CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 21-201 Asclera (polidocanol for small varicosities)

Sponsor: Chemische Fabrik Kreussler

Review date: 22 December 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

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This memo conveys the Division's recommendation to approve Asclera (polidocanol) to sclerose spider and reticular veins.

The NDA was initially reviewed and Not Approved by DDDP in 2004. The current action package contains reviews that formed the basis for that action, including medical (Vaughn & Carr, 13 July 2004), statistics (Thomson, 7 June 2004), clinical pharmacology (Zhang, 12 and 19 July 2004), pharmacology/toxicology (See 6 May 2004), Chemistry (Hathaway, 13 July 2004; DFS date in 2008), and microbiology (Langille, 21 June 2004), and memos by Luke (13 July 2004) and Carr (1 April 2005).

The critical issue was inadequate evidence of effectiveness, based on two small sotradecol-controlled studies. The application was subsequently transferred to DCaRP, which has overseen the conduct of a study I will describe briefly below.

This resubmission has been the subject of reviews of CMC (Wilson-Lee, 3 December 2009), microbiology (Pawar, 30 November 2009 and 18 December 2009), clinical pharmacology (Hinderling, 25 November 2009), and medical/statistical (U and Lawrence, 25 November 2009). A memo regarding possible need for a REMS has been authored by Dr. Southworth (17 December 2009); OSE has opined on this matter in an email (Toyserkani, 16 December 2009) and in several internal meetings.

Most issues have been addressed in Dr. U's CDTL memo (18 December 2009). I summarize very briefly.

The product disrupts the endothelium of veins, leading to vasospasm, clot formation, and eventual fibrosis.

Most of the clinical trial experience is with the doses to be marketed. In the EASI study subjects with spider veins (<1 mm) or reticular veins (1-3 mm) were randomized to polidocanol (n=180; 0.5% for spider veins, 1% for reticular veins), sotradecol (n=105), or placebo (n=53) and assessed the quality of the response photographically, 12 weeks after treatment, by a small panel of blinded adjudicators. The mean improvement was about 2.3 units on a 5-point rating scale, $p<<0.01$ for the comparison with placebo, and very similar in effect size to sotradecol. These effects persist at 26 weeks.

Pharmacokinetics of polidocanol has not been well characterized. In the most recent attempt, 22 subjects in the EASI study had plasma samples obtained, but the data are largely uninterpretable because of high variability and baseline levels in some subjects. Variability seems unavoidable as subjects probably trap various amounts of the drug in the affected limb. The review team seems to conclude that the state of knowledge about kinetics is adequate, considering this is not, in the usual, receptor-mediated sense, a classical drug. In this, I concur.

Although the number of subjects in controlled trials at relevant doses is only a few hundred, there is substantial information from use post-marketing in other countries.

The review team did not recommend an Advisory Committee. The product is not the first detergent sclerosing agent (sotradecol was marketed from 1946 to 2002 and reappeared as a generic in 2004). Polidocanol was reviewed in 2004; the only new information was the EASI study. Polidocanol is marketed in many other countries. The only minor controversy is with regard to a REMS; an Advisory Committee was not believed to add much to that discussion.

All team members concur on approvability.

An issue to be resolved is how to address the risk of anaphylaxis. There are no such cases in the controlled experience, but there are other allergic reactions—urticaria, hives, sneezing, and what sounds like angioedema. Similar cases to these appear in post-marketing use. Post-marketing, there appears to be one reasonably clear anaphylaxis case following low-volume administration to treat a leg varicosity. Drs. U and Southworth describe two treatment-associated deaths that do not appear to me to be obviously related to polidocanol.

Overall, the team has the impression that the risk of anaphylaxis may increase with dose, and that seems plausible. A goal of labeling and any additional post-marketing safety-related activities ought to be discourage off-label use for larger varicosities where the volume of drug necessary will be much higher than it is for the indicated uses.

Dr. Southworth recommends a bolded warning, similar to the one sotradecol has. I concur with this. She recommends a communications plan for healthcare providers for the first few years, and annual review of hypersensitivity reactions. (These can be done outside of a REMS.) I concur with these, too. She is equivocal on a medication guide, citing the closely monitored setting of administration. I do not favor a medication guide; there is ample opportunity for the patient and physician to discuss treatment options, and practitioners are generally familiar with the risks from use of sotradecol. While I agree with Dr. Southworth that the cosmetic use creates a low threshold for taking conservative measures, I do not think the bar should be quite this low.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1%(b) (4)

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/s/

NORMAN L STOCKBRIDGE
12/22/2009