CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	21,201
Applicant Name	Chemische Fabrik Kreussler & Co, Gmbh
Date of Submission	Sept 29, 2003
PDUFA Goal Date	Jan 8, 2010 (priority review)
Proprietary Name / **Established (USAN) Name**	Asclera™/polidocanol
Dosage Forms / Strength	Injection/0.5% and 1.0% solution
Proposed Indication(s)	1. Treatment of varicose veins of the lower extremities
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Khin U, MD
Statistical Review	John Lawrence, PhD
Pharmacology Toxicology Review	William Link, PhD
CMC Review/OBP Review	Wendy Wilson-Lee, PhD
Microbiology Review	Vinayak B. Pawar, PhD
Clinical Pharmacology Review	P Hinderling
DDMAC	Michelle Safarik
DSI	Lauren Iacono-Connor
CDTL Review	Khin U, MD
OSE/DEpi	
OSE/DMEPA	Shirley Zeigler
OSE/DRISK	G Toysarkani
Other – Div Dir Review Dep Dir for Safety Review	Norman Stockbridge, MD Mary Ross Southworth, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Introduction

Asclera (polidocanol) 0.5% and 1.0% for injection is a sclerosing agent intended for direct injection into spider veins (≤ 1 mm diameter) and reticular veins (1-3 mm diameter), two kinds of variceal veins, in the lower extremities. It is not intended for larger varices of the legs or for esophageal varices, although it (in other countries) and a US-marketed similar sclerosing agent, Sotradecol (sodium tetradecyl), have been used for these purposes, raising some concern about off label use and increased risk of severe allergic reactions because of the larger doses and possibly greater systemic exposure with such uses. Sotradecol has been available in the US since 1946. Asclera has been marketed in many European countries, including France, Germany, Finland, Sweden, and the Netherlands, for about 4 decades.

Polidocanol is a long-chain fatty acid that functions as a non-ionic surfactant. It damages venous endothelium, yielding a thrombogenic surface that creates a mesh of platelets, cellular debris, and fibrin, with ultimate replacement of the vein by fibrous connective tissue. Unlike a thrombotic obstruction, which can be recanalized, the resulting fibrous cord cannot be recanalized. Although larger varices can cause pain and swelling, and can be injured (and bleed), and the smaller vessels for which Asclera is indicated can also bleed, the principal adverse consequence of spider and reticular veins is cosmetic. This is not to dismiss the importance to people of appearance, but it needs to be recognized when considering the risks of the drug.

The initial NDA submission of Asclera to the Division of Dermatology and Dental Drug Products was on 10/01/99, and there was a resubmission on 11/10/2003; this led to non-approval because of data integrity concerns at a number of sites in one of the two trials submitted (MICA) and because neither trial used a placebo, leaving effectiveness uncertain. In the small (n =46) OHIO trial, response rates (for complete disappearance) on polidocanol and the Sotradecol control were quite modest (13-26% in various groups), raising the concern that without a placebo or a well-defined non-inferiority margin, it was not possible to conclude that the drug was effective. After some false starts, the EASI, the study that is the basis for showing effectiveness in the current submission, was designed and carried out.

There are no remaining CMC, pharm-tox, or clinical pharmacology issues. In the main effectiveness study (EASI), described below, 22 patients had blood level measurements as part of a side study. As Dr. Stockbridge notes, these were variable but figure 1 in Dr. U's MOR shows that polidocanol does appear in serum after injection, with peak levels at about 20 minutes, fairly rapid disappearance (low at 120 minutes, gone at 6 hours) and with blood levels after the 1% solution about 3 times those after 0.5%. The study is small and results were quite variable, but the study does show that despite the intent to sclerose locally, same drug becomes available systematically and could lead to allergic reactions.

II. Effectiveness

The principal support for effectiveness comes from the EASI Trial conducted at 19 centers in Germany by investigators with no disclosable financial interests. In the trial, patients with spider veins or reticular veins were randomized to polidocanol (155 patients), Sotradecol (105 patients) or placebo (53 patients). Polidocanol patients with spider veins got polidocanol 0.5% while those with reticular veins got 1.0%. All but 3 of the 316 patients were evaluable. The treatments were compared at 12 and 26 weeks after injection based on assessment of change in digital photograph scores by 3 blinded observers (the investigator and 2 independent medical experts) on a 5 point scale:

1 = worse than before
2 = same as before
3 = moderate improvement
4 – good improvement
5 = complete treatment success

The mean changes from baseline at 12 weeks on the full data set (all patients) and on a per protocol (omitting 47 protocol violators) data set are shown in the following table (similar photographic results were seen at 26 weeks).

	Treatment		
	Polidocanol n = 155	Sotradecol n = 105	Placebo n = 53
All patients	4.52 n = 135	4.49 n = 84	2.19 n = 47
Per protocol	4.55	4.45	2.09

The differences from placebo (which averaged close to no change) were highly significant for both treatments ($p < 0.0001$). Note that in the earlier studies only complete disappearance was considered a success. In contrast, in EASI, improvement short of that (good improvement, moderate improvement) was considered.

Patients' subjective satisfaction scores on a scale of 1-5 were also examined and showed that a significantly ($p < 0.0001$) larger fraction of patients were "satisfied" or "very satisfied" on polidocanol (88%) than on Sotradecol (64%) or placebo (13%) at 12 weeks, with similar results at 26 weeks.

Many patients needed more than 1 session (56% with reticular veins and 82% with spider veins. Doses were, for spider veins 0.1-0.3 ml per injection and up to 12 injections per day.

III. Safety

Safety data in the current submission are derived from the 685 patients in previously submitted studies, 338 in EASI, 1605 patients from the French Polidocanol Registry who were surveyed for long-term adverse effects after 6444 sclerotherapy sessions, 2041 of them with polidocanol. The post-marketing experience in Europe and elsewhere was also considered. There clearly are common local reactions that occur in substantial fractions of patients (40-50% hyperpigmentation, hematoma, burning; 10-20% itching, pain, warmth). In general Sotradecol had higher (by 50-100%) rates of most of these and placebo showed rates about half of polidocanol.

There sere no deaths in the clinical studies or in the French registry. In trials there were individual cases of ecchymosis, swelling and severe hives, and numbness in tongue and lips. Few significant effects were seen in the French registry.

The principal, indeed only, important safety concern is anaphylaxis and how to reflect this risk in labeling. Drs. Stockbridge, Southworth, and U all discuss this. There is complete agreement that 1) anaphylaxis can occur but 2) that it is very, very rare, particularly after treatment of spider and reticular veins. It is probably more common with use in larger veins, where larger volumes are needed and where higher systemic exposure seems more likely. Dr. U's CDTL memo enumerates controlled and uncontrolled databases from US, Europe, China, Australia with upward of 20,000 treatments with polidocanol showing no cases of anaphylaxis. Dr. Southworth, however, in reviewing foreign post-marketing experience, identifies a number of CIOMS cases of relatively severe allergic reactions, some of them fairly clear cases of fatal anaphylaxis; almost all of these, however, were associated with relatively large doses of polidocanol used for esophageal varices or GI bleeding. Dr. U's CDTL memo discusses all of these cases. All but 5 were for large vein treatments (esophageal varices, bleeding ulcer, hemorrhoids), non-specified use (1 case), or a spinal coagulation, and only one appeared to have died after an anaphylactic reaction. Among 5 patients treated for leg varices (size not clear) there was one case of anaphylaxis. Sotradecol (used in the US and abroad for both large and small varices) has had documented cases of fatal anaphylaxis, and its label bears a bolded warning urging

- Availability of resuscitation equipment
- Use of a trial dose

Recent AERS reports (since 2004) reveal one case of probable Sotradecol anaphylaxis.

As noted, there is agreement that the risk of anaphylaxis with the labeled use is very low, and no one considers the risk of anaphylaxis a basis for non-approval. Sotradecol, with similar risk, has been marketed for more than half a century and polidocanol has been marketed in many countries for 4 decades. The only issues, and some degree of disagreement, have been about how to notify physicians about the risk, and the probable greater risk with larger (off label) doses used to treat large leg varices. Specifically there has been discussion about whether to have a bold warning, as has been used for Sotradecol, or a boxed warning, and whether to notify patients about the risk in a Medguide. Dr. Toyserkani's helpful DRISK memo examines

these possibilities. DRISK had mixed views about a Medguide for a drug given in the doctor's office but in the end recommended that one "be considered" as a way to assure that settings in which polidocanol is used will be equipped with appropriate resuscitation equipment, together with a Boxed Warning. DRISK suggested that the Medguide might not be needed if there were a Communication Plan together with a Boxed Warning. The Division (Dr. Stockbridge and Dr. U, the CDTL) is recommending against a Medguide and does not believe the warning needs to be boxed, given the rarity of the anaphylactic event. Dr. Southworth thought a Boxed Warning could be considered but recommended that the warning be bolded.

In discussing a Boxed Warning DRISK noted these are used for adverse reactions so serious in proportion to benefit that patients must consider them in deciding whether to be treated. They noted that the benefit here is cosmetic and suggested that the fact the Sotradecol lacks a box may not be determinative, as standards have evolved since that drug was approved. They therefore thought a box should be considered. On the other hand, in describing 3 drugs that cause anaphylaxis where a box warning and Medguide have recently been used, DRISK identified drugs with 0.2%, 3.9%, and 5% rates of severe anaphylactoid reactions, rates some (given (b) (4) polidocanol exposures and at most several reasonably solid cases of serious anaphylaxis, with almost all of them following larger doses than are given for the labeled polidocanol use) 3-4 orders of magnitude (3 if you believe there is a much greater rate of under-reporting) higher than polidocanol at these higher doses. Drs. Stockbridge and U therefore do not believe the bolded warning should be elevated to a Box Warning or that a Medguide is needed and I concur. The sponsor has been asked to communicate with physicians about the increased risk with off-label use of larger doses and has agreed to do so.

IV. Conclusions

Polidocanol 0.5 and 1% should be approved for treatment of small varices (spider veins and reticular veins) with limited doses and a bolded warning about use of larger doses and injection of larger veins. The sponsor will communicate these concerns to physicians and remind them of the need to have provisions for dealing with allergic reactions. The rates of serious allergic/anaphylactic reactions in long-standing foreign use and with US marketed Sotradecol are so low that a Boxed Warning or Medguide do not appear warranted.

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

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/s/

ROBERT TEMPLE
03/30/2010