

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-201s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF RISK MANAGEMENT**

Date: December 30, 2009

To: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products (DCRP)

Through: Mary Willy, Ph.D., Deputy Director
Division of Risk Management (DRISK)

From: Gita Toyserkani, Pharm.D., MBA,
Senior Risk Management Analyst, DRISK

Subject: Evaluation of potential risk evaluation and mitigation strategies (REMS) for
Asclera™

Drug Name(s): Asclera™ (polidocanol) 0.5% & 1.0% solution for injection

Application NDA 21-201

Applicant/Sponsor: Chemische Fabrik Kreussler & Co., GmbH

OSE RCM #: 2009-2474

1 INTRODUCTION

This memorandum is in response to the December 11, 2009 request from the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to evaluate and comment on potential Risk Evaluation and Mitigation Strategies (REMS) for Asclera™ (polidocanol).

DRISK has considered labeling, including a boxed warning, as well as the following potential risk mitigation strategies for Asclera™ (polidocanol): a Medication Guide, a Communication Plan, Elements to Assure Safe Use, and a Timetable for Submission of Assessments. Below are DRISK's recommendations and rationales for each strategy.

2 MATERIALS REVIEWED

The following materials were reviewed:

- 1) Draft Guidance for Industry: Format and content of proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and proposed REMS Modifications, dated September 2009.
- 2) Approved Risk Evaluation and Mitigation Strategies (REMS): <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>, accessed December 14, 2009.
- 3) Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products Content and Format, dated January 2006.
- 4) Polidocanol proposed labeling.
- 5) Khin U, Clinical Review dated November 16, 2009.
- 6) Southworth, MR, Safety review of Anaphylaxis Cases, dated December 17, 2009.
- 7) Sotradecol® (sodium tetradecyl sulfate) approved label.
- 8) Kalbitor® (ecallantide) approved label and REMS dated November 27, 2009.
- 9) Plenaxis® (abarelix) approved label dated November 25, 2003.
- 10) Xolair (omalizumab) approved label dated July 2, 2007.

3 BACKGROUND

Asclera™ (polidocanol) is a sclerosing agent proposed for the indication of treatment of spider veins (≤ 1 mm in diameter) and reticular veins (b 1 to 3 mm in diameter) of the lower extremities.

Polidocanol is a non-ionic surfactant that induces local endothelial damage of the blood vessels. It has a concentration and volume-dependent damaging effect on the endothelium of blood vessels. The proposed dose is 0.1 to 0.3 ml per injection (multiple injections may be needed). The proposed label recommends a (b) (4) total maximum volume of 10 ml per sclerotherapy session.

Asclera™ is not currently marketed in the United States but has been available in Europe and other countries for over 40 years. It is currently licensed for the treatment of varicose veins in 13 countries including Argentina, Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, the Netherlands, Spain, Sweden, and Switzerland. The

only currently approved sclerosing agent for the treatment of small varicose veins in the United States is Sotradecol[®] (Sodium Tetradecyl Sulfate) (approved 1946).

On December 11 2009, DCRP met with DRISK to discuss the risk of anaphylaxis following the injection of polidocanol and to determine whether a REMS, particularly a communication plan only REMS, was necessary to ensure that the benefits outweigh the risks. The two main safety concerns expressed by the review team in DCRP were the risk of anaphylaxis associated with off-label use of the product and the use of the product in settings that would not have emergency resuscitation equipment readily available in case of an allergic or anaphylactic reaction. DRISK subsequently met internally on December 15, 2009 to discuss potential risk mitigation strategies for Asclera[™].

4 SAFETY CONCERN

The review team in DCRP has identified the risk of anaphylaxis associated with the use of polidocanol in post-marketing reports from other countries. The medical officer opines that the post-marketing cases of “anaphylaxis” were associated with doses, concentration, volumes, and for other diseases (large varicose veins, esophageal varices, gastric and duodenal ulcer bleeding, etc.) that are outside of those specified in the proposed labeling.

The safety data submitted in the application for the specified C₁ (spider and reticular) veins with the specified dose, concentration and volume did not show any deaths or anaphylaxis:

- 338 patients in the pivotal EASI trial (**E**fficacy and safety of **A**ethoxysklerol[™] compared to **S**odium tetra-decyl sulfate and **I**sotonic saline (placebo) for the treatment of reticular and spider veins),
- 501 patients in seven earlier clinical trials, and
- 1605 patients in the subsample of over 3000 patients in the French Polidocanol Registry who had received at least one polidocanol injection in 6444 sclerotherapy sessions in 2004, when surveyed for the AES they had experienced.

The sponsor submitted 19 post-marketing adverse reaction reports (CIOMS) with a fatal outcome. Of the 19 cases, one fatal case was associated with anaphylactic shock following the injection of 2% polidocanol for the treatment of leg varices (undefined).

The sponsor also submitted 29 CIOMS reports of allergic reaction including angioedema, urticaria, anaphylactic shock, or dyspnea, with no fatal outcome. Of the 29 cases, 9 patients experienced some form of anaphylactic reaction. Despite the fact that there is some dissent among the reviewers in DCRP whether these 29 cases were associated with the use in C₁ veins and within doses recommended by the proposed labeling, these cases are suggestive of an association between polidocanol therapy and allergic and anaphylactic adverse events. These events are considered rare (sponsor reports worldwide use of polidocanol to be ^{(b) (4)} exposures) and are primarily observed with the use of larger volumes than those recommended in the proposed labeling and with off-label indications such as larger veins and esophageal varices.

5 ROUTINE LABELING AND BOXED WARNING

The label for Sotradecol[®] contains information about the risk of anaphylaxis in the Warnings section. The Sotradecol[®] label includes the requirement of having emergency resuscitation equipment available as well as recommending a test dose and to observe the patient for several hours prior to administration of a second or larger dose of Sotradecol[®].

DRISK recognizes that Asclera[™] has a similar adverse event profile to the currently approved product, Sotradecol[®]. However, Sotradecol[®] was approved in 1946 and Agency's risk-benefit threshold may have been different. Considering that the proposed indication for Asclera[™] is for a cosmetic benefit and not a life-threatening disease, the risk benefit profile shifts such that a boxed warning may be warranted.

A boxed warning is ordinarily used to highlight for prescribers one of the following situations (§ 201.57(c)(1)):

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21CFR part 314, subpart H, § 314.520 "Approval with restrictions to assure safe use").

A boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber. Information included in the warnings and precautions and contraindications sections should therefore be evaluated to determine whether it should also be placed in a boxed warning. DCRP may want to consult the Division of Dermatology and Dental Products (DDDP) on the level of risk that is tolerated for a cosmetic product and the threshold for requiring a boxed warning.

Additionally, if there is a concern that the product may be extensively marketed resulting in Asclera[™] being used off-label and in settings not equipped with necessary emergency resuscitation equipment, a boxed warning may be useful in limiting the marketing of the product. A boxed warning would have an impact on limiting reminder advertisements and ensuring that the safety message is captured in the promotional materials targeted to both healthcare providers and patients.

6 RISK EVALUATION AND MITIGATION STRATEGY

On September 27, 2007 the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA). Title IX, Subtitle A, section 901 of this statute created a new section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) which

authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

REMS are intended to meet specific risk mitigation goals for a product that requires strategies beyond professional labeling (the package insert) to ensure safe use in the post-marketing setting. These tools may consist of a Medication Guide (MG), Communication Plan (CP), elements to assure safe use (ETASU), and a timetable for submission of assessments. It is important to determine if such additional measures are feasible, appropriate, effective, and necessary to mitigate the risks. It is important to use this authority judiciously as to not over burden the health care system as well as dilute the effect of a REMS. In making a determination on when to require a REMS, the following factors should be considered:

- (A) The estimated size of the population likely to use the drug involved.
- (B) The seriousness of the disease or condition that is to be treated with the drug.
- (C) The expected benefit of the drug with respect to such disease or condition.
- (D) The expected or actual duration of treatment with the drug.
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such event in the population likely to use the drug.
- (F) Whether the drug is a new molecular entity.

Currently, there are three drugs that are associated with the risk of anaphylactic reactions for which the FDA has required a REMS (Xolair[®] and Kalbitor[®]) or deemed to have a REMS in effect (Plenaxis[®]).

Xolair[®] (omalizumab) was approved in June 2003 for the indication of moderate to severe persistent asthma in patients who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. In the clinical studies, 0.1% of the patients treated with Xolair[®] experienced anaphylaxis. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair[®] use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. The labeling for Xolair[®] includes a boxed warning regarding the risk of anaphylaxis. On June 24, 2009, the FDA approved a Medication Guide only REMS for Xolair[®].

Kalbitor[®] (ecallantide) is an orphan drug approved in November 2009 for treatment of acute attacks of hereditary angioedema. In the clinical studies, 10 patients (3.9%) treated with intravenous or subcutaneous Kalbitor[®] experienced anaphylaxis. The labeling for Kalbitor[®] includes a boxed warning and the FDA required REMS with a Medication Guide and a communication plan. The purpose of the communication plan was to inform the health care providers about the risk of anaphylaxis associated with Kalbitor[®] as well as the importance of distinguishing between hypersensitivity reaction and the disease itself.

Plenaxis[®] (abarelix) was approved in November 2003 under a restricted distribution program for the treatment of men with advanced symptomatic prostate cancer. In the clinical studies, 5% of the patients treated with Plenaxis[®] experienced a severe anaphylactoid-type allergic reaction. Plenaxis[®] was voluntarily removed from the U.S. market (b) (4) and is currently not marketed. Plenaxis[®] is deemed to have in effect a REMS with a Medication Guide, communication plan, and elements to assure safe use. The labeling for Plenaxis[®] includes a boxed warning regarding the anaphylactic reactions.

1.1 MEDICATION GUIDE

A Medication Guide is considered part of the labeling and is also a potential element of a REMS. A Medication Guide may be required as part of the REMS if it is necessary to ensure that the benefits of the drug outweigh the risks and the following conditions (under 21 CFR 208.1) are met:

1. The drug product is one for which patient labeling could help prevent serious adverse effects.
2. The drug product is one that has serious risks (relative to benefits) of which patients should be made aware of because information concerning the risks could affect patients' decisions to use, or to continue to use, the product.
3. The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Since Asclera[™] is dispensed by a physician in an office setting, the assumption is that the risk-benefit discussions would take place prior to dispensing of the product. Also, the likelihood that patients have the opportunity to read the Medication Guide in an office or practice setting prior to the administration of the drug is doubtful. Furthermore, the documented hypersensitivity reactions developed within minutes of the injections so they would be identified and treated in the physicians office. Additionally, if the risk of anaphylaxis is associated with the off-label use of the product, patients most likely will not be aware of the "off-label" use and will not be in a position to make an informed or conscious decision.

For the reasons mentioned above, some members of DRISK questioned the value of a Medication Guide for this product. However, the majority of the DRISK team felt that if there is a risk of anaphylaxis for the proposed indication, patients should be made aware of the risk since the risk of anaphylaxis relative to the cosmetic benefit obtained could affect patients' decision to use, or to continue to use the product.

1.2 COMMUNICATION PLAN

A communication plan targeted at health care providers may be considered a necessary element of a REMS if it supports the implementation of the REMS. The communication plan may include sending letters to health care providers; disseminating information about REMS elements to encourage implementation by health care providers or to explain certain safety protocols; or disseminating information to health care providers

through professional societies about any serious risks of the drug any protocol to assure safe use.

The two main safety concerns expressed by the review team in DCRP were the risk of anaphylaxis associated with the off-label use of the product and the use of the product in settings that would not have emergency resuscitation equipment readily available. At the time of prescribing and administering, health care providers are more likely to refer to the labeling than recall a communication plan that was mailed to them; therefore, displaying the information prominently in the labeling, such as a boxed warning, should have the greater impact.

In addition, the purpose of a communication plan for Asclera™ would be to emphasize and reinforce the safety messages that are highlighted in the labeling. We believe that if the safety concern does not rise to a boxed warning, a REMS consisting of a communication plan is not warranted. In general, for products that the FDA has required a REMS with a communication plan or elements to assure safe use, the labeling of the product has included a boxed warning to highlight and prominently display the serious risk. There are a few cases, though, where the FDA has required a REMS with a communication plan or ETASU and the labeling did not include a boxed warning. In these circumstances the risk was considered theoretical and therefore was not elevated to a boxed warning.

Finally, a communication plan, whether implemented once or repeated, would not ensure that the product is not dispensed in “inappropriate” settings and most likely would not reach those settings.

1.3 ELEMENTS TO ASSURE SAFE USE

Elements to assure safe use (ETASU) are intended to provide safe access for patients to drugs with known serious risks that would otherwise be unavailable. An ETASU is an activity that requires the use of more stringent criteria to assure the safe use of a drug, such as a restricted distribution system. Asclera™ is intended to be administered by physicians in their practice setting, which is a more controlled setting that should allow the necessary monitoring of patients. Therefore, we do not believe that the approval of Asclera™ at this time should be contingent on requiring ETASUs.

1.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Since Asclera™ is proposed for a cosmetic indication, it will not be covered by most insurance plans and therefore the extent of off-label use will be difficult to determine through currently available databases. Furthermore, surveys of patients and healthcare providers would likely not provide information on off-label use necessary to assess the effectiveness of a communication plan in achieving this goal.

7 RECOMMENDATIONS

If the goal is to 1) mitigate the risk of anaphylaxis associated with off-label use of Asclera™ and 2) assure the administration of the drug in settings that are equipped with emergency resuscitation equipment, we recommend the following:

1. Labeling:

- a. Consider requiring a boxed warning highlighting:
 - i. the risk of anaphylaxis, particularly when used in larger volumes and for off-label indications.
 - ii. the need to be administered by a healthcare provider in a setting that has emergency resuscitation equipment readily available.
- b. DCRP may want to consult DDDP on the level of risk that is tolerated for a cosmetic product and the threshold for requiring a boxed warning.

2. REMS elements:

- a. If there is a risk of anaphylaxis associated with the proposed indication, patients need non-promotional information to decide whether to use Asclera™ despite the risk of anaphylaxis; therefore, we recommend a Medication Guide.
- b. A REMS consisting of only a Communication Plan may be justified if the risk is elevated to a boxed warning in the labeling. If the review division feels strongly about a having a communication plan, such as a Dear Health Care Provider (DHCP) letter, it can also request a letter outside of a REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	Asclera (polidocanol) 0.5%/1%

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/s/

GITA A AKHAVAN TOYSERKANI
12/30/2009

MARY E WILLY
12/30/2009
I concur