ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

REGRANEX 0.01% gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REGRANEX contains100 μg of becaplermin per gram of gel. Becaplermin is a recombinant human Platelet Derived Growth Factor-BB (rhPDGF-BB). It is produced by insertion of the gene for the B chain of human platelet derived growth factor into the yeast, *Saccharomyces cerevisiae*. rhPDGF-BB is a dimeric protein with a molecular weight of approximately 24,500 daltons.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Gel

REGRANEX is a clear colourless to straw-coloured preserved gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REGRANEX is indicated, in association with other good wound care measures, to promote granulation and thereby the healing of full-thickness, neuropathic, chronic, diabetic ulcers less than or equal to 5 cm^2.

4.2 Posology and method of administration

Treatment with REGRANEX should be initiated and monitored by physicians (specialists or non-specialists) who are experienced in the management of diabetic wounds.

REGRANEX should always be used in conjunction with good wound care consisting of initial debridement (to remove all the necrotic and/or infected tissue), additional debridement as necessary and a non-weight-bearing regimen to alleviate pressure on the ulcer. Wound-related infection should be identified and treated with appropriate antimicrobial therapy prior to the use of REGRANEX. Prior to the use of REGRANEX, related underlying conditions such as osteomyelitis and peripheral arteriopathy should be excluded or treated if present. Osteomyelitis should be assessed by X-ray examination. Peripheral arteriopathy should be excluded by assessment of the pedal pulses or other techniques. Ulcers with a suspicious appearance should be biopsied to exclude malignancy.

REGRANEX should be applied as a continuous thin layer to the entire ulcerated area(s) once daily using a clean application aid. The site(s) of application should then be covered by a moist saline gauze dressing that maintains a moist wound-healing environment. REGRANEX should not be used in conjunction with occlusive dressings.

REGRANEX should not be used for more than 20 weeks in any individual patient.

If during treatment with REGRANEX no meaningful healing progress is evident after the first ten weeks of continuous therapy, treatment should be re-evaluated, and factors known to compromise healing (such as osteomyelitis, ischaemia, infection) should be re-assessed. Therapy should be continued to the maximum of 20 weeks as long as healing progress is seen on periodic evaluations.

REGRANEX is not intended for repeated use.

REGRANEX has not been studied in children.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients of this product
- Known neoplasm(s) at or near the site(s) of application.

4.4 Special warnings and special precautions for use

Safety and effectiveness in children and adolescents below the age of 18 years have not been established.

In view of the lack of data, REGRANEX should be used with caution in patients with known malignancies.

REGRANEX should not be used in patients with ulcers that are not of primarily neuropathic origin, such as those due to arteriopathy or other factors.

REGRANEX should not be used in clinically infected ulcers. Infection should be treated prior to the use of REGRANEX. Should a wound become infected during REGRANEX therapy, the product should be discontinued until the infective process is controlled.

REGRANEX should not be used in ulcers of baseline surface area > 5 cm^2, or for more than 20 weeks in any individual. There are insufficient data to support safe use of the product for more than 20 weeks (see 5.1 Pharmacodynamic properties). Efficacy has not been demonstrated for ulcers of baseline surface area > 5 cm^2.

4.5 Interaction with other medicinal products and other forms of interaction

It is not known whether REGRANEX interacts with other topical medications applied to the ulcer site. Consequently, it is recommended that REGRANEX should not be applied to the ulcer site in conjunction with other topical medications.

4.6 Pregnancy and lactation

Pregnancy

No studies in pregnant women have been conducted. Therefore, REGRANEX should not be used in pregnant women.

Nursing mothers

It is not known whether becaplermin is excreted in human milk. Therefore, REGRANEX should not be used in nursing mothers.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following adverse events, which are not clearly related to REGRANEX therapy, were reported in the randomised clinical trials: Infection, skin ulceration, skin disorder, including erythema and pain. Bullous eruption and oedema were reported rarely.

Rare cases (frequency ≥1/10000, <1/1000) of hypertrophic granulation have been reported in post marketing experience.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparation for treatment of wounds and ulcers, ATC code: D 03 AX06

REGRANEX contains becaplermin, a recombinant human Platelet Derived Growth Factor-BB (rhPDGF-BB). Becaplermin is produced by insertion of the gene for the B chain of human platelet derived growth factor into the yeast, *Saccharomyces cerevisiae*. The biological activity of becaplermin includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair. Thus it helps the growth of normal tissue for healing. In animal wound models, the predominant effect of becaplermin is to enhance the formation of granulation tissue. From data combined from 4 clinical trials conducted over a 20 week treatment phase for ulcers of baseline surface area less than or equal to 5 cm^2, 47% of ulcers treated with becaplermin 100 µg/g gel completely healed, compared to 35% which were treated with placebo gel alone. Subjects recruited into these studies were diabetic adults aged 19 years or over who were suffering from at least one stage III or IV diabetic ulcer of at least 8 weeks duration.

Since becaplermin is a growth factor, which stimulates the proliferation of cells, it must be cautiously used in patients with malignancies.

5.2 Pharmacokinetic properties

Absorption

Clinical absorption studies were conducted in patients with a mean diabetic ulcer area of 10.5 cm^2 (range 2.3 - 43.5 cm^2). Following 14 consecutive daily topical applications of REGRANEX, only insignificant systemic absorption of becaplermin occurred.

5.3 Preclinical safety data

Becaplermin was not mutagenic in a battery of *in vitro* and *in vivo* tests. Since absorption is insignificant from the site of topical application in man, carcinogenesis and reproductive toxicity studies have not been conducted with REGRANEX. In the process of healing the wound, becaplermin induces cell proliferation. However, skin tumours have not been reported in the clinical trials at the site of application or in close proximity.

In a preclinical study designed to determine the effects of PDGF on exposed bone, rats injected at the metatarsals with 3 or 10 µg/site (concentration of 30 or 100 µg/ml/site) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodelling consisting of periosteal hyperplasia and subperiosteal bone resorption and exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

Preclinical absorption studies through full-thickness wounds were conducted in rats with a wound area of 1.4 - 1.6 cm². Systemic absorption of a single dose and multiple applications for 5 consecutive days of becaplermin to those wounds was insignificant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

carmellose sodium (E466)
sodium chloride
sodium acetate
glacial acetic acid (E260)
methyl parahydroxybenzoate (methylparaben) (E218)
propyl parahydroxybenzoate (propylparaben) (E216)
m-cresol
lysine hydrochloride
water for injections

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

1 year.

Use within 6 weeks after first opening.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and content of container

REGRANEX is supplied in 15 g laminated polyethylene-lined multidose tubes.

6.6 Instructions for use and handling, and disposal

(See section 4.2).

- A tube of REGRANEX should be used on a single patient only.
- Care should be taken during use to avoid microbial contamination and spoilage.
- Hands should be washed thoroughly before applying REGRANEX.
- The tip of the tube should not come into contact with the wound or any other surface.
- The use of a clean application aid is recommended and contact with other parts of the body should be avoided.
- Before each application, the ulcer should be gently rinsed with saline or water to remove residual gel.
- The tube should be closed tightly after each use.
- After treatment is completed, any unused gel should be discarded.

7. MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg, 30
B-2340 Beerse
Belgium

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/99/101/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

March 29, 1999

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Chiron Corporation, Vacaville Manufacturing Facility, 2010 Cessna Drive, Vacaville, CA 95688, USA (Fermentation and recovery).

Chiron Corporation, Chiron Manufacturing Facility, 4560 Horton Street, Emeryville, CA 94608, USA (Purification, concentration and filtration).

Name and address of the manufacturer responsible for batch release

Janssen-Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, 4.2)

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

REGRANEX 0.01% gel
becaplermin

2. STATEMENT OF ACTIVE SUBSTANCE

100 microgram / g gel becaplermin

3. LIST OF EXCIPIENTS

Contains carmellose sodium (E466), sodium chloride, sodium acetate, glacial acetic acid (E260), methyl parahydroxybenzoate (methylparaben) (E218), propyl parahydroxybenzoate (propylparaben) (E216), m-cresol, lysine hydrochloride and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Multidose tube containing 15 gram of gel

5. METHOD AND ROUTE OF ADMINISTRATION

For cutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp. Date

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C) Do not freeze
Close tightly after each use

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:
JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg, 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/99/101/001

13. MANUFACTURER'S BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

Read the package leaflet before use
Use within 6 weeks after first opening

Date opened:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

TUBE

1. NAME OF THE MEDICINAL PRODUCT

REGRANEX 0.01% gel
becaplermin

2. STATEMENT OF ACTIVE SUBSTANCE

100 microgram / g gel becaplermin

3. LIST OF EXCIPIENTS

Contains carmellose sodium (E466), sodium chloride, sodium acetate, glacial acetic acid (E260), methyl parahydroxybenzoate (methylparaben) (E218), propyl parahydroxybenzoate (propylparaben) (E216), m-cresol, lysine hydrochloride and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Multidose tube containing 15 gram of gel

5. METHOD AND ROUTE OF ADMINISTRATION

For cutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp. Date

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C) Do not freeze
Close tightly after each use

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:
JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg, 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/99/101/001

13. MANUFACTURER'S BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

Read the package leaflet before use
Use within 6 weeks after first opening

Date opened:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Please read this leaflet carefully because it contains important information about your medicine. If there is anything that you do not understand or if you need further information or advice, you should ask your doctor or your pharmacist who will have more details.

In this leaflet

REGRANEX 0.01% Gel
Becaplermin

The active substance in REGRANEX is becaplermin. Each gram of REGRANEX contains 100 micrograms of becaplermin.

The other ingredients are: carmellose sodium (E466), sodium chloride, sodium acetate, glacial acetic acid (E260), methyl parahydroxybenzoate (methylparaben) (E218), propyl parahydroxybenzoate (propylparaben) (E216), m-cresol, lysine hydrochloride and water for injections.

Marketing Authorisation Holder

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg, 30
B-2340 Beerse
Belgium

Manufacturer

JANSSEN PHARMACEUTICA NV
Turnhoutseweg, 30
B-2340 Beerse
Belgium

1. WHAT REGRANEX IS AND WHAT IT IS USED FOR

Becaplermin is a human recombinant Platelet Derived Growth Factor (rhPDGF), which helps the growth of normal tissue in order to heal ulcers.

REGRANEX is a clear colourless to straw-coloured non-sterile preserved gel and is filled in multidose tubes containing 15 grams.

REGRANEX is used in association with other good wound care measures to promote the healing of skin ulcers that measure less than or equal to 5 square centimetres which are due to complications of diabetes and have adequate blood supply. By using REGRANEX, it is more likely that your ulcers will heal completely and that the time needed for your ulcers to heal will be reduced.

2. BEFORE YOU USE REGRANEX

Do not to use REGRANEX:

- If you are allergic to the active substance or to the other ingredients of REGRANEX.

- If you have a skin tumour at or near the site of application of REGRANEX.

- If your ulcer is infected. Should your wound become infected during the use of REGRANEX, the product should be discontinued until the infection is under control.

- If your ulcer is larger than 5 square centimetres

Take special care with REGRANEX

- *Special warning*
  You should inform your doctor if you have any malignant condition(s).

- *Pregnancy and breast-feeding*
  REGRANEX should not be used by pregnant women or by nursing mothers.

- *Children and the elderly*
  REGRANEX has not been tested in children under the age of 18.
  There are no special instructions necessary for the elderly.

- *Other medicines*
  You should not apply other topical medicines on your ulcer while using REGRANEX. Only saline sodium chloride solution or water should be used to clean the ulcer.

- *Driving and operating machinery*
  Not applicable

3. HOW TO USE REGRANEX

Please observe these instructions for use, in order to fully benefit from REGRANEX

Before treatment with REGRANEX, your ulcer should be cleaned. It is very important to make sure that you also take very good care of your ulcers while using REGRANEX to help them heal quickly and as fully as possible. If you experience signs of infection of the ulcer (e.g. redness, swelling, fever, pain, odour), you should consult your doctor immediately for specific treatment. You should not apply pressure or walk on the ulcer during treatment and should closely follow your doctor's advice on proper care of the ulcer together with other measures that may be needed to relieve pressure from your ulcer.

Before REGRANEX you should wash your hands thoroughly. Before each application, the ulcer should be gently rinsed with saline or water to remove residual gel.

Apply REGRANEX as a continuous thin layer to the entire wound area(s) once daily using a clean application aid (e.g. a cotton swab or a tongue depressor). Contact with other parts of the body should be avoided. The tip of the tube should not come into contact with the wound or any other surface and care should be taken during use to avoid any other forms of possible microbial contamination or spoilage.

Once REGRANEX has been applied, cover the ulcer with a moist saline gauze dressing. The dressing should be changed at least once a day to keep the wound moist. REGRANEX should only be applied

once daily even if you change your dressing more frequently. REGRANEX should not be used with occlusive dressings.

REGRANEX should not be used for more than 20 weeks.

If there is no sign of healing after the first ten weeks of continuous therapy, please contact your doctor. Your doctor will decide whether treatment should be continued. REGRANEX is not intended for repeated use.

This medicinal product has been prescribed for you personally and you should not pass it on to others. Any unfinished gel should be discarded after treatment is completed.

If you use more REGRANEX than you should:

If you accidentally apply too much REGRANEX, it is unlikely to do you any harm. However, always try to exactly follow the instructions for use.

4. POSSIBLE SIDE EFFECTS

Like all medicines, REGRANEX can have side effects.

The following conditions, which are not clearly related to REGRANEX therapy were reported during clinical trials: infection, skin ulceration and skin disorders (including redness and pain). Blisters and swelling were reported rarely.

Cases of excessive production of tissue in the ulcer due to an exaggerated healing response have rarely been observed in patients receiving REGRANEX.

If you start to feel unwell or notice any undesirable effects including effects not mentioned in this leaflet or if you are unsure about the effect of this product, do not hesitate to contact your doctor or pharmacist.

5. STORING REGRANEX

Store in a refrigerator (2°C to 8°C). Do not freeze.

Keep out of the reach and sight of children.
Close the tube tightly after each use.

Do not use your medicine after the expiry date (MM/YY) as indicated on the tube and the outer carton.

Use within 6 weeks after opening the seal of the tube. Please record the date of opening on the tube label.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on