal, fungicidal, virucidal and sporicidal. Iodine on coming into contact with water releases nascent Oxygen, which damages the nuclei of the pathogens. Because of this unique mode of action, development of resistance has not been a clinical problem with the use of Iodine. Although Iodine is considered as one of the best all round antiseptic, its use is associated with irritation and excessive staining in a significant number of patients. In addition aqueous solutions of Iodine are unstable.

To overcome these problems iodophors were developed (Iodine carriers or Iodine-releasing agents). Iodophors are complexes of Iodine and a solublising agent or carrier, which acts as a reservoir for the active "free" Iodine. The most widely used Iodophor throughout the world is 'Iodinated- Povidone". Although iodophors such as

Iodinated-Povidone have good germicidal activity, Iodophors are less effective against anaerobic bacteria. This dissuades many physicians from prescribing Iodinated-Povidone preparations.

Metronidazole is a member of the Imidazole class of anti-bacterial agents and is effective against a wide variety of anaerobic bacteria such as Bacteroides spp, Fusobacterium, Peptococcus and Peptostreptococcus spp. that are commonly found in contaminated wounds. In malodorous skin lesions (primarily fungating tumors and decubitus ulcers) the offending bacteriae appear to be anaerobes, specifically the Bacteroides species. Topical Metronidazole has shown promise for odor control without the cost or side effects of a systemic drug.

Mode of action

The microbicidal activity of Iodinated-Povidone is due to the strong oxidising effects of free Iodine on functional groups of amino acids, nucleotides and double bonds of unsaturated fatty acids. These studies indicate that Iodinated-Povidone interacts with cell walls of Micro-organisms cause pore formation or generating solid liquid interfaces at the lipid membrane level which lead to loss of cytosol material in addition to enzyme denaturation.

Metronidazole is a prototype Nitroimidazole and has broad spectrum cidal activity against protozoa and many anaerobic bacteria. After entering the cell by diffusion its Nitrogroup is reduced by certain redox proteins operative only in anaerobic microbes by highly reactive nitroradical exerts cyctotoxicity by damaging DNA and other critical biomolecules. It has been found to inhibit mediated immunity, to induce mutagenesis and to cause radiosensitization.

5.2 Pharmacokinetic properties

Only very small quantities of iodine are absorbed through an intact skin, (Reynolds, 1989). Iodine can be absorbed by wounds and abrasions. Enhanced absorption occurs through denuded skin, decubitus ulcers, mucosal surfaces with high absorptive capacity (vagina), or large areas of intact skin, (Dela Cruz et al., 1987; Vorherr et al., 1989; Prager & Gardner 1979; Cosman et al., 1988).

Distribution is poor due to low absorption through intact skin. Enhanced distribution occurs through denuded skin.

Serum metronidazole levels have been shown to be below detection limits (<25 ng/mL) at the majority of time points after administration of topical metronidazole. At the time points that it could be detected, topical metronidazole produced blood levels (C max 40.6 ng/mL) that were approximately 80% less than a similar dose administered orally (C max 212 ng/mL). Therefore, with normal usage, topical metronidazole results in minimal blood levels of metronidazole.

Absorption of metronidazole after topical application of in lotion is less complete and more prolonged than after oral administration. Detectable plasma levels were found in all subjects following the administration of a single 1 gram dose of Topical Lotion (containing 7.5 mg of metronidazole) to the faces of 12 healthy volunteers. The highest concentration (64 ng/mL) seen was approximately 100 times lower than the peak concentrations produced by a single 250 mg tablet of metronidazole. The mean relative bioavailability of metronidazole from Topical Lotion was 47.4%.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Toxicity & Carcinogenicity:

Metronidazole has a very high margin of safety. No lethal dose has been described in humans as yet.

Relevant animal data

Iodinated Povidone

LD_{50} oral (rats)	5990 mg/kg
LD_{50} i.p. (mice)	360 mg/kg

Metronidazole

LD_{50} oral (rats)	1 to 5 g/kg
LD_{50} oral (mice)	1 to 5 g/kg

No serious toxicity has been reported in rats dosed with Metronidazole at 150 mg/kg/day, dogs at 50 to 75 mg/kg/day or monkeys at 225 mg/kg/day. Promotion of pulmonary tumour at a very high level in the mouse (500 mg/kg/day), produced a statistically significant increase in live tumours. Two lifetime studies in hamsters were negative.

In higher doses, testicular dystrophy and prostatic atrophy have been reported in rats and dogs which showed ataxia, muscular atrophy and tremors.

In long-term toxicity studies involving rats for 2 years (normal life span) high doses have been given and the results have been conflicting. Cohen (1973) reported no increase in tumour incidence, while Rustia & Shubik (1972) found increased incidence of tumours in male mice, female mice showed increased incidence of lung tumour, but absolute incidence was actually less than male mice controls. Female mice also had lymphomas more often when given two higher doses.

There is no evidence as to whether iodine is carcinogenic or not. However, connections have been established with deliberate or inadvertent intake of radioactive elements or their compounds that concentrate in certain organs or tissues. Thus intake of labelled iodine and derivatives concentrating in the thyroid gland, have been known to give rise to cancer in that organ (Harbison, 1980; Dukes, 1988)

Subchronic Toxicity

In a 12-week dietary study in rats, ingestion of povidone iodine at an average povidone iodine dosage of approximately 75 to 750 mg/kg/day produced a dose dependent increase in serum protein-bound iodine and nonspecific, reversible microscopic changes in the thyroid. No other gross or microscopic Iodinated Povidone induced changes were observed. At equivalent iodine dosages, dietary potassium iodide produced similar thyroid changes of equal or greater severity.

Teratogenicity:

Metronidazole crosses the placental barrier and enters fetal circulation. Studies in rats in doses upto 5 times human doses have not reported any harm to foetuses. Although Metronidazole has been given in all the stages of pregnancy orally no adverse report has been received. However, it is not recommended for use in first trimester of pregnancy.

Iodides diffuse across the placenta. Infant and neonatal death from respiratory distress secondary to goitre has been reported in mothers taking iodides (Parmalee et al., 1940; Galima et al., 1962).

Chronic topical maternal use of povidone-iodine during pregnancy has been associated with clinical and biochemical hypothyroidism in the infant (Danziger et al., 1987).

Exposure to I^{131} can damage or ablate the developing thyroid of the human foetus. Hypothyroidism, either congenital or of late onset, has been reported in at least 5 children whose mothers were exposed to I^{131} during pregnancy (Shepard, 1980)

Mutagenicity:

Metronidazole is mutagenic in rodents in high doses for prolonged periods. It is also mutagenic in bacteria (Voogde, 1981). Mutagenic activity associated with Metronidazole has been reported in the urine of patients receiving therapeutic doses. Tests on Chinese hamsters, the micronucleus test and the dominant lethal test indicate that iodinated povidone is not mutagenic.

Bacterial mutagenicity: negative

Bone marrow (hamster): negative

Dominant lethal assay (mouse): negative

Mouse lymphoma: negative

Mouse micronucleus: negative

6 Pharmaceutical Particulars :

6.1 List of excipients

Anhydrous Disodium Hydrogen Phosphate, Glycerin, Polyoxyethylene (9.5) nonyphenol, Citric Acid Monohydrate, Sodium Hydroxide, Povidone and Purified Water.

6.2 Incompatibilities: None reported.

6.3 Shelf life: 24 months

6.4 Special precautions for storage:

Store in a well closed container at a temperature not exceeding 30°C. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container:

30 ml, 100 ml amber coloured glass bottles with printed labels packed in an outer carton with a pack inserts.

500 ml amber coloured PET bottles with printed labels.

6.6 Special precaution for disposal

No special requirement.

7. REGISTRANT

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8. MANUFACTURER

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