

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

9-386/S-019

Medical Review(s)

MEDICAL OFFICER REVIEW
DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)

CONSULTATION TO
OCPB/HFD-860 – John Z. Duan, Ph.D.

NDA#: 09-386

DRUG: Myleran® (busulfan) 2 mg scored tablets

SPONSOR: GlaxoSmithKline

DATE RECEIVED: 04 February 2002

DATE COMPLETED: 08 February 2002

MEDICAL OFFICER: Gregory K. Frykman, MD (x4-5757)

TEAM LEADER: John Johnson, MD

DOCUMENTS REVIEWED: sNDA Volume 6, OCPB Review

A review of the limited clinical data arising from the bioequivalence study of the old and new formulations for Myleran® (busulfan) indicates that there was a relatively higher incidence of headache in the group assigned to the new formulation (volume 6, p. 61/95)

From the time-concentration profiles provided in the review (p. 8), it appears possible that headache is related to the higher C_{max} observed with the new formulation. The scale used, the duration, quality of the headache and other associated factors are not provided in the clinical material provided.

The clinical concern is that if headache is found to be a true adverse effect of the new formulation, patients who are uncomfortable from their headache may be less motivated to continue their busulfan oral administration. The efficacy of busulfan in CML could be compromised if patient compliance diminishes.

To more carefully determine the clinical significance of this finding, I recommend a randomized controlled trial whose purpose is to determine a difference in the incidence of headache between the new and old formulations. The recommended difference to detect is approximately 20%, which is based on the following assumptions of a baseline incidence of headache of 5% and an observed incidence of headache of 25%. Because busulfan is administered chronically, I suggest 2-4 mg/m² or 0.1 mg/kg p.o. daily until the WBC decreases by 50%. This should then be followed by a 50% dose reduction to maintain the WBC count between 20,000 and 50,000/mm³.

Reference

DeVita VL, et al. eds. Principles and Practice of Oncology 6th ed, pp. 2347-2355; Lippincott, 2001

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Greg Frykman
2/8/02 11:35:23 AM
MEDICAL OFFICER