

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : ALL REGIONAL FOOD AND DRUG DIRECTORS
AND DISTRICT DIRECTORS
ATTN: NAS/NRC COORDINATORS
COMPLIANCE BRANCH CHIEFS

DATE: March 9, 1977

DLC-Rx Drug Study
Bulletin #226

FROM : Prescription Drug Compliance Branch, HFD-515
Division of Drug Labeling Compliance

SUBJECT: Adenosine Alone or in Combination.
Request for District Follow-Up.

We are preparing to implement follow-up to firms marketing adenosine preparations alone or in combination with other drugs which are regarded to be new drugs and are not covered by approved New Drug Applications.

This action is based upon a lack of substantial scientific evidence that products containing adenosine alone, or in combination with other ingredients, are generally recognized as safe and effective for any labeled indication and are, therefore, regarded to be new drugs within the meaning of Section 505 of the Act.

In the past, regulatory letters have issued against isolated adenosine single entity products in addition to a previous class action against adenosine with vitamin B-12 combination products (Drug Study Bulletins #122 & 160). It has come to our attention that usual reference sources contain several adenosine preparations. Therefore, we are now seeking to clear the market of any such remaining violative products via a class action.

Please submit FD-3055's for the following firms and products, and for any other such products of which you are aware, for which FD-3055's are not on file.

BOSTON DISTRICT:

My-B-Den

Miles Laboratories
West Haven, CT

DETROIT

Adeno

Fellows Medical Division
Chromalloy, Inc.
Oak Park, MI

KANSAS CITY DISTRICT

Adenosine B-12 Gel
Adenosine Gel Forte

Douglas Pharmacal Industries, Inc.
Lenexa, KS

LOS ANGELES DISTRICT

Mycasine Gel

Garter-Glogau
(formerly Myers-Carter Labs)
Glendale, AZ

NEW ORLEANS DISTRICT

Adenosine Phosphate

Ambort Medical, Inc.
Little Rock, AR

PHILADELPHIA DISTRICT

ADCO

Foy Laboratories
Wernersville, PA



Albert Lavender, Chief
Prescription Drug Compliance Branch

PRIORITY : HIGH
HIA-DCC No.: : BD-300-199
PROJECT CODE : 52
ESTIMATED TIME : 48 HOURS
REPLY REQUESTED BY : 3/25/77
PROJECT OFFICER : A.K. YELLEN
TELEPHONE NUMBER : 8-443-4206

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MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : ALL REGIONAL FOOD AND DRUG DIRECTORS
AND DEPUTY REGIONAL FOOD AND DRUG DIRECTORS
ATTENTION: NAS/NRC COORDINATORS

DATE: November 9, 1973

DRO Drug Study
Bulletin # 160

FROM : DESI Regulatory Control Staff (BD-317)
Compliance Evaluation Branch
Division of Regulatory Operations
SUBJECT: Adenosine - B12 Combination Drugs
See DRO Drug Study Bulletin # 122

FD 3033's submitted by District Offices disclosed a number of Adenosine-5-Monophosphate/Vitamin B12 combinations on the market. A file search showed that there are no approved NDA's for such a combination nor are they the subject of a DESI review.

Because a medical evaluation shows that injectable combinations containing "Adenosine-5-Monophosphate" and "Vitamin B12" are neither safe nor effective for their intended uses, i.e. - vasodilators, anti-inflammatory agents, etc. we have implemented a class action follow-up against this drug combination under DESI procedures.

We have issued letters on October 31, 1973 to 47 firms as manufacturers or distributors of injectable Adenosine-B12 combination drugs requesting that they discontinue marketing and a statement of intentions with respect to their removal of all outstanding stocks from the market down to the retail level.

Attached are copies of the letters issued to firms in your district and an information copy of the letter to districts in which no letters have been issued to date.

DRO will monitor the firms' replies, furnish districts with copies of such replies and issue assignments where indicated.

FD 3033's should be submitted on any other products marketed within the last two years but not previously reported, so that DRO letters may issue to these firms, if warranted.

We have brought to each firm's attention, where applicable, the Federal Register announcement of October 15, 1971 "General Policy on Fixed Combinations" (Reg 3.86).

Albert Lavender
Albert Lavender, Chief
DESI Regulatory Control Staff (BD-317)

Program Priority: High
Estimated Time: 8 Hours
Charge to: DESI BD-300-199
Reply Requested by : COB December 31, 1973
Project Officer: Paul Worden

Telephone: 301-443-4209

Enclosures



DATE: AUG 7 1996

FROM: Lana Ogram 
Director, Division of Prescription Drug Compliance
and Surveillance

SUBJECT: Request for Safety Assessment for Adenosine
Phosphate Injectable

TO: Dr. Raymond Lipicky
Director, Division of Cardio-Renal Drug Products

We are seriously considering the issuance of a regulatory action against an unapproved product, Adenosine Phosphate 25mg/ml. Its route of administration is by intramuscular injection, and is indicated for the symptomatic relief of varicose vein complications with stasis dermatitis. We are most concerned about any potential risk involving this product. Before we can implement regulatory action, a safety assessment is necessary.

On January 21, 1971 Dr. Edgar J. Martin, BD-350 did a literature assessment relating to the safety of Adenosine-Vit B12 injectable and Adenosine Phosphate injectable. (TAB A). As a result of his assessment three Drug Study Bulletins were issued.

Adenosine in combination with other active ingredients such as Vitamin B-12, was the subject of Drug Study Bulletins #122 in 1972 (TAB B) and #160 in 1973. (TAB C)

In 1977 Drug Study Bulletin # 226 (TAB D) was issued to remove from the market place Adenosine alone or in combination. However, Adenosine Phosphate 25mg/ml is found to be marketed today without the benefit of an approved application. It is this product that is the subject of this request.

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Page 2 - Dr. Raymond Lipicky

In 1996 Steris Laboratories Inc., Phoenix, AZ is the only manufacturer of Adenosine Phosphate 25 mg/ml (TAB E). Based on a search of our available references, we found that this product was not marketed prior to 1962. We believe that this product is an unapproved new drug.

Please advise on any safety concerns you might have regarding Adenosine Phosphate 25 mg/ml. We are available to meet with you and discuss this request at your convenience if you feel it would be helpful.

While we recognize your heavy work load, we ask your cooperation for an expeditious response.

If you need additional information you may contact Sonia Crisp at 594-0101.

Attachments

TAB A

RE: Adeno-Lin-Vit B12 Intectable 5 AMP

Summary: The article is a new drug. The safety of the article has never been tested by contrived studies, and safety and efficacy have not been established by scientifically credible observations. We are not aware how to write adequate directions for its use. The article is misbranded for several causes:

There are no rational theoretical grounds and no credible clinical evidences that the label recommended administration of adenosine-5-monophosphoric acid (SAMP) is effective for the intended purposes. The label is false, or misleading, or deceptive in that it (1) suggests and/or claims SAMP therapeutic effectiveness in certain conditions and (2) quotes 4 literature references as support of its clinical claims while these references contain no credible support for the claims of efficacy, and two of them are not even pertinent to the claims for which they are quoted.

The drug is not mentioned in representative texts such as Success, R. I. Diseases of the Skin, The C. V. Mosby Co., St. Louis, 1956.

Allen, A. C. The Skin. Gruen and Stratton publ. 1967, 2nd ed:
Remington's Pharmaceutical Sciences, 13th ed. Mack Publ. Co. Easton,
Pa., 1965. Grollman, A. Pharmacology and Therapeutics, 6th ed. Lea
Febiger, Philadelphia, 1965.

Previous FDA statements hold true:

A similar article was rated misbranded, and it was noted that its
efficacy was not established, _____ Dr.

_____ objected against another similar article,

_____ We believe the label claims are not acceptable
in the opinion of medical experts.

REVIEW

Label reference #1. Buell, M. V. and M. E. Perkins. J. Biol. Chem
76:95, 1928. Chemical analytical data on 5AMP determination in blood.
The study does not provide any physiological or medical information
and is not designed for such purposes.

Reference #2. A. Rocchino. Relief from pruritus following upon
administration of adenylic acid. Proc. Soc. expt. Biol. Med. 71:3
1949.

_____ The statements are vague testimonials
an uncontrolled study. The study is designed with an irrational
of pruritus. The author finally states ". . . there is much yet to

done clinically and in the laboratory before the full implications of adenylic acid administration to human beings can be evaluated . . ."

Rostenberg, A. et al. Failure of adenosin-5-monophosphate to affect favorably pruritus of atopic dermatitis, J. Invest. Dermat. 14:401, 1950

and Sawicky, H. H. et al. Adenosine-5-monophosphate (My-B-Den) for the relief of pruritus, J. Invest. Dermat. 17:265, 1951

tested Rottino's claims in controlled experiments, and found SAMP was useless in the treatment of pruritus. The label, revised in 1964, is false and misleading in that it fails to give proper consideration to Rostenberg's and Sawicky's findings.

Reference No. 3. Palmer, L. and S. Waldman. The use of adenosine-5-monophosphate in the treatment of acute subdeltoid

bursitis. New York State J. Med. 52:1774, 1952. An uncontrolled

experiment; the paper is unconvincing in its claim of SAMP efficacy

in bursitis treatment. The paper also supports its claims by refer

to Rottino's alleged results with SAMP in pruritus

but fails to mention that Rottino's findings were not confirmed by

Rostenberg and Sawicky

Thus the paper by

Palmer and Waldman is scientifically inadequate and lacks credibil

Both Palmer and Waldman stated in recent telephone conversations t

they had ceased using SAMP since other drugs do a better job.

Reference No. 4. Vilter, W. R. et al. J. Lab. Clin. Med. 27:527, 1941

The paper is not convincing since it has no, or only inadequate, controls, and its statistics are false. The authors claim they studied "29 selected patients with nutritional deficiency disease. The count of the patients shows that only 26 had such diseases while 3 "had no evidence of nutritional deficiency" and served as controls. There was no control group within the malnourished series. Even if the paper were scientifically acceptable it would not support the label claims. As shown in the following details the label is false and misleading in that it states and/or suggests that the paper support its claims:

1. The paper gives statistics on the authors experience with intravenous 5AMP medication. In contrast, the label indication is for intramuscular use only and warns specifically against intravenous use.

2. The paper specifically states the usefulness of its 5AMP treatment is limited to malnourished patients with pellagra and peripheral neuritis. The label is false and misleading in that it conceals these limitations.

3. The paper specifically states that its 5AMP treatment is lacking efficacy in persons who have no nutritional deficiency. The label is false and misleading in that it conceals this restriction of the paper:

Mills, J. and E. H. Mensted. Lancet 1, 237, 1951. "Vitamin B12 in pernicious anaemia.

The article does not mention 5AMP

or anything that could be related to SAMP. The label is false and misleading in that it states or suggests that this paper supports its SAMP claims.

Edgar J. Martin, M.D., BD-350



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

Date: 8 August 1996
From: Robert R. Fenichel, HFD-110
Subject: Adenosine Phosphate 25 mg/ml
To: Lana Ogram, HFD-333

This will respond to your memo of 7 August to Raymond Lipicky.

Adenosine Phosphate 25 mg/ml is not familiar to this Division, but we have approved two different intravenous adenosine preparations from Fujisawa USA, one to terminate certain arrhythmias (ADENOCARD[®], given as a bolus of 6-12 mg) and one as an adjunct to cardiac nuclear imaging using ²⁰¹Th (ADENOSCAN[®], given as a 6-minute infusion of 0.14 mg/kg/min, working out to a total of 60 mg in a 70-kg patient).

Because of adenosine's extraordinarily short half-life (less than 10 seconds), these preparations have turned out to be relatively safe. Nevertheless, they are associated with nontrivial incidences of

- cardiac dysrhythmias, including ventricular fibrillation, complete heart block, and cardiac arrest, **sometimes fatal**; and
- bronchospasm, especially (but not only) in known asthmatics, rarely requiring respiratory support. I think there may have been a few deaths in this category too.

Because of these hazards, the labeling of ADENOCARD includes the recommendation that "[a]ppropriate resuscitative measures should be available."

This Division has no experience with intramuscular administration of any formulation of adenosine, and we cannot comment on the possibility of untoward local effects (sterile abscesses, for example). Degradation of circulating adenosine is so rapid that true intramuscular administration is probably harmless (and valueless), with serum levels effectively unchanged from those endogenously present, but that is not the end of the story. Attempted intramuscular administration will always result in a certain incidence of inadvertent intravenous injection, with all of the risks noted above.

Such risks may be acceptable, **if they are offset by demonstrated benefits**. We have not attempted to replicate Dr. Martin's scholarship, but we doubt that any such benefits have ever been properly attributed to Adenosine Phosphate 25 mg/ml.

Please let us know if we can be of any further assistance.

* This recommendation is, I just noticed, not present in the labeling of ADENOSCAN. It should be.