CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21252

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 21-252
Name of drug: Fiv-ASA/Canasa (mesalamine/5-aminosalicylic acid/5-ASA) suppository
Applicant: Axcan
Indication: ulcerative proctitis
Documents reviewed: volumes 2.1, 2.19
Project manager: Melodi McNeil
Medical officer: Raymond Joseph, M.D.
Classification: 5P
Dates: received 6 July 2000; user fee goal (6 months) 6 January 2001
Reviewer: Thomas Permutt

INTRODUCTION

Mesalamine suppositories were sold in the United States by Solvay Laboratories as Rowasa under NDA 19-919, approved 18 December 1990. In 1999 Solvay voluntarily ceased marketing Rowasa because of manufacturing problems resulting in failures in dissolution testing. No other approved mesalamine suppository exists. The subject NDA is for a putatively identical formulation by a different manufacturer, Axcan. Since the cessation of marketing of the approved product, the Axcan product has been sold in the United States without an NDA because of medical need.

The NDA proposes to rely on the same two clinical studies on which the approval of Rowasa was based, studies "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use" under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Apparently, however, Axcan does have rights in a subset of the data from one of these two studies (Study 300). These are data from 27 patients (14 mesalamine and 13 placebo) treated at two Canadian centers in an international, multi-center trial. Data from this subset are analyzed separately in the present submission.

The NDA poses some regulatory complications. If the new product is similar enough to the Solvay product, the agency's findings of safety and efficacy of the Solvay product also apply to this new product. The most usual methods of establishing such similarity are not available, however, for two reasons. One is that the reference product, though not formally withdrawn, is not presently available for comparison. The other is that the product is locally active at the site of administration, so that blood levels do not indicate delivery of drug to target sites. I understand that these issues will be discussed in detail in clinical, chemical and biopharmaceutics reviews. The only matter requiring statistical review is the newly submitted analysis of the Canadian subset.

CANADIAN DATA

Study 300 was a randomized, double-blind, multicenter comparison of mesalamine to placebo. Study drug was administered three times a day for six weeks. About half the patients were also using either sulfasalazine or prednisone or both. As mentioned above, the applicant has rights in data from two centers in this trial, and has analyzed and submitted the results as though they were a separate, "Axcan-sponsored controlled clinical trial." The distinction between these centers and the others appears to be purely a matter of rights to the results. There is no indication in the statistical section of the NDA that a different product was used in the Canadian centers, nor any other reason to suppose that data from these centers are more scientifically relevant to the present application than those from the other centers.

Twenty-seven patients were treated at the two centers, 14 with mesalamine and 13 with placebo. The application reports several measures of effectiveness, but there is no indication of a primary measure or of any prospective plan of analysis. A Disease Activity Index is defined as the sum of four measures on scales from 0 to 3: evacuation frequency, rectal bleeding, mucosal appearance on sigmoidoscopy, and an overall assessment by the physician. After commenting on the lack of baseline difference between treatment groups in this variable and the changes from baseline within each group, the report continues, "This difference in improvement between the two groups after three weeks of treatment was highly significant in favor of mesalamine suppositories ($p < 0.001$). At six weeks, the DAI in the active group was 0.29 ± 0.61 and 3.73 ± 2.49 in the placebo group ($p < 0.001$)." It is curious that significant results of one analysis (change from baseline) are reported at three weeks and of a different analysis (raw scores) are reported at six weeks, while the report is silent on the two complementary analyses. In the absence of a prospective plan, one possible explanation is that only positive results are reported.

The individual components of the composite score are also discussed. Ninety-three percent of patients on mesalamine had no blood in stool at the end of the study compared to 36 percent on placebo ($p = 0.03$), and borderline significant differences were seen as early as the first week. Patients on mesalamine had significantly fewer evacuations; a p-value (<0.05) is given but no numerical result. Physicians rated 93 percent of mesalamine patients "much improved" at the end of the study compared to 15 percent of placebo patients.

It is noted that female patients had higher severity of disease than male patients, but this seems to refer to the baseline condition; interaction between sex and treatment is not discussed. There is also no analysis of efficacy by age or race. Of course, considering the small numbers involved, it seems unlikely that such analysis would have shown anything.

CONCLUSIONS AND RECOMMENDATIONS

Analysis of the Canadian subset produced nominally significant differences in the Disease Activity Index and in its individual components. No prospective plan of analysis is apparent, and there is some indication that the report selectively presents positive results.

Thus, the analysis should clearly be considered post hoc, and concerns about multiplicity cannot be dealt with unambiguously after the fact. Some of the differences, however, are dramatic. If they are considered clinically meaningful, they may speak for themselves.

I do not, however, see the value of this analysis in understanding the effectiveness of the subject product. If data from the two trials in the Solvay NDA are applicable to the subject product, then all such data seem equally applicable. There seems to be no scientific reason to consider the subset data as specially relevant, just because they happen to be in the control of Axcan. And if all the data are relevant, all the data have already been evaluated by the agency and formed the basis of findings that mesalamine suppositories are safe and effective. In other circumstances such findings might need to be re-evaluated in the light of new concerns, but that is clearly not the case here: the agency's position has been that mesalamine suppositories are not only safe and effective but medically necessary.

From a statistical point of view, I see no bar to the approval of the subject application, so long as the old data remain relevant from the standpoint of chemistry, biopharmaceutics and clinical judgment. I think it is important, however, that this approval not be considered to be based on the newly submitted analysis of the Canadian subset. Interpretation of post-hoc subset data is fraught with problems of multiplicity that may be impossible to resolve unambiguously after the fact. This analysis adds essentially nothing, I believe, to what was already known from analysis of the whole trial 300 as well as the other controlled trial and other information in the Solvay NDA. Nothing needed to be added, however, as that information was already found to be sufficient for approval of an NDA for mesalamine suppositories. There appears to be no reason it should not remain sufficient.