Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product

Brand Name:

REGEN-D®150

Generic Name:

Recombinant Human Epidermal Growth Factor Gel, 150µg/g

2. Qualitative and Quantitative Composition:

Each gram of gel contains:

Purified bulk of rh-Epidermal Growth Factor	150 µg
Sodium methyl paraben	1.8 mg
Sodium propyl paraben	0.2 mg
Excipients	q.s

3. Pharmaceutical Form:

Gel.

4. Clinical Particulars:

4.1 Therapeutic indications:

REGEN-D®150 is indicated for healing diabetes mellitus associated foot ulcers, bedsores (pressure ulcers), chronic Venous Ulcer (venous ulcers).

4.2 Dosage and method of administration:

Posology:

Cleanse the ulcer wound and surroundings surface with water or saline and pat dry with sterile cotton before the gel is applied. Apply the gel evenly (topical application) on the affected area of the skin using sterile cotton swab twice a day till the ulcer area heals. **REGEN-D®150** therapy should be continued up to period of 2 to 3 weeks after the wound heals. The continuation of the therapy is at the discretion of the physician.

A single tube should be used for individual patient.

Avoid direct of the tube with wound area

Any unwarranted use of the product is not the responsibility of the manufacturer.

4.3 Contraindications:

REGEN-D®150 is generally well tolerated. However, the product should not be repeatedly given to persons known to be hypersensitive to any of the components of the product. Also, it should not be applied to individuals who receiving immunosuppressive or immune stimulant therapy in immune compromised individuals.

4.4 Special warnings and precautions for use:

It is suggested that the medical practitioner ascertain the hypersensitivity status of the subject.

4.5 Interaction with other medicinal product and other forms of interaction:

REGEN-D®150 must not be used with other growth factor containing gel or cream.

4.6 Pregnancy and lactation:

REGEN-D®150 is contraindicated for use in pregnant and lactating woman.

4.7 Effect on ability to drive and use machine:

Since the product is topical application, systemic absorption is not expected. However, no studies on the effect of **REGEN-D®150** on the ability to drive and use machines has been performed.

4.8 Undesirable Side effects:

REGEN-D®150 has proven low reactogenicity and is well tolerated. However, skin irritation/pain rash at the application site may be seen in very few cases.

4.9 Over dose:

Not applicable.

5.0 Pharmacological Properties:

5.1 Pharmacodynamic properties:

EGF is a part of a complex network of growth factors and receptors that together help to modulate the growth of cells. EGF is released by cells and then is picked up either by the cell itself, stimulating its own growth, or by neighboring cells, stimulating their ability to divide. Receptors on the surface of the cell bind to EGF and relay the signals inside. When the receptor binds to EGF, it is activated by forming a dimer with other receptors. EGF is essential for mediating the de-differentiation of keratinocytes to an epithelial linage and to reestablish the epithelial barrier. EGF binds to the EGFR, a protein tyrosine kinase receptors expressed on the majority of cells in the skin. Activation of EGFR leads to a number of biological responses, including migration, proliferation, cytoprotection, cellular differentiation and apoptosis. In wound healing EGFR Plays an important role in re-epithelialization and dermal maturation. Topical use of recombinant human EGF has been shown to increase re-epithelialization and enhance wound healing.

5.2 Pharmacokinetic properties:

Subjects were followed up for various period of time to evaluate the systemic absorption of **REGEN-D®150** in blood. Sera was analyzed for anti-EGF titers by indirect ELISA method. The test serum absorbance was less than the seroconversion cutoff value. Hence this samples were negative for anti-rHuman EGF antibody.

Patients with wounds were tested for the presence of rhEGF by collecting the samples from the site of Application, the result clearly shows that rhEGF is available at the site of application. Protease enzyme present in the body degrades rhEGF at the site of applications, however when **REGEN-D®150** was applied there was sufficient high concentration of rhEGF locally.

5.3 Pr-Clinical & Clinical Trial Experience

Pre-clinical toxicological studies done on rats and rabbits concluded that the rh-EGF is safe and well tolerable with no systemic observations. The study was conducted to

evaluate the potential toxicity of repeated doses (75-300 µg/Kg) of recombinant human Epidermal Growth Factor applied topically to rats and New Zealand white rabbits groups. The rh-EGF was not absorbed systematically as revealed in the systemic absorption study conducted in rabbit. There has been significant increase in the DNA and collagen contents in the skin samples treated with rh-EGF. No significant changes were observed control and treated groups with respect to protein contents in the skin.

In another study with rats (Wistarfurth) and rabbits (New Zealand white) to evaluate the potential toxicity of repeated doses (75-300 µg/Kg) of rh-EGF applied topically to rats and rabbits, it was found that there was no observable antibody response in the treated groups with EGF in both rats and rabbits. The DNA content in skin sample of treated group has significantly increased in high dose in both the species on 15th and 31st day. The protein content in the control and treated groups did not differ significantly in both the species studied. The collagen content was significantly increased in medium and high dose groups in males and females both the species on 15th and 31st days.

In a multi-centre, double-blind, randomised, parallel, placebo-controlled phase 3 study to evaluate the safety and efficacy of **REGEN-D®150** as a treatment for diabetic foot ulcers, there was a reduction of healing time to an average of 9 weeks compared to the controls within the cut off observation period of 15 weeks. When compared at 15 weeks, 86% healed whereas only 50% healed in the placebo group.

A study conducted in Wistar NIN rats to study the effects of rhEGF on naproxen induced gastric ulcer, showed that treatment with 100 µg/Kg rhEGF significantly resulted in healing of ulcers by 14 days. There was a significant increase in immunoreactivity for cox-2 was observed, when compared to control group.

A multi-centre, randomized, double-blind phase 3, placebo-controlled study was conducted to evaluate the safety and efficacy of recombinant human epidermal growth factor (**REGEN-D®150**) in patients with bed sores (pressure ulcers). Topical application of **REGEN-D®150** gel applied twice daily for 12 weeks was found to be safe and efficacious as it significantly accelerates the rate and number of healing compared to placebo in subjects with bed sores (pressure ulcer). On an average, it took about 40 days

to heal bed sores, in contrast it took about 78 days to heal with placebo. There was one case of rash in in EGF group and two cases of irritation in placebo group. Both these conditions resolved within 48 hours and the subjects continued in the study. These adverse reactions are similar to that reported in previous studies. There were no serious adverse reactions reported. None of the enrolled subjects were withdrawn from study for drug related adverse reaction.

A phase 3 multicenter double-blind, randomized (1:1) parallel study was conducted at 3 centers to evaluate the efficacy and safety of **REGEN-D®150** gel applied topically in patients with Grade I or II (Wagner's classification) diabetic foot ulcers to compare the time required for complete healing of the ulcer in the test group and control group. Healing occurred in about 13 weeks for placebo treated ulcers and 9 weeks for the rhEGF gel treated ulcers. The percent of completely healed ulcers in the gel treated population in week 5, week 10 and week 15 was roughly 18%, 66% and 84% respectively. Studies on EGF in diabetic foot ulcers have documented similar results. EGF was found to be a practical treatment solution for diabetic foot ulcers. Treatment with **REGEN-D®150** was not cumbersome and does not involve complicated dressing procedures.

In a study conducted by Rajesh Kesavan et al, **REGEN-D®150** was compared with placebo in patients with uninfected diabetic foot ulcers. The study showed that **REGEN-D®150** increased collagen content of the wound by 3.6-fold, whereas it was 2.6 -fold increase in the placebo group. Collagen type 1 expression was more in **REGEN-D®150** than in placebo group. The MMP-9 expression was more in the **REGEN-D®150** on the 15th day, where it was on the 30th day in the placebo group. The study established the safety and efficacy of **REGEN-D®150** in healing DFU.

Post-marketing Experience

Post - marketing surveillance (PMS) study **of REGEN-D®150** in 135 patients with diabetic foot ulcer in India was compared with phase 3 clinical trial data of **REGEN-D®150** in India. Statistical analysis of study data determined that the empirical survival probability distribution, in terms of non-healing of ulcers, was lowest in the case of PMS

study, better than that for phase 3; more DFU patients were healed in PMS study. Percentage of patients cured in any given week (e.g. in week 10) is above 90% in PMS study, as compared to 69% in phase 3 clinical trial; this percentage was around 18% for the placebo - control group in the phase 3 trial. The average wound healing time was significantly lower in PMS study, 4.8 while it was 9 weeks in phase III clinical trials while the average wound healing with **REGEN-D®150** was found to be 86% in this study. **REGEN-D®150** has been found to result in healthy granulation and stimulate epithelization, thus leading to final wound closure. The PMS study has established the efficacy of **REGEN-D®150** in faster healing of chronic non healing diabetic foot ulcers. Phase 4, post marketing surveillance study of **REGEN-D®150** was undertaken to study the efficacy of rhEGF in diabetic foot ulcers. Parameters evaluated included ulcer outcome; percentage of healing; duration of healing; and quality of healing and epithelization. All patients (n=54) who were enrolled for the study resulted in good clinical outcome, i.e., ulcers had significantly improved in terms of both percentage of wound closure and quality of healing. The average time required for the healing of an ulcer in this cohort was around 5.5 weeks. An average of 83% wound closure in the cohort was documented. Moreover, the quality and epithelization were excellent.

6.0 Pharmaceutical Particulars

Category: Growth Factor

6.1 List of excipients:

Each gram of gel contains:

Sodium methyl paraben BP

Sodium propyl paraben BP

6.2 Incompatibilities:

Recombinant human EGF is combined along with silver sulfadiazine and Chlorohexidine marketed as SLVRGEN is manufactured by Bharat Biotech and is used for the treatment of first and second degree burns and ulcers like abrasions, incisions, minor cut and wounds. No other studies were performed to look for incompatibilities with **REGEN-D®150.**

6.3 Shelf life*:*

The expiry date of the product is indicated on the carton.

6.4 Special precautions for storage:

Store at +2°C to +8°C. Do not freeze.

6.5 Nature and content of the container:

REGEN-D®150 is presented in aluminium tube with polypropylene screw cap. The pack sizes are 7.5 gram, 15 gram, 30 gms, 50 gms, and 150 gms presentations.

6.6 Special precautions for disposal

Not Applicable

7.0 Marketing Authorisation Holder:

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