The chronic toxicity studies do not support safety of administration to man for unlimited periods because the rate study ran for only twelve months and because Voranil produced signs of tolerance in dogs given 50 mg./hg./day orally after three to four months of treatment.

The reproduction and teratology data submitted appear to be equivocal, and raise questions regarding the embryotoxic and terategenic potential of Voranil. Since toxicity data in rats indicated that this species could tolerate as much as 80 mg./kg./day for two months without affecting weight gain significantly, further terntological studies at greater unltiples of the prepared human dose would appear to be feasible. Higher dosages could probably be achieved by utilizing pair fed animals in the study design.

The application is also not approvable under section 505(b)(4) or the Act in that it fails to contain a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the drug.

The application is not approvable under section 505(b)(5) of the Act in the absence of some of the required samples and full information pertaining to them including detailed results of all laboratory tests made to determine the identity, strength, quality and purity of the batch represented by each sample. It is required that each sample consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory tests procedures described in the application for identity and essays.

Insufficient reference sample of clortermine hydrochloride, lot S-68-6, has been submitted to perform the tests for identity and the assays described.

Information covering samples submitted: As the Voranil Powder (new drug substance) is identified only with the codes * * *, and the analytical results are labeled p.o. Batch no. * * *, Control no. 1720, it is not clear whether the analytical results submitted refer to the batch represented by the sample. Also, the analytical data for the batch specify that assay requirements for the batch are 97% minimum. This is inconsistent with the specifications submitted for control af the new drug substance.

For the reference standards represented by batch number S-68-6, clortermine hydrochloride, and batch number S-69-7, the major impurity normally encountered in the new drug substance, complete descriptions of their preparation are needed, and for the latetr, come additional evidence, other than elemental analysis, for the structure proposed.

Although we are withholding final comment on the proposed labeling until above deficiencies are corrected, we call your attention to the following at this time:

The draft label for market packages of 1000 tablets should be submitted.

Carton labels for the market packages, if any, should also be submitted, and the manner in which they accompany the package should be indicated.

Also, the chemical structure pictured in the package insert is somewhat confusing. We suggest revisions to the more conventional geometric format of side chains attached to the ring.

This file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, the law provides you an opportunity to obtain a hearing, if requested within 30 days from the date of issuance of this letter, on the question of whether the application, as you have presented it, is approvable. This may be obtained by a written request for filing over protest, as authorized by section 130.5(d) of the regulations. Notice of opportunity for a hearing will be published in the Federal Register.

Sincerely yours,

JOHN JENNINGS, M.D.,
Acting Director,
Bureau of Medicine.