CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

08-848/ S-018

Trade Name: Pamine 2.5 mg

Generic Name: Methscopolamine Bromide

Sponsor: The Upjohn Company

Approval Date: September 4, 1986

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

08-848/s-018

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Reviews / Information Included in this NDA Review.

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EA/FONSI	
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Statistical Review(s)	
Microbiology Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-848

APPROVAL LETTER

NDA 8-848/S-018

SEP 4 1986

APPROVAL

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-232 (with labeling)
HFN-110/THassall/8/1/86
cb/8/7/86/0995v
R/D init: AThompson/8/[illegible]/86
CBHenrey/8/27/86
DCunningham/8/[illegible]/86
THassall/8/[illegible]/86
WBachrach/8/14/86

The UpJohn Company
Attention: George H Ishler, M.D.
Kalamazoo, Michigan 49001

Dear Dr Ishler:

We acknowledge the receipt on July 22, 1986 of your July 15, 1986 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pamine (methscopolamine bromide) Tablets.

The supplemental application provides for final printed labeling revised to include the following additions or changes:

- Under DESCRIPTION
  - Added inactive ingredients
  - Added chemical name, structure and molecular weight
- Under HOW SUPPLIED
  - Added tablet shape and color
  - Added storage conditions
- ACTIONS is renamed CLINICAL PHARMACOLOGY
- INDICATIONS is renamed INDICATIONS and USAGE
- TREATMENT OF OVERDOSAGE is renamed OVERDOSAGE and is placed after PRECAUTIONS.

We have completed the review of this supplemental application and it is approved. Our letter of November 28, 1980 detailed the conditions relating to the approval of this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Mr. Thomas Hassall
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

RX 9/4/86

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

TomH 8/30/86

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVED LABELING

Pamine®
brand of methscopolamine bromide tablets, USP

Upjohn

811 377 302

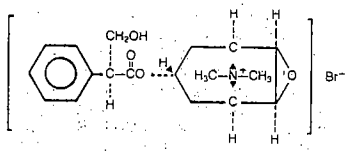
DESCRIPTION

PAMINE Tablets contain methscopolamine bromide. Methscopolamine bromide occurs as white crystals, or as a white odorless crystalline powder. It melts at about 225° with decomposition. The drug is freely soluble in water, slightly soluble in alcohol, and insoluble in acetone and in chloroform.

The chemical name for methscopolamine bromide is 3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9, 9-dimethyl-, bromide, [7(*S*)-(1α,2β,4β,5α,7β)]-and the molecular weight is 398.30.

Pamine
brand of methscopolamine bromide tablets

The structural formula is represented below:



Each PAMINE tablet for oral administration contains 2.5 mg of methscopolamine bromide. Inactive ingredients: calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose.

CLINICAL PHARMACOLOGY

Methscopolamine bromide is an anticholinergic agent which selectively inhibits gastric secretion and gastrointestinal motility.

INDICATIONS AND USAGE

Adjunctive therapy for the treatment of peptic ulcer.

CONTRAINDICATIONS

Glaucoma; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis, etc); paralytic ileus; intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis.

Pamine
brand of methscopolamine bromide tablets

WARNINGS

Safety for use in pregnancy has not yet been established.

In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful.

PAMINE Tablets may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug.

PRECAUTIONS

Use with caution in patients with:
- Autonomic neuropathy.
- Hepatic or renal disease.
- Ulcerative colitis—large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon.
- Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hypertension and non-obstructing prostatic hypertrophy.
- Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Pamine
brand of methscopolamine bromide tablets

It should be noted that the use of anticholinergic drugs in the treatment of gastric ulcer may produce a delay in gastric emptying time and may complicate such therapy (antral stasis).

Do not rely on the use of the drug in the presence of complication biliary tract disease.

Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate.

With overdosage, a curare-like action may occur.

ADVERSE REACTIONS

Anticholinergics produce certain effects which may be physiologic or toxic depending upon the individual

Pamine
brand of methscopolamine bromide tablets

patient's response. The physician must delineate these.

Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; dilatation of the pupil; cycloplegia; increased ocular tension; loss of taste; headaches; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestation; some degree of mental confusion and/or excitement especially in elderly persons.

Decreased sweating is another adverse reaction that may occur. It should be noted that adrenergic innervation of the eccrine sweat glands on the palms and soles make complete control of sweating impossible. An end point of complete anhidrosis cannot occur because large doses of drug would be required, and this would produce severe side effects from parasympathetic paralysis.

OVERDOSAGE

While overdosage has not been reported, gastric lavage should be done with a solution containing an alkaloid precipitant, such as tannic acid. After lavage, additional antidote and a large dose of saline cathartic should be administered before the stomach tube is withdrawn.

DOSAGE AND ADMINISTRATION

The average dosage of PAMINE Tablets is 2.5 mg one-half hour before meals and 2.5 to 5 mg at bedtime. A starting dose of 12.5 mg daily will be clinically effective in most patients without the production of appreciable side effects.

Patients whose dosage has been reduced to eliminate or modify side effects often continue to show adequate response both subjectively in relief of symptoms and objectively as measured by antisecretory effects.

If the patient is having severe symptoms which demand prompt relief, the drug may be started on a daily dosage of 20 mg, administered in doses of 5 mg one-half hour before meals and at bedtime. If very unpleasant side effects develop promptly, the daily dosage should be reduced. If neither symptomatic relief nor side effects appear, the daily dosage may be increased. Some patients have tolerated 30 mg daily with no unpleasant reactions.

The ultimate aim of therapy is to arrive at a dosage which provides maximal clinical effectiveness with a minimum of unpleasant side effects. Many patients report no side effects on a dosage which gives complete relief of symptoms. On the other hand, some patients have reported severe side effects without appreciable symptomatic relief. Such patients must be considered unsuited for this therapy. Usually they have been or will prove to be similarly intolerant to other anticholinergic drugs. If methscopolamine bromide is to be used in a patient who gives a history of such intolerance, it should be started at a low dosage.

HOW SUPPLIED

PAMINE Tablets (round, white) are supplied in the following sizes:

Bottles of 100 (NDC 0009-0061-01)
Bottles of 500 (NDC 0009-0061-02)

Store at controlled room temperature 15°-30° C (59°-86° F).

Caution: Federal law prohibits dispensing without prescription.

The Upjohn Company
Kalamazoo, Michigan 49001, USA
Revised April 1986 811 377 302

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-848/s018

CHEMISTRY REVIEW(S)

5.1

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	8-848

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER
The Upjohn Company 7000 Portage Road Kalamazoo, MI 49001	12-868

AUG 1 1986

5. SUPPLEMENT (S)	
NUMBER(S)	DATE(S)
S-018	7/15/86

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Pamine	Methscopolamine bromide

8. SUPPLEMENT(S) PROVIDES FOR:

Changes in labeling.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Anticholinergic agent	☒ RX ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY (Iso)
Tablets	2.5 mg/tab.

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT ☐ YES ☐ NO

REVIEWED ☐ YES ☐ NO

17. COMMENTS

Under Description inactive ingredients are listed, chemical name, structure and molecular weight are added. Under How Supplied tablet shape and color, and storage conditions are added. ACTIONS were renamed CLINICAL PHARMACOLOGY, INDICATIONS were renamed INDICATIONS AND USAGE, TREATMENT OF OVERDOSAGE was renamed OVERDOSAGE and placed after PRECAUTIONS.

18. CONCLUSIONS AND RECOMMENDATIONS

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

8/1/86

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Danute G. Cunningham	Danute G. Cunningham	8-1-86

DISTRIBUTION ☒ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

1 1 OC80

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
8-848/s018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SEVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT	DATE OF SUBMISSION
The Upjohn Company	July 15, 1986
ADDRESS *(Number, Street, City, State and Zip Code)* 7000 Portage Road Kalamazoo, MI 49001	TELEPHONE NO. *(Include Area Code)* (616) 323-4126

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
8848

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
methscopolamine bromide tablets USP	PAMINE® Tablets

CODE NAME *(If any)*	CHEMICAL NAME
	3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-, bromide, [7(S)-(1α,2β,4β,5α,7(S))]-

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
tablet	oral	2.5mg

PROPOSED INDICATIONS FOR USE

Treatment of peptic ulcer

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)*

☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION *(ANDA) (21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ ORIGINAL APPLICATION

☐ AN AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☒ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*

☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

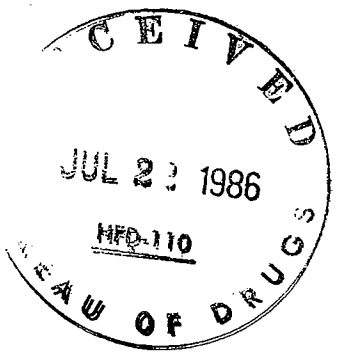
NDA NO. 8848 REF. NO S-018
NDA SUPPL FOR LE

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001, U.S.A.

ORIGINAL

US PHARMACEUTICAL REGULATORY AFFAIRS
Office of
GEORGE H. ISHLER, M.D
Executive Director
TELEPHONE: *(616) 323-4126*



July 15, 1986

Division of Cardio-Renal Drug Products, HFN-110
Center for Drugs and Biologics
Document Control Room #16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SPECIAL SUPPLEMENT
CHANGES BEING EFFECTED

RE: NDA #8848
PAMINE® Tablets
(methscopolamine bromide
tablets USP)

Gentlemen:

We are supplementing our NDA for PAMINE under the provisions of 21CFR§314.70(c)(2)(i) to provide for a revised package insert. Twelve copies of the final printed insert (Code 811 377 302) are enclosed.

This action is in keeping with the agreement between the Agency and the Pharmaceutical Manufacturers Association to incorporate inactive ingredient information in prescription drug labeling (reference: letter of 1/28/85 from H.M. Meyer, Jr., MD to B.J. Brennan, Vice President and General Counsel, PMA).

We have made the following additions/changes:

- Under DESCRIPTION
  - Added inactive ingredients
  - Added chemical name, structure and molecular weight
- Under HOW SUPPLIED
  - Added tablet shape and color
  - Added storage conditions
- ACTIONS renamed CLINICAL PHARMACOLOGY
- INDICATIONS renamed INDICATIONS and USAGE
- TREATMENT OF OVERDOSAGE renamed OVERDOSAGE and placed after PRECAUTIONS

At the next printing we will add "of" to the fifth paragraph under PRECAUTIONS -" ....complication of biliary tract disease". This word was inadvertently omitted when the insert was printed.

For your convenience, I have included a mock-up of the insert showing the changes.

The new insert (Code 811 377 302) is being put into immediate use.

Sincerely,

THE UPJOHN COMPANY

Robert Baalbergfor

G. H. Ishler, MD
Executive Director
US Pharmaceutical Regulatory Affairs

GHI:RAP:jrb
Enclosure

2 page(s) of draft labeling has been removed from this portion of the review.