QUICK & SCARLESS HEALING

VENOUS ULCERS

BEDSORES (PRESSURE ULCERS)

DIABETIC FOOT ULCER
**EPIDEMIOLOGY - GLOBAL & INDIAN SCENARIO**

**GLOBAL**

1. **Diabetes Foot Ulcer (DFU)**
   - Prevalence: 15-25% for all diabetes patients develop DFUs.
   - **Diabetes Patients** (2017): 424.9 M
   - **Diabetes Patients** (2045): 628.6 M
   - Every 20 seconds, a lower limb is amputated due to diabetes.

2. **Pressure Ulcers**
   - Prevalence rates: 8.8% to 53.2%.

3. **Venous Leg Ulcer**
   - Prevalence: 0.18% to 1%.
   - (up to 4% over the age of 65)

**INDIA**

1. **2nd Largest Adult Diabetes Populated Country**
   - Prevalence: 25% Diabetes patients develop DFUs.
   - **Diabetes Patients** (2017): 72.9 M
   - **Diabetes Patients** (2045): 134.3 M

**5-YEAR MORTALITY RATES OF DFU OR DFU RELATED AMPUTATIONS COMPARED TO OTHER DISEASES**

Adapted from Almekinder E, 2018.

**Amputation largely impacts Quality of Life & Life Expectancy**

**Epidermal Growth Factor (EGF) - Mechanism of Action**

- EGF facilitates diverse array of cellular pathways to promote wound healing & tissue recovery.
- EGF promotes migration, proliferation, cytoprotection, cellular differentiation, collagen synthesis and inhibition of apoptosis.
- Matrix metalloproteinases (MMPs) are enzymes responsible for collagen & other protein degradation in extracellular matrix (ECM) that is essential for wound re-epithelialization.

**Indications of REGEN-D®150:**

- **Diabetic Foot Ulcers**
- **Pressure Ulcers Including Bedsores**
- **Venous Leg Ulcers**

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**Role of EGF in wound healing**

- Re-epithelialization
- Angiogenesis
- Collagen Production
Established Efficacy & Safety of REGEN-D®150 in Several Clinical Trials

DFU - Phase III Study

Average healing time:
- Test group (REGEN-D®150): 9 weeks.
- Control group (placebo): 15 weeks.

Efficacy of REGEN-D®150 Gel

- The average wound healing in patients was 86% & the average wound healing time was 4.8 weeks in the PMS study.
- No adverse events were reported in patients during the PMS study.

DFU - Post-marketing Surveillance (PMS) Study & Phase III Trial

- The proportion of patients cured by week 10 was ~92%, ~69% and ~21% in the PMS study, Phase III (Test Group) and Phase III (Control Group), respectively.

Venous Leg Ulcers - Phase III Study

Average time to complete healing
- Test group REGEN-D®150: ~40 days.
- Control group: ~79 days.

Efficacy of REGEN-D®150 Gel

- Test group: ~40 days.
- Control group: ~79 days.

Bedsores (Pressure Ulcers) - Phase III Study

Average time to complete healing
- Test group REGEN-D®150: ~40 days.
- Control group: ~95 days.

Efficacy of REGEN-D®150 Gel

- Test group: ~40 days.
- Control group: ~95 days.

Adapted from Viswanathan V, 2006.

Adapted from Mohan VK, 2007.

The proportion of patients cured by week 10 was ~92%, ~69% and ~21% in the PMS study, Phase III (Test Group) and Phase III (Control Group), respectively.
Efficacy of REGEN-D®150 in Healing of DFU at Biochemical & Molecular Levels

Punch biopsy and histological analyses* revealed the role of REGEN-D®150 in healing of diabetic foot ulcers vs placebo.

**REGEN-D®150 group has shown significant increase in**
- Collagen content (3.6 fold ↑ compared to 2.6 fold ↑ in placebo).
- The number of fibroblast seen in the matrix.
- Prominent angiogenesis.

**REGEN-D®150 group has shown decrease in**
- MMP-9 (Matrix metalloproteinase) expression.
- Healing time (~50% ↓ compared to placebo).

*There was no evidence of any premalignant or carcinogenic changes in the histological evaluation of the wound lesion.

### Photographs Depicting Quick Healing After Application of REGEN-D®150

**Healing time: 13 weeks**
Dr. Sharad Pendsey, Diabetes Research Centre, Nagpur
Condition: Diabetes foot ulcer
Ulcer Size: 12 cm²

**Healing time: 5 weeks**
Dr. V. Vishwanathan, MVJ Hospital, Chennai
Condition: Diabetes foot ulcer
Ulcer Size: 3.80 cm²

**Healing time: ~8 weeks**
Dr. Ajay Yadav, Gangaram Hospital, New Delhi
Condition: Venous leg ulcer
Long-term Surveillance Study for Safety

- A 2-year follow-up study was conducted to assess the long-term safety of REGEN-D™ 150 in all subjects enrolled in this Phase III clinical trial.³ ¹⁴
- No incidents of recurrence of ulcers from the subjects using REGEN-D™ 150 post-study period.¹⁴
- None of the subjects observed a detection of premalignant or malignant lesion.
- The surveillance established no complaints from the subjects regarding the use of REGEN-D™ 150 proving its clinical safety & efficacy in accelerating healing of DFUs.¹⁴

Publications

- **A Phase III Study to Evaluate the Safety and Efficacy of Recombinant Human Epidermal Growth Factor (REGEN-D™ 150) in Healing Diabetic Foot Ulcers**
  - Vijay Viswanathan, MD, PhD, Sharad Pendsey, MD, KDDC, Niladri Sutar, MS, MNAMS, MCh, FICS, G. S. R. Murthy, PhD
  - VOLUMES 2016;15:166-176

- **Recombinant human epidermal growth factor (REGEN-D™ 150): Effect on healing of diabetic foot ulcers**
  - V. Krishna Mohan *
  - Bharat Biotech International Limited, Genome Valley, Shameerpet (M), Hyderabad 500078, A.P., India
  - Received 15 March 2007; accepted 3 June 2007
  - Available online 23 July 2007

**References**

Composition: Each gram of gel contains Recombinant Human Epidermal Growth Factor 150 µg. Indications: REGEN-D®150 is indicated for the use of 1. Diabetic Foot Ulcers, 2. Bedsores, 3. Chronic Venous Ulcer. 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. The product is contraindicated with immunosuppressive or immune-stimulant therapy. Dosage & administration: After cleaning the ulcer area, apply the gel so as to cover the entire ulcer area. Dosage of the gel depends on the specific size of the ulcer & it should as per physician’s advice. REGEN-D®150 is in the form of a gel. It is to be spread evenly (topical application) on the affected part with a sterile cotton swab, twice a day, until the ulcer heals completely. Precautions: It is suggested that the medical practitioners ascertain the hypersensitivity status of the subject. REGEN-D®150 therapy should be continued up to a period of 15 to 20 weeks. The continuation of the therapy is at the discretion of the physician. Adverse reactions: REGEN-D®150 has proven low reactogenicity & is well tolerated in humans. Clinical trials so far, have not shown any adverse reactions to human subjects. Clinical data: A Phase III, double blind, randomized, placebo controlled, parallel study was conducted to evaluate the safety & efficacy of REGEN-D®150 in diabetic foot ulcers, chronic leg ulcers (venous ulcers) & bed sores (Pressure ulcers). In all of the conditions mentioned, the healing time was less in REGEN-D®150 group compared to the placebo. A Phase IV, double blind, randomized, placebo controlled, parallel study was conducted to evaluate safety & efficacy of REGEN-D®150 in diabetic foot ulcers compared to reference group & the results found REGEN-D®150 to be safe & tolerable. Pharmacodynamic properties: Activation of EGFR leads to a number of biological responses, including migration, proliferation, cryoprotection, cellular differentiation, & apoptosis. In wound healing EGFR plays an important role in re-epithelialization & dermal maturation. Topical use of recombinant human EGF has been shown to increase re-epithelialization & enhance wound healing. Storage & stability: Store at room temperature (25°C). 1. Bodnar RJ. Epidermal growth factor & epidermal growth factor receptor: The yin & yang in the treatment of cutaneous wounds & cancer. Adv Wound Care (New Rochelle). 2013;2(1):24–29. 2. Tokumaru S. Ectodomain shedding of epidermal growth factor receptor ligands is required for keratinocyte migration in cutaneous wound healing. J Cell Biol. 2000;151(2):209-20.