UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C 20460

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DEC 20 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP 2F2707/FAP 2H5355. Cyromazine (Larvadex®). Review of Additional Information and Comments Submitted by Ciba-Geigy.

TOX Chem. No. 167 B

TO: Timothy A. Gardner, Product Manager #17
Registration Division (TS-767C)

FROM: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 12/17/84

THRU: William L. Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

WLB 12-19-84

THRU: Ted Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Background:

In a letter from T. A. Gardner (PM #17) to C. G. Rock (Ciba-Geigy), dated August 8, 1984, EPA listed the "data and related information that the Agency will require before we can reconsider conditional registration of cyromazine (Larvadex®)."

Ciba-Geigy has responded to the Agency's letter in a submission, dated September 27, 1984 (EPA Accession No. 254878), which contains responses to all the toxicological requirements and concerns listed in the August 8, 1984 letter.

Ciba-Geigy's responses to EPA requirements and concerns relating to the rabbit and rat teratology studies will be considered in a separate memorandum. This memorandum addresses Ciba-Geigy's responses to issues related to the 2-year chronic feeding/oncogenicity study in rats and the oncogenicity study in mice.

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Conclusions:

All data and related information requested of Ciba-Geigy on the chronic feeding/oncogenicity study in rats was presented in the September 27, 1984 submission (or otherwise satisfactorily supplied to EPA). This additional data and information has been reviewed and found to be sufficient to resolve all the outstanding issues related to this study -- pending concurrence by the Toxicology Branch pathologist, Dr. L. Kasza, who is unavailable at this time. (Dr. Kasza is expected to return in early January.)

This rat chronic feeding/oncogenicity study has tentatively been classified as Core-Minimum. The NOEL for this study is 30 ppm. The LOEL is 300 ppm. Effects observed at the LOEL were decreased mean body weights and possibly decreased mean food consumption. An oncogenic potential for Larvadex® was not demonstrated in this study at dosage levels up to and including 3000 ppm. As mentioned earlier, this conclusion is tentative pending Dr. L. Kasza's concurrence.

It is not possible at this time to reach even a tentative conclusion on the issue of malignant lymphomas in the mouse oncogenicity study. Proper interpretation of the data will require a direct input from Dr. L. Kasza since one of the main issues involves the classification scheme used by the examining pathologist to classify the various types of lymphomas observed in this study. Until this issue is satisfactorily resolved, it is not possible to meaningfully calculate the incidences of lymphoma types in the various groups of mice in this study.

Toxicological Considerations:

2-Year Chronic and Oncogenicity Study with CGA-72662 Technical in Albino Rats (IRDC Study No. 382-081).

1. Ciba-Geigy has submitted the requested historical control data for interstitial cell tumors of the testes. The data covers 1140 Charles River CD-1 control male rats that were examined from fourteen 2-year rat studies conducted at IRDC in 1979, 1980 and 1981. The incidences of "interstitial cell tumor/adenoma" in the male control animals in these studies ranged from 0.0 to 11.1%. Incidences in IRDC Study No. 382-081 were 1.7, 3.4, 1.7 and 10.5% for the control, low, mid and high dosage levels respectively. Toxicology Branch has concluded that interstitial cell tumors observed in male rats in this study are not likely to be related to the administration of test material.

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2. Ciba-Geigy has submitted the requested historical control data for renal pelvic epithelial hyperplasia in males and females. The data covers 1145 control males and 1142 control females from the same fourteen IRDC studies described above. The incidences of "renal pelvic hyperplasia" in the males ranged from 0.0 to 5.0%. Incidences in IRDC Study No. 382-081 were 1.7, 5.1, 0.0 and 0.0% for the control, low, mid and high dosage levels respectively. Toxicology Branch has concluded that for male rats in this study, this lesion is not related to the administration of test material.

The incidences of "renal pelvic hyperplasia" in the female historical control rats ranged from 0.0 to 21.3%. Incidences in IRDC Study No. 382-081 were 1.8, 15.3, 10.3 and 25.4% for the control, low, mid and high dosage levels respectively. Toxicology Branch has considered the totality of relevant data relating to this lesion in female rats in this study and has concluded that the increased incidence of this lesion in the high dosage level group is likely to be related to the administration of test material. Data supporting this conclusion includes:

a) The increased incidence of this lesion in the high dosage level group (25.4%) compared to the concurrent control group (1.8%),

b) The incidence of this lesion in the high dosage level group (25.4%) exceeding the highest incidence in the hitorical control data (21.3%),

c) The apparent decrease in the incidence of chronic nephropathy (changes other than hyperplasia of the pelvic epithelium) in the high dosage level group compared to the other female groups,

d) The consistent decrease in specific gravity and increase in urine volume (for both sexes) in the high dosage level groups throughout the study compared to other groups,

e) The lack of urinary tract calculi and/or gritty material in the kidney pelvis of female rats dying during the study as compared to the other female groups.

Toxicology Branch has also concluded that for the female rats in this study, renal epithelial hyperplasia observed at the low and mid dosage levels is not likely to have been related to the administration of test material. Data supporting this conclusion includes:

a) The lack of a dose response relationship with respect to the low (30 ppm) and mid (300 ppm) dosage levels where in spite of the ten fold increase in dosage, there was, in fact, a decrease in the incidence of renal pelvic hyperplasia from 15.3% at the low dosage level to 10.3% at the mid dosage level,

b) The incidences of this lesion at both the low (15.3%) and mid (10.3%) dosage levels being below the highest historical control incidence (21.3%) for this lesion,

c) Similarity in other kidney related data between the control, low and mid dosage level groups with respect to those observations described above under c), d) and e) (viz incidence of chronic nephropathy, changes in urinary specific gravity and volume, and the presence of urinary tract calculi and/or gritty material).

Based on all the above considerations, it has been determined that the NOEL for "renal pelvic epithelial hyperplasia" in female rats in this study is the mid dosage level (300 ppm).

Concern had previously been expressed in a memorandum from Dr. O. E. Paynter to E. Budd (dated July 31, 1984), in several subsequent memoranda from E. Budd to Registration Division and in several meetings with Ciba-Geigy that it was possible that there may be no NOEL for this lesion in the female rats in this study. It is noted here that Dr. O. E. Paynter has also reviewed the subject data submission from Ciba-Geigy and concurs with the conclusions presented above. See also 3) below.

3. Ciba-Geigy has apparently submitted the requested microscopic slides for kidneys for all animals in this study to EPA for an independent histopathological examination. The result of this examination are not yet available. The conclusions reached in 2) above should not be considered final until these results are available.

4. Ciba-Geigy has submitted the requested summary table for malignant lymphoma on an animal by animal basis for this study. Toxicology Branch has concluded, based on this and other data, that the test material did not affect the incidence of malignant lymphoma in this study.

5. It should be recalled that all the above conclusions will require concurrence from the Toxicology Branch pathologist, Dr. L. Kasza, before they can be considered final.

Oncogenicity Study with CGA-72662 in Albino Mice (IRDC Study No. 382-082).

1. Ciba-Geigy has submitted the requested historical control data for malignant lymphomas in male and female mice. Separate listings for "lymphocytic lymphoma" and "histiocytic lymphoma" were also submitted, as suggested in the EPA letter of August 8, 1984.

2. A re-reading of microscopic slides for male and female mice with "histiocytic lymphoma", in order to distinguish between "type A" and "type B", has not been performed by Ciba-Geigy. This requirement, however, will most likely be rescinded since a subsequent discussion between Dr. J. Hardisty of EPL (who performed the original reading of the slides) and Dr. L. Kasza has, according to the Ciba-Geigy submission, apparently satisfactorily answered EPA's questions concerning the pathological interpretation of these slides. This mutual understanding must be confirmed with Dr. L. Kasza when he returns.

3. Until Dr. L. Kasza returns and comments on the issue of malignant lymphomas in the mice in this study, EPA's concerns on this matter remain outstanding and not resolved at this time.

cc: O. E. Paynter (HED)
L. Kasza (TOX)

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