Peripheral and Central Nervous System Drugs Advisory Committee

January 28, 2000

Consideration of Immunex, NDA 21-120, Novantrone®(mitoxantrone hydrochloride)

Proposed Indication: To slow progression of neurological disability and reduce the relapse rate in patients with progressive multiple sclerosis.

The meeting was held at the Hilton, in Gaithersburg, Maryland. Prior to the meeting, the members, consultants and guests had reviewed background material from the FDA and from Immunex. In order for the public to be informed, the background material was also available on the Dockets page the day before the meeting. There were approximately 200 persons in attendance. The meeting started at 8 a.m. and ended at 5:45 p.m.

Attendance:
PCNS Members Present: Sid Gilman, M.D., Chair, Claudia Kawas, M.D., Richard Penn, M.D., Gerald Van Belle, Ph.D., James Grotta, M.D., Ella Lacey, Ph.D., LeRoy Penix , M.D.

PCNS Members Absent: Harold Adams, M.D., David Drachman, M.D., Zaven Khachaturian, Ph.D., Michael Brooke, M.D.

PCNS Consultants:
Oncologists: Sandra Swain, M.D., Bill Dahut, M.D.;
MS Experts: Jerry Wolinsky, M.D., Howard Weiner, M.D.
Neurologists: Richard Lipton, M.D., Michael Grundman, M.D., MPH

FDA Participants: Robert Temple, M.D., Russell Katz, M.D, Gerard Boehm, M.D.

Overview of FDA's Presentation:

Russell Katz, M.D., gave an overview of the FDA issues. In summary, he urged a discussion on the relevance of the different populations used in the two studies, on the significance of the unblinded diagnoses of relapse, and on the meaning of the MRI findings as a surrogate marker.

Overview of Immunex Presentation: The introduction was presented by Ann Hayes, M.D., Senior Vice President Medical Developments. Richard Ghalie, M.D., and Senior Director Clinical Development did the main presentation on efficacy and safety. In addition, Fred Lublin, M.D., Professor of Neurology, MCP Hahnamann University, gave an overview of the varying ways that MS progresses.

Open Public Hearing:

Three members from the public presented statements which represented their views of living with MS.

Discussion:

The committee had a discussion dealing with the issues raised by the FDA. In general, the committee felt that the label should not dwell on whether it was indicated for primary or secondary MS. Several members indicated that it would be very hard to know who would be the appropriate candidate to treat with Novantrone. Furthermore, the trials and the current nomenclature in DSM IV were not consistent which added another level of confusion. Further, if it were labeled for secondary MS it could raise false hopes in patients with MS that there now was a drug that was really going to help all patients with secondary MS.

The committee discussed the impact of the unblinded measures and in general was not greatly disturbed by this validity issue. The committee also discussed the meaning of the MRI and whether it can be viewed as a clinical surrogate. The two experts in MS both argued that MRI results were reasonable extemporaneous surrogates and that they believed the measures reflected the underlying pathology. There is no hard evidence that the number of lesions detected would correlate with whether a person did or did not worsen.

The committee voted on the following questions:

Questions:

1. Has the sponsor submitted substantial evidence of effectiveness to support their proposed indication?

The committee altered this question in the following way: The proposed indication would be changed to something like **"To slow the accumulated neuro-disability and reduce the relapse rate in patients with worsening multiple sclerosis."** The committee said the FDA could create the actual words – they were just suggesting some possible ones.

With the indication redefined the committee voted

Yes=7 **No = 0**

2. If not, have they submitted substantial evidence of effectiveness for any claim in any well-defined MS population?

   Not voted on because the committee redefined question 1 and altered the claim definition.

3. Has the sponsor submitted sufficient safety data?

   Yes = 6 **No = 1**

A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the January 28, 2000 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Sandra Titus

Sandra Titus, Ph.D. Date
Executive Secretary, PDAC

Sid Gilman

Sid Gilman, M.D. Date 2·7·00
Chair, PCNS