JUNE 29, 1966.

To: Acting Chief, DSB/DMR.
From: A. L. Kaminsky, M.D., Medical Officer, DSB/MBR.
Subject: Lomotil NDA12-462, 12-699. Toxicity and lethal effects in children.

(G. D. Searle & Co., Chicago, Ill., AF 13-505.)

Hospital records and autopsy protocols received in deaths of Terrence J. Erich 3 years old and James Besse 2 years old. The former due to toxicity to "therapeutic" (?) dose and the latter to overdosage.

Dr. Charles Jarvis, Pathologist to Children's Hospital, St. Paul, Minn., sums up the substance of the death in a letter to Dr. Goddard dated May 19, 1966 quote:

". . . I gather they (Searle & Co.) do not know what an overdose is, or how it reacts on the living organism. I find this state of affairs appalling. . . ."

Conclusion

It was recommended in a Summary of Supplement of September 16, 1965 dated April 27, 1966 signed Aaron L. Kaminsky, M.D. that:

1. "Dosage—Children: Delete entire section"

No studies have been performed using diphenexylate hydrochloride with 0.05 mg. atropine sulfate in children. The uncontrolled studies on children were accomplished using R1135 (diphenoxylate hydrochloride). Adverse reactions, including deaths, have been reported in children using therapeutic doses. Furthermore, fraction of tablets and teaspoons (varying from 4-5 cc.) are really not proper dosage forms for children who are very sensitive to the action of atropine.

2. "Summary: It is recommended that":

1. The drug be discontinued for children under 12 years of age. No valid, well controlled and double blind, studies were performed delineating the safety and efficiency of diphenoxylate hydrochloride with atropiue sulfate (0.025 mg.) for children.

2. A warning label to indicate the dangerous nature of the drug on children e.g. "Warning: Keep Out of Reach of Children, Dangerous Drug."

3. Labeling change are necessary as enumerated to labeling action. The labeling is in dire need of updating, correction, amendment, additions and deletion of dosage for children.

4. Atropine, even in subtherapeutic doses, should be removed from the mixture especially to obviate mortality in children.

It is the considered opinion of the undersigned, agreed to by G. M. Carroll, M.D. (Pediatrician), that Lomotil HC1 with atropine sulfate is not safe for children under 12 years of age. There are no adequate controlled studies for various age groups and for delineation of absorption, degradation, and excretion in children in a time sequence.

SUMMARY OF SUPPLEMENT

NDAs 12-462 (tablet), 12-699 (liquid).
G. D. Searle & Company, Chicago, Illinois AF 13-505.
App. Date: 9/29/60 (NDA 12-462); 1/17/61 (NDA 12-699).
Nov. 22, 1961 (Supplement).
Aug. 9, 1965 & Sept. 16, 1965—(Supplement).
Type of Drug.—Antidiarrheal.
Trade Name.—Lomotil.
Generic Name.—Diphenoxylate Hydrochloride and Atropine Sulfate 0.025 mg. (1/2400 gr.).
Dosage Form.—Tablets 2.5 mg.; Liquid 2.5 mg. per 5 cc.
Date of Supplement.—Nov. 22, 1961, Aug. 9, 1965 and Sept. 16, 1965
Chemist Summary.—see Chemist Summary
Pharmacologist Summary.—No new pharmacology. Vol. I three III, 130.13 report of September 14, 1965.
Clinical Evaluation.—Diphenoxylate Hydrochloride, a congener of meperidine (Demerol) with atropine sulfate 0.025 mg. (Lomotil) is indicated in the treatment of diarrhea secondary to motor disturbance, acute or chronic diseases of the gastrointestinal tract, and systemic disease. It is an adjuvant to specific and general therapy for the various functional, organic and post operative disorders of the gastrointestinal tract manifested by diarrhea.