

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-902

CHEMISTRY REVIEW(S)

INTEROFFICE MEMORANDUM

DATE: 10/26/2006
TO: NDA 21-902
FROM: ELAINE MOREFIELD, PH.D.
DIRECTOR, PRE-MARKETING ASSESSMENT DIVISION II
SUBJECT: TERTIARY REVIEW OF NDA 21-902, VEREGEN 15% OINTMENT

NDA 21-902, Veregen (Kunecatechins) 15% Ointment, was submitted by Medigene AG. The chemistry and manufacturing controls have been reviewed by Dr. Rajiv Agarwal and Approved by Dr. Moo-Jhong Rhee. They have made a recommendation that this NDA may be approved from a CMC perspective.

I have completed a tertiary review of this application. I have reviewed the API and finished product specifications and process controls and find them to be acceptable from a scientific and regulatory perspective. The labeling appears acceptable from a CMC perspective. All CMC related issues appear to be resolved in an acceptable manner. Therefore, I concur with the recommendation that NDA 21-902 may be approved from a CMC perspective.

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/s/

Elaine Morefield
10/26/2006 10:09:28 AM
CHEMIST

NDA 21-902

Veregen

(Kunecatechins)

15%

Ointment

MediGene AG.

Division of Dental and Dermatology Products

Rajiv Agarwal

DIVISION OF PRE-MARKETING DRUG QUALITY ASSESSMENT
(Branch III, Division II)

Chemistry Review Data Sheet

1. NDA 21-902
2. REVIEW # 1
3. REVIEW DATE: 25-OCT-2006
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL	23-SEP-2005
AMENDMENT	09-DEC-2005
AMENDMENT	16-JAN-2006
AMENDMENT	30-JAN-2006
AMENDMENT	16-FEB-2006
AMENDMENT	28-FEB-2006
AMENDMENT	02-MAR-2006
AMENDMENT	17-APR-2006
AMENDMENT	20-APR-2006
AMENDMENT	20-APR-2006
AMENDMENT	21-APR-2006
AMENDMENT	25-APR-2006
AMENDMENT	18-MAY-2006
AMENDMENT	06-JUN-2006
AMENDMENT	11-JUL-2006
AMENDMENT	10-AUG-2006
AMENDMENT	14-AUG-2006
AMENDMENT	14-AUG-2006
AMENDMENT	18-AUG-2006
AMENDMENT	14-SEP-2006
AMENDMENT	28-SEP-2006
AMENDMENT	04-OCT-2006
AMENDMENT	06-OCT-2006
AMENDMENT	13-OCT-2006
AMENDMENT	23-OCT-2006
AMENDMENT	24-OCT-2006

7. NAME & ADDRESS OF APPLICANT:

Name: MediGene, AG.

Address: Lochhamer Str.11; 82152 Planegg/Martinsried
Germany

Representative: Ms. Pam Larson

Telephone: 858-586-2252

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Veregen

b) Non-Proprietary Name (USAN): Kunecatechins

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c) Code Name/# (ONDQA only): None

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: External genital and perianal warts (Condylomata acuminata)

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 15%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

1. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

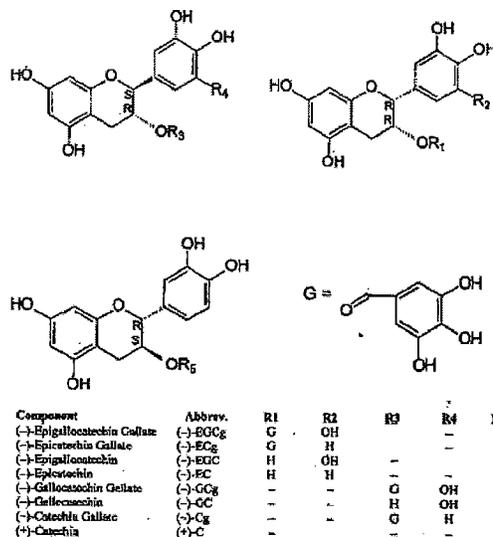
Not a SPOTS product

2. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name	Abbrev.	CAS #	Content (Wt %) g/100 g	Molecular structure	Molecular weight
(-)-Epigallocatechin Gallate	EGCg	989-51-5		$C_{22}H_{18}O_{11}$	
(-)-Epicatechin	EC	490-46-0		$C_{15}H_{14}O_6$	
(-)-Epicatechin Gallate	ECg	1257-08-5		$C_{22}H_{18}O_{10}$	
(-)-Epigallocatechin	EGC	970-74-1		$C_{15}H_{14}O_7$	
(-)-Gallocatechin Gallate	GCg	4233-96-9		$C_{22}H_{18}O_{11}$	
(-) Gallocatechin	GC	3371-27-5		$C_{15}H_{14}O_7$	
(-)-Catechin Gallate	Cg	130405-40-2		$C_{22}H_{18}O_{10}$	
(+)-Catechin	C	154-23-4		$C_{15}H_{14}O_6$	

* Sum of GC, Cg and C = _____

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17. RELATED/SUPPORTING DOCUMENTS:

- EES inspection report: Submitted 17-DEC-2006 (see the attached EER report; Appendix -1)
- Meeting minutes dated 11-JUN-2001
- Pre-NDA meeting dated 24-JAN-2005
- Meeting minutes dated 1-AUG-2006
- Meeting minutes dated 08-AUG-2006
- Meeting minutes dated 21-SEP-2006

Type/Number	Subject	Holder	Status	Review Date	Letter Date
—	Polyphenon E (Kunecatechins) botanical drug substance	—	Adequate	18-OCT-2006	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	12-SEP-2006	Ms. Shawnte Adams
DMETS	Acceptable	16-JUN-2006	Ms. Alina Mahmud
Method Validation	The method validation package will be sent to and validated by FDA laboratories after approval.		

The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA may be approved from the CMC point of view.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is an ointment containing 15% (w/w) Kunecatechins drug substance suspended in a _____ base. Excipients are isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate (also known as propylene glycol monopalmitostearate), and oleyl alcohol. Oleyl alcohol is identified as a _____ in this formulation.

The drug product is packaged in aluminum tubes. The aluminum tubes are _____ . The tubes are _____ in _____ . After the tube is filled with 15 g of ointment, the tube ends are sealed with _____ and _____ resulting in a finished tube length of _____ . The tube cap located on the blind end of the tube consists of a _____ cap. _____

Upon review of the process validations of the clinical (_____) and validation batches (manufactured at CPM in Germany), the manufacturing process for the to-be marketed product is deemed reliable and consistent, and would result in consistent batch production. This conclusion is based on the fact that the applicant used the same SOPs and controls as well as the same formulation, quality of excipients (i.e. melting points), and manufacturing process on the clinical and validation batches. The manufacturing processing parameters for the 10% and 15% formulations are somewhat similar and provide confidence in the manufacturing process of the two.

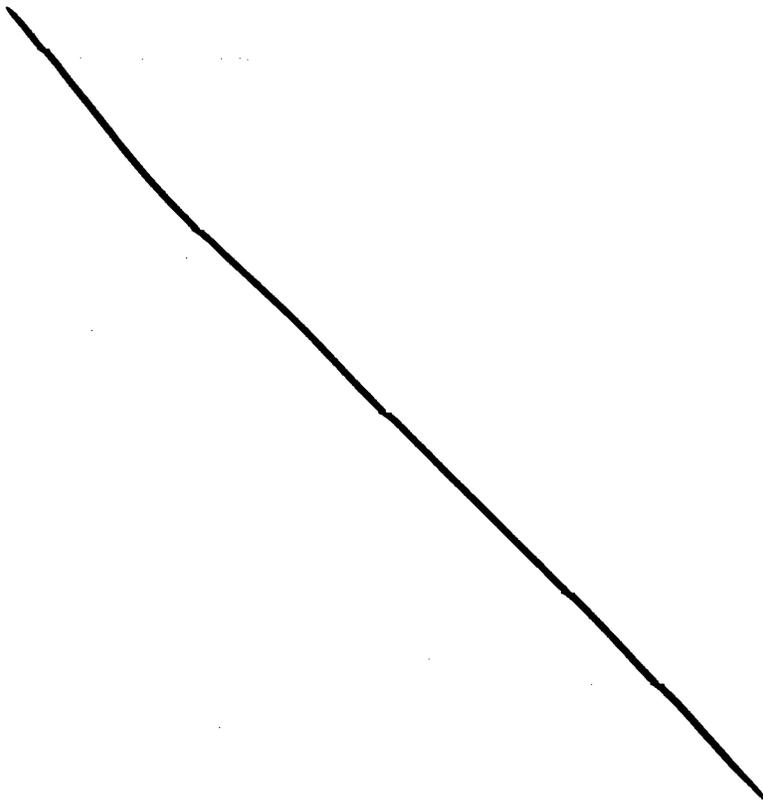
The in vitro release rates of the ointment manufactured at _____ and CPM (same formulation) are deemed to be comparable based on the requirements in the "FDA Guidance: SUPAC-Semi Solid". Taking the 90% confidence interval estimated for the test preparation to reference preparation ratio into account, the data are within the acceptance range. Additionally, the release rate of the ointment is not adversely impacted by the relative age of the _____ and CPM samples.

As a botanical drug product, the drug substance is a mixture of chemical species (catechins and other related compounds) and activity is considered to be from the whole mixture and not from an individual component. It is not known if the total activity from individual catechin components is additive or synergistic. Drug product specifications have an HPLC _____ test for all catechin components, but this test shows only their presence and not the amounts. Therefore, it is important to assure that these components are present at least at the levels which were seen in clinical batches to address efficacy, but not above those levels to address safety. So far stability

Chemistry Review Data Sheet

data at long term storage does not show a substantial negative trend for catechins. Since it is assumed that each catechin is active, to address the overall quality of the drug product, the minor catechin components in the drug product should also be controlled. The applicant proposed to control all the catechins, which provides additional assurance of quality. Since there is no independent biological assay to estimate the activity, acceptance criteria should reflect the clinical batches which gives us a benchmark for efficacy and safety. Therefore, the acceptance criteria of catechins in the drug product should be based on the $\pm 10\%$ of lower (efficacy) and higher amounts (safety) of each component present in the clinical batches. The applicant accepts the recommendation.

A total of 8 catechins are identified and quantitated in the drug product. The four major peaks



To further provide an assurance that the quality of the drug product will be maintained over the shelf life, tests for viscosity, consistency, and microbial content are provided. In-process tests at the critical steps are provided. To further control the quality of the drug product, the applicant is asked to perform testing of the particle size _____ and assay for oleyl alcohol at release and during stability testing. Both of these parameters will have a direct impact on product quality.

The primary stability batches are used to establish the expiration date even though the assay values of catechins in these batches are different (lower or higher) than the acceptance criteria set based

Chemistry Review Data Sheet

on clinical efficacy. When the stability characteristics of the catechins and ointment matrix is evaluated, it is found that catechins and ointment matrix is stable when stored at room temperature.

Based on the stability characteristics of the drug product at intermediate and at accelerated conditions, it is deemed that prior to dispensing to the patient, the drug product should be stored refrigerated at 2°C to 8°C (36°F to 46°F). After dispensing, consumer should not store the drug product above 25°C (77°F). *The stability data supports only 12 months of expiry dating when the ointment is stored below 25°C.*

the FDA recommends that prior to dispensing to the patient, the drug product needs to be stored at refrigerated temperature [2°C to 8°C (36°F to 46°F)]. After dispensing to the consumer, consumer should not store the drug product above 25°C (77°F).

The manufacturer of the drug product is CPM in Germany. An **acceptable** recommendation from the Office of Compliance is received on 12-SEP-2006 for the drug substance and drug product manufacturing/testing sites (see **Appendix-1**).

Drug substance: Kunecatechins is a botanical drug substance containing a mixture of catechins originating from the leaves of green tea [*Camellia sinensis* (L.) O. Kuntze]. The catechins are enriched in Kunecatechins by

Kunecatechins is a mixture of catechins (85 – 95% by weight). The major component is (-)-Epigallocatechin gallate (EGCg), which comprises 55- \ % of the total. A total of 8 catechins are identified and quantitated (five individual catechins and three as a group) in this partially purified green tea extract and they are (-)-Epigallocatechin (EGC), (-)-Epicatechin gallate (ECg), (-)-Epicatechin (EC), (-)-Gallocatechin gallate (GCg), (-)-Catechin gallate (Cg), (-)-Gallocatechin (GC), and (+)-Catechin (C). In addition to the known catechin components, Kunecatechins also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the botanical drug substance contains undefined mixtures of tea-related compounds, which is also controlled in the drug substance.

The _____ steps _____ some active components into other active components. Since the activity of each individual catechins peak is not known, it must be assumed that each _____ component is equally active. Small individual drug substance batches were pooled together to manufacture a drug product batch. The pooled drug substance lot was not tested before it is added to manufacture the drug product (i.e. quantitative blending of the components is not performed either by the drug substance manufacturer or drug product manufacturer). Testing was performed by the DMF holder on the small drug substance batches.

Based on the information provided by the NDA holder (lot # and amounts of each batch in a lot) and

Chemistry Review Data Sheet

information provided on catechin components present in each batch, a _____ was performed by the FDA and the acceptance criteria of catechins in the drug substance were proposed based on the amounts contained in clinical batches which were determined to be efficacious. It is deemed that the acceptance criteria of Kunecatechins should be based on the $\pm 10\%$ of lowest (efficacy) and highest amounts (safety) of each component present in the clinical batches.

Additionally, based on the type of formulation (_____) and the assumed mechanism of drug release (dissolution of drug substance only at the interface between the ointment and skin), particle size and its shape were deemed to be the most critical, relevant and meaningful physical characteristic of drug substance. The applicant expanded the drug substance specifications to include particle size specifications (at release and during stability testing). The acceptance criterion of particle size of drug substance has also been included in the drug substance specifications via an amendment to the DMF on 12-OCT-2006.

The Chemistry, Manufacturing and Controls information of the Kunecatechins is located in DMF _____ and deficiencies were conveyed to the DMF holder and satisfactory responses were received on 12-OCT-2006 via an amendment to the DMF.

B. Description of How the Drug Product is Intended to be Used

The drug product is to be applied three times per day to all external genital and perianal warts. It is recommended that a 0.5 cm strand of the ointment (~ 250 mg) be applied to each wart using the finger, dabbing it to ensure complete coverage and leaving a thin layer of the ointment on the warts.

C. Basis for Approvability or Not-Approval Recommendation:

- Tea cultivars are identified and are well controlled.
- Manufacturing procedures for extraction, fractionation of the drug substance and formulation of the drug product are deemed robust.
- Specifications for drug substance and drug product are tight enough to assure safety and efficacy.
- Container/closure to package the drug product is adequate for protecting the product.
- The applicant has responded satisfactorily (via amendments dated 28-SEP-2006 and 4-OCT-2006) to the CMC issues.
- The stability data supports only 12 months of expiry dating when the ointment is stored below 25°C.
- Prior to dispensing to the patient, the drug product needs to be stored at refrigerated temperature [2°C to 8°C (36°F to 46°F)]. After dispensing to the consumer, consumer should not store the drug product above 25°C (77°F). The applicant accepts the recommendation (via amendments dated 23-OCT-2006 and 24-OCT-2006).
- An **acceptable** recommendation from the Office of Compliance is received on 12-SEP-2006 for the drug substance and drug product manufacturing/testing sites (see **Appendix-1**).

III. Administrative

A. Reviewer's Signature Electronically captured in DFS

B. Endorsement Block

Rajiv Agarwal/Moo-Jhong Rhee/EMorefield
Date: 25-OCT-2006

69 Page(s) Withheld

8 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

*Withheld Track Number: Chemistry*_____

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/s/

Rajiv Agarwal
10/25/2006 10:36:16 AM
CHEMIST

Moo-Jhong Rhee
10/25/2006 11:05:06 AM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch II/III
Pre-Marketing Assessment Division II

OND Division: Division of Dermatology and Dental Products
NDA: 21-902
Applicant: MediGene AG
Stamp Date: Sep. 30, 2005
Trademark: Polyphenon® E Ointment
Established Name: Not provided.
Dosage Form: Ointment
Route of Administration: Topical
Indication: External genital and perianal warts (*Condylomata acuminata*)
Reviewer: Rajiv Aganwal
PAL: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues

A. Summary

NDA 21-902 is the first botanical NDA submitted to the agency. The proposed drug product is Polyphenon® E Ointment, 15% for topical treatment of external genital and perianal warts (*Condylomata acuminata*) in adult patients.

Polyphenon E ointment, 15% contains a botanical drug substance, Polyphenon® E, which is derived from green tea leaves of *Camellia sinensis*. The proposed drug substance is not highly purified; it is a complex mixture of catechins and other tea associated materials. The predominant catechin is (-)-Epigallocatechin gallate (EGCg), which comprises 55-60% of the drug substance. Besides EGCg, there are at least 7 other known catechins present in Polyphenon E. The total catechin content in Polyphenon E is 85-95% (w/w). Additionally, the drug substance also contains 5-15% of poorly characterized tea associated materials such as caffeine, theobromine, and gallic acid.

The eight known catechins have been isolated and purified. Their structure elucidation data are provided, and a reference standard is available for each of them.

The proposed botanical raw material is tea leaves, harvested from tea plants which grow on _____ farms. The dried leaves are shipped to _____

_____, Polyphenon E. _____

_____ and undergoes _____ to produce a Polyphenon E concentrate. After further concentration by _____ the _____ concentrate is _____ and becomes the proposed bulk drug substance, Polyphenon E. The most critical step identified by the applicant for the production of Polyphenone E is the _____ step. The step is monitored by a _____ at _____.

The table below summarizes some of key information provided by the applicant for the various stages of drug substance manufacture and controls:

The to-be-marketed formulation was used in the two pivotal Phase 3 clinical studies (CT 1017 and CT 1018). The comparability of the Phase 3 clinical supplies for CT 1017 and CT 1018 _____ to the commercial batches (_____) was linked by the applicant using an *in-vitro* release test. The applicant claims that they are comparable.

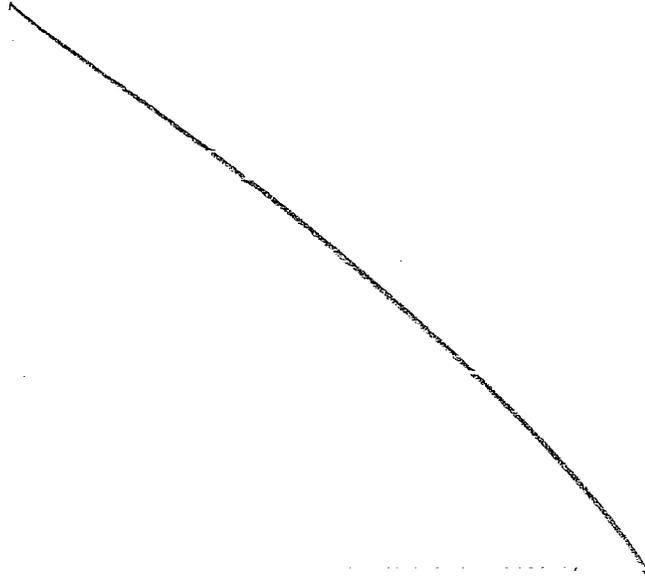
To support the proposed expiry period of _____ months for the drug product under the storage condition not above 25°C, the applicant provides six months of stability data (long term and accelerated) from three commercial scale validation batches. Additional supporting data of _____ months (long term and accelerated) from three pilot/development batches are also provided.

B. Critical issues for review

Name:

There is no established name proposed. The proposed proprietary name for the drug product is Polyphenon® E Ointment, 15%. The established name supposedly should capture the essence of the product. Since the proposed drug substance is a complex mixture and not highly purified, which "name" would be considered to be representative for the essence of this proposed product?

Drug Substance:



1 Page(s) Withheld

b § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

C. Comments for 74-Day Letter

- Provide samples for all container labels for review.
- Provide Phase 3 clinical supply samples for Polyphenon E ointment (10% and 15%) and the placebo.
- Provide samples for the to-be-marketed product packaged in the intended container/closure system for commercialization.
- Provide samples for the intended container/closure system for commercialization.
- Provide formulation compositions for all pharmacokinetic studies.
- Inconsistency in drug product specification is noted between the specification provided on p. 1 of 4 in Section 3.2.P.5 and that provided on p. 54 of 81 in Module 2.3 Quality Overall Summary. Please clarify which set is correct.
- Add a specification for the identity and assay of _____, oleyl alcohol, to the drug product specification.
- Provide information for the characteristics (size, nature, and solid structure) of the particles in the bulk drug substance and the drug product.
- Update stability data for drug product.
- Apply a United States Adopted Name (USAN) for the proposed drug substance.

D. Comments/Recommendation:

This NDA is **fileable** from chemistry, manufacturing and controls (CMC) perspective. Comments to be forwarded to the applicant in the 74-day letter are listed above. The major review issues include the following:

Drug substance:

- Is the process for the production of botanic raw material (tea leaves) well controlled, and adequately described?
- Is the process for the production of _____ well controlled, and adequately described?
- Should the tea-associated materials be _____ If so, what will be the appropriate specification?
- Does the firm provide adequate data and information to support the exclusion of a specification on degradant?
- Is the HPLC assay method stability indicating, and adequately validated?

Drug product:

- Does the firm adequately test the bulk product?
- Does the firm provide adequate data and information to support the exclusion of a specification on degradant?
- Is the HPLC assay method stability indicating, and adequately validated?
- Is the link between the Phase 3 supplies and commercial batches adequately established?

Inspection

Should the tea farms and the extraction facility _____ be inspected for GMP or for compliance with other regulations?

Shulin Ding
Pharmaceutical Assessment Lead, Branch III

Moo-Jhong Rhee
Chief, Branch III

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/s/

Shulin Ding
11/23/2005 09:54:13 AM
CHEMIST

Moo-Jhong Rhee
11/23/2005 02:46:21 PM
CHEMIST
Chief, Branch III