VEREGEN™

(sinecatechins)

Ointment, 15%

Rx Only

For Topical Dermatologic Use Only

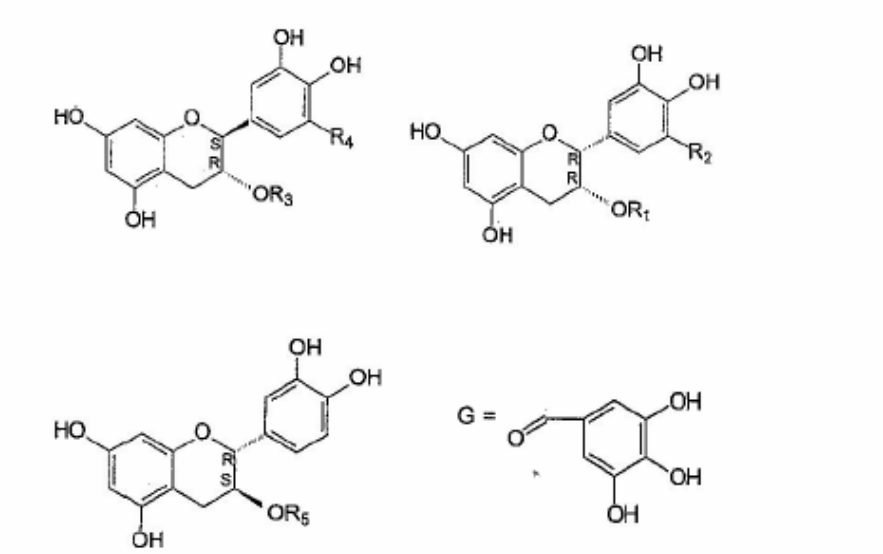
Not for Ophthalmic, Oral, Intravaginal, or Intra-anal Use

DESCRIPTION

Veregen™ is a botanical drug product for topical use. The drug substance in Veregen™ is sinecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg) and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

General Structure of Catechins



Component	Abbrev.	R1	R2	R3	R4	R5
(–)-Epigallocatechin Gallate	(–)-EGCg	G	OH		–	–
(–)-Epicatechin Gallate	(–)-ECg	G	H		–	–
(–)-Epigallocatechin	(–)-EGC	H	OH	–		–
(–)-Epicatechin	(–)-EC	H	H	–	–	
(–)-Gallocatechin Gallate	(–)-GCg	–	–	G	OH	–
(–)-Gallocatechin	(–)-GC	–	–	H	OH	–
(–)-Catechin Gallate	(–)-Cg	–	–	G	H	–
(+)-Catechin	(+)-C	–		–	–	H

Each gram of the ointment contains 150 mg of sinecatechins in a water free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mode of action of Veregen™ Ointment, 15% involved in the clearance of genital and perianal warts is unknown. In vitro, sinecatechins had anti-oxidative activity; the clinical significance of this finding is unknown.

Pharmacokinetics

The pharmacokinetics of topically applied Veregen™ Ointment has not been sufficiently characterized at this time. However, data suggest that systemic exposure to catechins after repeated topical application of Veregen™ Ointment 15% is likely to be less than observed after a single oral intake of 400ml green tea.

CLINICAL STUDIES

Two Phase 3 randomized, double-blind, vehicle-controlled studies were performed to investigate the safety and efficacy of Veregen™ Ointment in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The subjects applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment).

Over both studies the median baseline wart area was 51 mm^2 (range 12 to 585 mm^2), and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16, presented in Tables 1 and 2 for all randomized subjects dispensed medication.

Table 1: Efficacy by Region

	Complete Clearance
All Countries (includes the United States)	
Veregen™ 15% (*N* = 397)	213 (53.6%)
Vehicle (*N* = 207)	73 (35.3%)
United States	
Veregen™ 15% (*N* = 21)	5 (23.8%)
Vehicle (*N* = 9)	0 (0.0%)

Table 2. Efficacy by Gender

	Complete Clearance
Males	
Veregen™ 15% (*N* = 205)	97 (47.3%)
Vehicle (*N* = 118)	34 (28.8%)
Females	
Veregen™ 15% (*N* = 192)	116 (60.4%)
Vehicle (*N* = 89)	39 (43.8%)

.

Median time to complete wart clearance was 16 weeks and 10 weeks, respectively, in the two phase 3 clinical trials.

The incidence rate of recurrence of external genital and perianal warts after treatment in patients with complete clearance is unknown.

INDICATION AND USAGE

Veregen™ is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

CONTRAINDICATIONS

Veregen™ is contraindicated in individuals with a history of sensitivity reactions to any of the components of the ointment. In case of hypersensitivity, treatment should be discontinued.

WARNINGS

Veregen™ has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions.

PRECAUTIONS

General

Use of Veregen™ on open wounds should be avoided.

The safety and efficacy of Veregen™ in immunosuppressed patients have not been established.

Safety and efficacy have not been established for Veregen™ in the treatment of external genital and perianal warts beyond 16-weeks or for multiple treatment courses.

Patients should be advised to avoid exposure of the genital and perianal area to sun/UV-light as Veregen™ has not been tested under these circumstances.

Information for Patients

General Information

Patients using Veregen™ should receive the following information and instructions:

1. This medication is only to be used as directed by a physician. It is for external use only. Eye contact should be avoided as well as application into the vagina or anus.
2. It is not necessary to wash off Veregen™ prior to the next application. When the treatment area is washed or a bath is taken, the ointment should be applied afterwards.
3. It is common for patients to experience local skin reactions such as erythema, erosion, edema, itching, and burning at the site of application. Severe skin reactions can occur and should be promptly reported to the healthcare provider. Should severe local skin reaction occur, the ointment should be removed by washing the treatment area with mild soap and water and further doses held.
4. Sexual (genital, anal or oral) contact should be avoided while the ointment is on the skin, or the ointment should be washed off prior to these activities. Veregen™ may weaken condoms and vaginal diaphragms. Therefore the use in combination with Veregen™ is not recommended.
5. Female patients using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental application of the ointment into the vagina must be avoided.
6. Veregen™ may stain clothing and bedding.
7. Veregen™ is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16 –week treatment period, these should also be treated with Veregen™.
8. The effect of Veregen™ on the transmission of genital/perianal warts is unknown.
9. Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as Veregen™ has not been tested under these circumstances.

10. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
11. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The Maximum Recommended Human Dose (MRHD) of Veregen™ Ointment, 15% was set at three times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg sinecatechins for the animal multiple of human exposure calculations presented in this labeling. Dose multiples were calculated based on the human equivalent dose (HED).

In an oral (gavage) carcinogenicity study, sinecatechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD). Treatment with sinecatechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Veregen™ Ointment, 15% has not been evaluated in a dermal carcinogenicity study.

Sinecatechins was negative in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay.

Daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

Pregnancy Category: C

Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of sinecatechins during the period of organogenesis (gestational Days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of sinecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study.

A combined fertility / embryo-fetal development study using daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating

until Day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of Veregen™ Ointment, 15% at doses of 0.05, 0.10 and 0.15 mL/rat/day from Day 6 of gestation through parturition and lactation. The high and intermediate dose levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F_0 dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction and fertility at any dose tested.

There are no adequate and well-controlled studies in pregnant women. Veregen™ Ointment, 15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topically applied Veregen™ is excreted in breast milk.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

Seven patients (1.4%), older than 65 years of age were treated with Veregen™ in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Adverse Events / Local Skin Reactions

In Phase 3 clinical trials, a total of 397 subjects received Veregen™ Ointment, 15% three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Serious local adverse events of pain and inflammation were reported in two subjects (0.5%), both women.

In clinical trials, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simples, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

Local and regional reactions (includes adenophathy) occurring at >1% in the treated group are presented in Table 3.

Table 3: Local and Regional Adverse Reactions During Treatment (% Subjects)

	Veregen™ *(N=397)*	Vehicle *(N=207)*
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/Ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6
Regional Lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

A total of 266/397 (67%) of subjects in the Veregen™, 15% group had either a moderate or a severe reaction that was considered probably related and of these 120 (30%) subjects had a severe reaction. Severe reactions occurred in 37% (71/192) of women and in 24% (49/205) of men. The percentage of subjects with at least one severe, related adverse event was 26% (86/328) for subjects with genital warts only, 42% (19/45) in subjects with both genital and perianal warts and 48% (11/23) of subjects with perianal warts only.

Phimosis occurred in 3% of uncircumcised male subjects (5/174) treated with Veregen™ and in 1% (1/99) in vehicle.

The maximum mean severity of erythema, erosion, edema and induration was observed by week 2 of treatment.

Less common local adverse events included urethritis, perianal infection, pigmentation changes, dryness, eczema, hyperesthesia, necrosis, papules, and discoloration. Other less

common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash and staphylococcemia.

In a dermal sensitization study of Veregen™ Ointment in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

OVERDOSAGE

Overdosage with Veregen™ has not been reported.

DOSAGE AND ADMINISTRATION

Veregen™ Ointment, 15% is to be applied three times per day to all external genital and perianal warts.

It is recommended to wash the hands before and after application of Veregen™. About a 0.5 cm strand of the Veregen™ Ointment, 15% should be applied to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts.

It is not necessary to wash off the ointment from the treated area prior to the next application.

Treatment with Veregen™ should be continued until complete clearance of all warts, however no longer than 16 weeks.

Local skin reactions (e.g. erythema) at the treatment site are frequent. Nevertheless, treatment should be continued when the severity of the local skin reaction is acceptable.

HOW SUPPLIED

Veregen™ Ointment, 15% is a brown ointment and is supplied in aluminium tubes containing 15 gram ointment per tube.

Storage Conditions

Prior to dispensing to the patient, store refrigerated 2°C to 8°C (36°F to 46°F). After dispensing, store refrigerated or up to 25°C (77°F). Do not freeze.

Keep out of reach of children

NDC # 10337-450-15

The VEREGEN trademark is used by Bradley Pharmaceuticals, Inc. under license from MediGene AG.

Manufactured by:

C.P.M. Contract Pharma GmbH & Co. KG
Frühlingstrasse 7
D-83620 Feldkirchen-Westerham
Germany

Manufactured for:

DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.

383 Route 46 West
Fairfield, NJ 07004 2402 USA
Co-marketed with Kenwood Therapeutics, a division of Bradley Pharmaceuticals, Inc.

December 2006

PATIENT INFORMATION

Veregen™

(sinecatechins)

Ointment, 15%

Rx Only

Read this leaflet carefully before you start using Veregen™ Ointment, 15% and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. If you have any questions about Veregen™ Ointment, 15% or your condition ask your doctor or pharmacist. Only your doctor can prescribe Veregen™ and determine if it is right for you.

What is Veregen™ Ointment, 15%?

Veregen™ Ointment, 15% is a medicine for skin use only (topical) for the treatment of warts on the outside of the genitals and around the outside of the anus. It is not a treatment for warts in the vagina, cervix, or inside the anus. Your doctor may recommend examination and screening tests (such as a Pap smear) to evaluate these areas.

Who should not use Veregen™ Ointment, 15%?

Do not use Veregen™ Ointment, 15% if you **are allergic** to an ingredient in Veregen™ Ointment, 15%. **The list of ingredients is at the end of this leaflet.**

What should I tell my doctor before taking Veregen™ Ointment, 15%?

Tell your doctor about all your health conditions and all the medicines you take including prescription, over-the-counter medicine, vitamins, supplements, and herbals. Be sure to tell your doctor if you are:

- **pregnant or planning to become pregnant,** as it is not known if Veregen™ Ointment, 15% can harm your unborn baby. Your doctor will determine whether the benefit outweighs the risk.
- **breastfeeding,** as it is not known if Veregen™ Ointment, 15% can pass into your milk and if it can harm your baby.
- **using any other type of skin product or have open wounds on the area to be treated.** Veregen™ Ointment, 15% should not be used until your skin has healed from other treatments applied to the same area.
- **immunocompromised**. This means that your immune system cannot fight infections as well as it should.

How should I use Veregen™ Ointment, 15%?

- Use Veregen™ Ointment, 15% only on the area affected **exactly** as prescribed by your doctor.

- **Wash your hands before and after application of Veregen™ Ointment, 15%**. A small amount of the ointment should be applied to all wart using your finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts as directed by your doctor.

- **Apply Veregen™ Ointment, 15% three times per day ---in the morning, at noontime and in the evening.**

- Do not wash off the ointment from the treated area before the next application. When you wash the treatment area or bathe, apply the ointment afterwards.

- Treatment with Veregen™ Ointment, 15% should be continued until complete clearance of all warts, however **no longer than 16 weeks.** If your warts do not go away, or if they come back after treatment call your doctor.

- Veregen™ Ointment, 15% is not a cure for warts on your genitals or around your anus with certainty. New warts may develop during or after treatment, and may need treatment.

What should I avoid while using Veregen™ Ointment, 15%?

- Do not apply Veregen™ Ointment, 15% on open wounds or into the vagina or into the anus.

- Genital warts are a sexually transmitted disease, and you may infect your partner.

- Avoid sexual contact (genital, anal or oral) when Veregen™ Ointment, 15% is on your genital or perianal skin. If you do choose to have sexual contact, you must wash off the ointment carefully before having protected sexual contact as the ointment may weaken condoms and vaginal diaphragms. Talk to your doctor about safe sex practices.

- Avoid contact with your eyes, nostrils and mouth while ointment is on your finger(s).

- Women using tampons: insert the tampon before applying the ointment. If you need to change your tampon while the ointment is on your skin, avoid getting the ointment into the vagina.

- Uncircumcised men treating warts under the foreskin should retract the foreskin and clean the area daily.

- Do not expose the genital area treated with Veregen™ Ointment, 15% to sunlight, sunlamps or tanning beds.

- Do not cover the treated area. Loose-fitting undergarments can be worn after applying Veregen™ Ointment, 15%.

- Veregen™ Ointment, 15% may stain your light colored clothes and bedding. It is recommended to wear darker colored undergarments while using Veregen™ Ointment, 15%.

What are the possible side effects of Veregen™ Ointment, 15%?

The most common side effects with Veregen™ Ointment, 15% are local skin and application site reactions including:

- redness
- swelling
- sores or blisters
- burning
- itching
- pain

Many patients experience itching, reddening or swelling on or around the application site during the course of treatment. Some of these side effects could be a sign of an allergic reaction. If you experience open sores or other severe reactions at the locations you applied Veregen™, stop treatment and call your doctor right away.

You may experience other side effects of Veregen™ Ointment, 15%, which are not mentioned here. Ask your doctor or pharmacist for more information.

Patients should be aware that new warts may develop during treatment as Veregen™ Ointment, 15% is not a cure.

How should I store Veregen™ Ointment, 15%?

- Store Veregen™ Ointment, 15% refrigerated or up to 77ºF (25 ºC).
- Do not freeze.
- Make sure the cap on the tube is tightly closed.
- Safely throw away Veregen™ Ointment, 15% tubes that are out of date or are empty.

Keep Veregen ™Ointment, 15% and all medicines out of the reach of children.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Veregen™ Ointment, 15% for a condition for which it was not prescribed. Do not give Veregen™ Ointment, 15% to other people, even if they have the same symptoms you have. It may harm them. Do not use Veregen™ Ointment, 15% after the expiration date on the tube.

This leaflet summarizes the most important information about Veregen™ Ointment, 15%. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Veregen™ Ointment, 15% that is written for the doctor.

What are the ingredients in Veregen™ Ointment, 15%?

Active ingredient:

A defined green tea extract named sinecatechins.

Inactive ingredients:

Isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Veregen™ is a trademark of MediGene AG, D-82152 Planegg/Martinsried, Germany.

Manufactured by: C.P.M. Contract Pharma GmbH & Co. KG, Frühlingstrasse 7, D-83620 Feldkirchen-Westerham, Germany.

Manufactured for:

DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.
383 Route 46 West
Fairfield, NJ 07004 2402 USA

Co-marketed with:

KENWOOD THERAPEUTICS
A DIVISION OF BRADLEY PHARMACEUTICALS, INC.

December 2006

Text for the Outer Carton Label [1]

NDC # 10337-450-xx [2]

Rx Only

VEREGEN™
(sinecatechins) Ointment
15%

For Topical Dermatologic Use Only.
Not for Opthalmic, Oral, Intravaginal, or Intra-anal Use.

Keep out of reach of children.

Description: Veregen™ is a botanical drug product. The drug substance in Veregen™ is sinecatechins, which is a partially purified fraction of the water extract of green tea leaves of *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins, their derivatives and other green tea components.

Active ingredient: sinecatechins (150 mg/g).

Excipients: isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Usual Adult dose: See accompanying package insert for full Prescribing Information.

Manufactured by: C.P.M. Contract Pharma GmbH & Co. KG, Frühlingstrasse 7, D-83620 Feldkirchen-Westerham, Germany.

Manufactured for:
DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.
383 Route 46 West, Fairfield, NJ 07004-2402 USA
Co-marketed with **Kenwood Therapeutics**, a division of Bradley Pharmaceuticals, Inc.

Lot:
Exp:
UPC/Bar Code

YY [3]g

Store in a refrigerator at 2-8°C (36-46°F) until dispensed to the patient.
Patient can store refrigerated or up to 25°C (77°F). Do not freeze.

U.S. Patent Nos. 5795911 and 5968973

---

[1] Text presented on the outer carton may not appear in the order outlined in this document.
[2] xx = 15 for the 15g ointment size, xx = 03 for the 30g ointment size
[3] YY = 15 for the 15g ointment size, YY = 30 for the 30g ointment size.

Text for the Immediate Container (Tube) Label [4]

NDC # 10337-450-xx [5]

Rx Only

Veregen™
(sinecatechins) Ointment
15%

YY [6] g

For Topical Dermatologic Use Only.
Not for Opthalmic, Oral, Intravaginal, or Intra-anal Use.

Keep out of reach of children. Keep tightly closed.

Description: Veregen™ is a botanical drug product. The drug substance in Veregen™ is sinecatechins, which is a partially purified fraction of the water extract of green tea leaves of *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins, their derivatives and other green tea components.

Active ingredient: sinecatechins (150 mg/g).
Excipients: isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Usual Adult dose: See accompanying package insert for full Prescribing Information.

Store in a refrigerator at 2-8°C (36-46°F) until dispensed to the patient.
Patient can store refrigerated or up to 25°C (77°F). Do not freeze.

For control number and expiration date, see crimp of tube.

Manufactured by: C.P.M. Contract Pharma GmbH & Co. KG, Frühlingstrasse 7, D-83620 Feldkirchen-Westerham, Germany.

Manufactured for:
DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.
383 Route 46 West, Fairfield, NJ 07004-2402 USA
Co-marketed with **Kenwood Therapeutics**, a division of Bradley Pharmaceuticals, Inc.

SAMPLE. NOT FOR SALE. [7]

U.S. Patent Nos. 5795911 and 5968973

---

[4] Text presented on the outer carton may not appear in the order outlined in this document.
[5] xx = 15 for the 15 g ointment size, xx = 03 for the 30 g ointment size, xx = 99 for the 4 g ointment (physician sample) size.
[6] YY = 15 for the 15 g ointment size, YY = 30 for the 30 g ointment size, YY = 4 for the 4 g ointment (physician sample) size.
[7] This statement only applicable for the 4 g ointment (physician sample) size.