1.6 Product information

1.6.1 Prescribing information (Summary of Product Characteristics)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

DIPEROXOCHLORIC ACID TOPICAL SOLUTION (WOXHEAL)

1.1 Strength:

Each pack contains:

Bottle A

Diperoxochloric Acid Concentrate

Each ml contains:

Diperoxochloric Acid Concentrate…… 1.16 mg

Bottle B

Sterile Sodium Chloride Solution BP 0.9% W/V

(Cutaneous Solution)

Reconstituted Solution (Bottle A + Bottle B) in Bottle B

Each ml contains:
Diperoxochloric Acid Concentrate…… 0.29 mg

Pack size : Bottle A 7.5 ml/ Bottle B 22.5 ml

Packing also contains:

1. Sterlised Gauze Swab (Inner & Outer) – 14 Nos. (Manufactured separately)
2. Sterlised Rolled Guaze – 7 Nos. (Manufactured separately)
3. 1 ml glass droper in polybag – 1 No. (Manufactured separately)
4. ½ inch 3 M microtape – 1 No. (Manufactured separately)

1.2 Pharmaceutical form:

Topical Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

DIPEROXOCHLORIC ACID TOPICAL SOLUTION (WOXHEAL)

Each pack contains:

Bottle A

Diperoxochloric Acid Concentrate

Each ml contains:

Diperoxochloric Acid Concentrate…… 1.16 mg

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Sterile Sodium Chloride Solution BP 0.9% W/V

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3. 1 ml glass droper in polybag – 1 No. (Manufactured separately)
4. ½ inch 3 M microtape – 1 No. (Manufactured separately)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM: Topical Solution

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Diperoxochloric Acid Topical Solution is indicated for wound healing in diabetic neuropathic ulcers of skin and subcutaneous tissues.

4.2 Posology

Before applying to the wound dressing, Diperoxochloric Acid concentrate [Bottle A] has to be "Reconstituted" by mixing the contents of bottle A into the contents of bottle B as per instructions provided below.

Instructions for preparation of Diperoxochloric Acid Topical Solution "Reconstituted" solution and wound dressing:

- Open 'Bottle A' and 'Bottle B'.
- Pour the contents of Bottle A into Bottle B. Close bottle B with bottle cap.
- Mix the content by moving the bottle upside down for 5 times gently.
- Diperoxochloric Acid Topical Solution "Reconstituted" solution is prepared
- For wound dressing we recommend a non-sticky, sterile multi wound dressing available in different sizes: 5 x 5 cm or 10 x 15 cm.

4.3 Method of administration:

- Wash hands thoroughly before applying Diperoxochloric Acid Topical Solution.
- Take out dropper from plastic bag (provided in the pack) and fit it on the bottle B.
- Apply 3.5 ml of this solution with help of the dropper on the 5 x 5 cm dressing (inner gauze swab) to bring the dressing to earth moist conditions or as directed by the Physician.
- Do not touch the dropper to the dressing / bandage.
- Then apply this inner gauze swab on the wound.
- Cover this inner gauze swab with outer gauze swab, which will prevent the wound area from running dry.
- Finally, tie bandage rolled gauze to secure the gauzes. Daily remove the outer gauze swab and apply Diperoxochloric Acid Topical Solution on inner gauze swab without removing the inner gauze swab from the wound.
- Change the outer gauze swab daily and inner gauze swab on every alternate day or as per your Doctor's advice.

- The Reconstituted Solution should not be used after 14 days of mixing/reconstitution.

4.4 Contraindications:

Diperoxochloric Acid Topical Solution is contraindicated in patients with hypersensitivity to the formulation or any of the components of the formulation.

4.5 Pediatric population

None.

4.6 Interaction with other medicinal products and other forms of interaction:

- There are no known drug-drug interactions of Diperoxochloric Acid Topical Solution.
- The phase II and III clinical trials conducted in patients did not reveal any data towards drug-drug interaction.
- In the clinical laboratory investigation done as safety evaluation in the phase II and III clinical trials, no change in clinical laboratory parameters was noted.
- During phase II and III clinical trials, Diperoxochloric Acid Topical Solution was co-prescribed along with insulin and oral hypoglycemic drugs such as sulfonylurea, biguanides, DPP-4 inhibitors or SGLT2 inhibitors for the treatment of underlying diabetes. No drug-drug interaction was noted.
- Drug-Drug Interactions with other topical Antimicrobials and Antiseptics is not studied.
- Diperoxochloric Acid Topical Solution did not have any interaction with dressing material [gauze]

4.7 Additional information on special populations

None.

4.8 Pediatric population

None.

4.9 Fertility, Pregnancy, and lactation:

- Pregnancy: Diperoxochloric Acid Topical Solution has not been tested in pregnant ladies. No reproductive toxicity studies were conducted.
- Lactation: Diperoxochloric Acid Topical Solution has not been tested in lactating females.
- Children: Diperoxochloric

4.10 Effects on ability to drive and use machines:

Not applicable

4.11 Undesirable effects:

In the phase II and phase III clinical trial conducted in patients of diabetic foot ulcer, no adverse drug reaction [ADR] could be allocated to Diperoxochloric Acid Topical Solution. Following is the complete listing of adverse events noted during the clinical trials:

Adverse event	Related to Test drug DPOCL	Related to active- control drug, isotonic normal saline	No relationship to test or control drug
Hypoglycemia	**-**	**-**	**2**
Hyperglycemia	**-**	**-**	**1**
Abscess	**-**	**-**	**2**
Anemia	**-**	**-**	**1**
Osteomyelitis	**-**	**-**	**1**
New ulcer or increase in ulcers	**-**	**-**	**2**
Gangrene	**-**	**-**	**1**
Allergic rash and edema	**-**	**-**	**1**
Injury	**-**	**-**	**1**
Death	**-**	**-**	**1**
Adverse event	**Related to Test drug DPOCL**	**Related to active- control drug, isotonic normal saline**	**No relationship to test or control drug**
Hypoglycemia	-	-	2
Hyperglycemia	-	-	1
Abscess	-	-	2
Anemia	-	-	1
Osteomyelitis	-	-	1
New ulcer or increase in ulcers	-	-	2
Gangrene	-	-	1
Allergic rash and edema	-	-	1

Injury	-	-	1
Death	-	-	1

4.12 Overdose:

Since there is no absorption from the site of topical application, no untoward systemic effects are expected.

5. PHARMACOLOGICAL PROPERTIES:

In the preclinical pharmacology, Diperoxochloric Acid Topical Solution was investigated to see if it fulfilled two important properties for the healing of open wounds,

(a) Fights bacterial infections in the wound, and

(b) Enhances cell proliferation of Fibroblasts specifically, to stimulate the healing and enforce closing of the wound.

Antibacterial action:

Diperoxochloric Acid Topical Solution is functionally antibacterial (especially against gram negative bacteria), which keeps the bacterial burden of open wounds low. Diperoxochloric Acid Topical Solution shares functional properties of Reactive Oxygen Species [ROS] at least concerning their antibacterial activity. Anti-bacterial activity according to the German standard DIN 58940 was shown against E. coli, P. aeruginosa and S. aureus bacteria.

Fibroblast cell proliferating action:

Diperoxochloric Acid Topical Solution shows fibroblast-proliferating activity towards MRC-5 fibroblast cells. This suggests that the ratio of vital to dying cells in the wound is improved by Diperoxochloric Acid Topical Solution. Significant growth stimulation was observed in a time course up to four days following stimulation with Diperoxochloric Acid Topical Solution.

Clinical experience:

Diperoxochloric Acid Topical Solution was effective in the treatment of neuropathic, chronic, cutaneous ulcers of the lower extremity in patients with diabetes, as noted in the multi-centric, randomized, double-blind; active-controlled, comparative, parallel-group phase II study was carried out in India. The overall success rate of Diperoxochloric Acid Topical Solution treated patients was 93% with an over threefold faster reduction of the wound area in the Diperoxochloric Acid Topical Solution-group than group receiving the "control" drug Isotonic Sodium chloride solution. The safety of the Diperoxochloric Acid Topical Solution-solution was excellent and comparable with the "control" drug Isotonic Sodium chloride solution as elucidated by safety evaluation.

In the phase III clinical trial, the efficacy and safety of Diperoxochloric Acid Topical Solution was investigated in over 300 patients suffering from diabetic foot ulcer in comparison with active-control solution i.e. isotonic normal saline [0.9%]. Following results were obtained:

1) **Complete wound healing:** 71.03% wound completely healed in Diperoxochloric Acid Topical Solution group as compared to only 57.53% in Active control. This figure was statistically significant [p = 0.0156]

2) **Time taken for complete closure of wounds:** Diperoxochloric Acid Topical Solution resulted in faster wound healing compared to active-control, as median time taken for complete closure of wounds in Diperoxochloric Acid Topical Solution group was 42 days as compared to 56 days in Active control group.

3) **Overall treatment responders:** More than 90% of the patients treated with Diperoxochloric Acid Topical Solution had positive response as compared to 66% of active-control [treatment response defined by at least 50% wound reduction in 4 weeks].

5.2 Pharmacokinetic properties

Pharmacokinetic evaluations are not applicable since Diperoxochloric Acid Topical Solution is not absorbed from the site of application.

5.3 Preclinical safety data

The toxicology studies were carried out on Diperoxochloric Acid Topical Solution at LPT2 labs, Hamburg, Germany and followed all concerned regulations of Good Laboratory Practice [GLP] and OECD Principles of Good Laboratory Practice, 2002. Following information was generated in the toxicological studies:

Toxicological data of WOXheal ®				
Toxicity	**Route**	**Dose**	**Species**	**Effect**
Acute	Intravenous	150 mg/ kg body weight single dose	Mice	No mortality, no toxicity
		250 mg/ kg body weight single dose	Mice	0-5 minutes after administration: Reduced mobility, dyspnea
		500 mg/ kg body weight single dose	Mice	0-5 minutes after administration: Reduced mobility, dyspnea
	Intravenous	150 mg/ kg body weight single dose	Rats	No mortality, no toxicity
		250 mg/ kg body weight single dose	Rats	0-5 minutes after administration: Reduced mobility, dyspnea
		500 mg/ kg body weight single dose	Rats	0-5 minutes after administration: Reduced mobility, dyspnea

Toxicological data of WOXheal ®				
Sub-chronic	Intravenous	10 mg/ kg body weight once daily for 28 days	Rats	No mortality, no toxicity
	Intravenous	10 mg/ kg body weight once daily for 28 days	Beagle dogs	No mortality, no toxicity
Local	Acute eye irritation/ corrosion test	Single instillation of 0.1 ml	Rabbits	Cornea, conjunctivae & iris not affected
	Acute dermal irritation [Patch test]	0.5 ml per patch - single dose	Rabbits	No skin reaction/ systemic intolerance

Mutagenicity:

Ames Test: No mutagenic effect (no increase in revertant colony numbers as compared with control counts) was observed for Diperoxochloric Acid Topical Solution tested up to cytotoxic concentrations of 1000 or 316 µg/plate in any of the 5 test strains in two independent experiments without and with metabolic activation (plate incorporation and pre-incubation test, respectively.

Micronucleus test on bone marrow cells: Diperoxochloric Acid Topical Solution tested up to the highest reasonable dose level of 150-mg/kg b.w. by intravenous administration showed no mutagenic properties in the rat bone marrow micronucleus study at the two tested sampling times of 24 hours and 48 hours. In the same system, cyclophosphamide (positive reference item) induced significant damage.

Other toxicity:

Pulmonary toxicity: Diperoxochloric Acid Topical Solution tested at dose levels of 15, 50 and 150 mg /kg b.w. by intravenous administration revealed no test item-related influence on pulmonary parameters

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

1. Bottle A – Diperoxochloric Acid Concentrate

There is no excipient added in Bottle A, as the Active solution of Diperoxochloric Acid Concentrate form bulk pack is refilled in 8 ml HDPE bottle under aseptic condition.

2. Bottle B – Sterile Sodium Chlorie Solution BP 0.9% w/v

The below table describes the excipients used in Sterile Sodium Chlorie Solution BP 0.9% w/v (Bottle B)

Sr. No.	Ingredients	Specification
1	Hydrochloric Acid	British Pharmacoepia
2	Water for Injections	British Pharmacoepia

6.2 Incompatibilities: Not applicable

6.3 Shelf life:24 months from the date of manufacture.

6.4 Special precautions for storage:

Bottle A – 7.5 ml Diperoxochloric Acid Concentrate Solution filed in 8 ml HDPE bottle: Store at a temperature not exceeding 25°C.

Bottle B – 22.5 ml Sterile Sodium Chloride Solution BP 0.9% w/v filled in 30 ml HDPE bottle: Store at a temperature not exceeding 25°C.

Reconstituted Solution: After mixing content of Bottle A in the content of Bottle B in Bottle B, Solution should not be used after 14 days of reconstitution and should be stored at a temperature not exceeding 25°C

6.5 Nature and contents of container:

Each pack contains:

Bottle A

Diperoxochloric Acid Concentrate

Each ml contains:

Diperoxochloric Acid Concentrate…… 1.16 mg

Bottle B

Sterile Sodium Chloride Solution BP 0.9% W/V (Cutaneous Solution)

Pack size : Bottle A 7.5 ml/ Bottle B 22.5 ml

Packing also contains:

1. Sterlised Gauze Swab (Inner & Outer) – 14 Nos. (Manufactured separately)
2. Sterlised Rolled Guaze – 7 Nos. (Manufactured separately)
3. 1 ml glass droper in polybag – 1 No. (Manufactured separately)
4. ½ inch 3 M microtape – 1 No. (Manufactured separately)

6.6 Special precautions for disposal and other handling:

No special requirements

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS:

Marketing Authorization holder:

Centaur Pharmaceuticals Pvt. Ltd.

Manufacturing Site address:

Centaur Pharmaceuticals Pvt. Ltd.

Address: Plant: I, Plot No: 3, Tivim Industrial Estate, Karaswada, Mapusa Goa-403526

8. MARKETING AUTHORISATION NUMBER

No. 158(488)/MFG/DFDA/2020/2063

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

26.10.2020

10. DATE OF REVISION OF THE TEXT: -

11. DOSIMETRY (IF APPLICABLE): NOT APPLICABLE.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

NOT APPLICABLE.