

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004P-0379]

Determination That Penthrane (Methoxyflurane) Inhalation Liquid, 99.9 Percent, Was Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. The agency will not accept or approve abbreviated new drug applications (ANDAs) for methoxyflurane inhalation liquid, 99.9 percent.

FOR FURTHER INFORMATION CONTACT: Mary Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (§ 314.162 (21 CFR 314.162)).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was the subject of NDA 13–056, held by Abbott Laboratories (Abbott). Penthrane is a potent inhalation anesthetic indicated to provide anesthesia for surgical procedures in which total duration of administration is anticipated to be 4 hours or less (not to be used at concentrations that provide skeletal muscle relaxation). Penthrane was also indicated to provide analgesia in obstetrics and in minor surgical procedures and for use by self-administration using hand held inhalers. In the **Federal Register** of August 16, 2001 (66 FR 43017), FDA withdrew approval of NDA 13–056 for Penthrane after Abbott notified the agency that Penthrane was no longer being marketed under NDA 13–056 and

requested withdrawal of that application. Penthrane was then moved to the “Discontinued Drug Product List” section of the Orange Book.

In a citizen petition dated August 25, 2004 (Docket No. 2004P–0379/CP1), submitted under § 10.30 (21 CFR 10.30), and in accordance with § 314.161, AAC Consulting Group requested that the agency determine whether Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness.

We have carefully reviewed our files for records concerning the withdrawal of Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, including the NDA file for this drug product. We have also independently evaluated relevant literature and data for possible postmarketing adverse event reports. FDA has determined under §§ 314.161 and 314.162(a)(2) that Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety. FDA’s review shows that methoxyflurane, a volatile anesthetic agent, is associated with serious, irreversible, and even fatal nephrotoxicity and hepatotoxicity in humans. FDA has also reviewed the latest approved labeling for Penthrane and has determined that this labeling is inadequate. FDA believes that the risks of toxicity outweigh any potential benefits if methoxyflurane is used according to the latest approved labeling. Since the initial approval of Penthrane in 1962, with a subsequent finding of efficacy in the **Federal Register** of December 11, 1981 (46 FR 60652), alternative safe and effective anesthetics have been approved by FDA and entered the market. FDA has determined that new clinical studies are necessary before methoxyflurane could be considered for reintroduction to the market. The agency has determined, under § 314.161, that Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent was withdrawn from sale for

reasons of safety. Therefore, Penthrane (methoxyflurane) Inhalation Liquid, 99.9 percent, will be removed from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

Dated: August 29, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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