CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74862

Trade Name Morphine Sulfate Extended-Release Tablets 15mg, 30mg and 60mg

Generic Name Morphine Sulfate Extended-Release Tablets 15mg, 30mg and 60mg

Sponsor AB Generics L.P.
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74862

APPROVAL LETTER
AB Generics L.P.
Attention: Mary Ann Traut
100 Connecticut Avenue
Norwalk, CT 06850-3590

Dear Madam:

This is in reference to your abbreviated new drug application dated February 23, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg and 60 mg.

Reference is also made to your amendments dated March 11, May 8, December 10, and December 27, 1996; July 1, and December 3, 1997; and February 17, March 6, March 11, March 30, and June 26, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg and 60 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (MS Contin® Tablets, 15 mg, 30 mg, and 60 mg, respectively, of Purdue Frederick Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253.
(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7-7-98
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER  74862

FINAL PRINTED LABELING
MORPHINE SULFATE EXTENDED-RELEASE TABLETS 15 MG
CONTAINER LABEL - BOTTLE OF 100 TABLETS
ARTWORK VERSION A5242

Morphine Sulfate
Extended-Release Tablets
15 mg

Warning—May be habit forming. Cautions: Federal law prohibits dispensing without prescription.
Morphine Sulfate Extended-Release Tablets 15 mg
WARNING. May be habit forming

DESCRIPTION:
Chemically, morphine sulfate is 7, 8-dideoxy-6, 14b-methyl-3, 6b, 10, 11-tetrahydro-2H-furo[3, 4-b]morphine. It has the molecular formula C_{17}H_{21}NO_3S and the molecular weight of 303.4. Morphine sulfate is a white, crystalline powder that has none of the characteristic features of morphine.

PHARMACODYNAMICS:
The effects described below are common to all morphine-containing products.
Caution: Use in the Dose-Supported System

The principal actions of the therapeutic values of morphine are analgesia and sedation (e.g., sedation and anxiolysis).

The primary mechanisms of the analgesic action are unknown. However, specific site receptors have been identified in the brain that are sensitive to morphine-like compounds. In the brain, the tritiated opioid binding is also present in the peripheral compartments, including the spinal cord and brain. The term “opiod” is used to describe the influence of these sites in the brain on the action of morphine.

Pharmaceuticals

Morphine may have a number of side effects, including constipation, nausea, vomiting, dizziness, and drowsiness. These side effects are common and may vary in severity. Morphine may also cause a decrease in appetite.

Indications and Usage:
Morphine sulfate extended-release tablets are a controlled-release analgesic formulation intended for the relief of moderate to severe pain. They are intended for use in patients who require frequent dosing with potent opioid analgesics on a number of times per day.

Contraindications:
Morphine sulfate extended-release tablets are contraindicated in patients with known hypersensitivity to morphine or any component of the formulation.

Warnings:

Impaired Respiration
Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in the elderly and debilitated patients and, as well as in those suffering from conditions that exacerbate cardiovascular effects of respiratory depression. Morphine may exaggerate the respiratory depression resulting from central nervous system depressant drugs and alcohol. In addition, respiratory depression may occur in patients with asthma, emphysema, and other chronic respiratory disorders.

Morphine sulfate extended-release tablets are contraindicated in patients who are at risk of having a history of respiratory depression.

Drug Interactions:
Morphine may reduce the effectiveness of certain drugs, including anticoagulants and antihypertensive medications. In addition, morphine may increase the risk of bleeding in patients taking anticoagulant medications.

Pharmacology:
The pharmacological properties of morphine are similar to those of other opioid analgesics. Morphine is a potent analgesic that produces analgesia by activation of specific receptors in the brain and spinal cord. It is a potent respiratory depressant at high doses and may cause hypotension, bradycardia, and respiratory depression at higher doses.

Stability:
Morphine sulfate extended-release tablets are stable under normal storage conditions. The tablets should be stored at room temperature and protected from moisture. The tablets should not be exposed to direct sunlight.

Information for Patients:
If the patient is taking morphine sulfate extended-release tablets, please refer to the following instructions.

1. Proper pain management requires regular use of the medication to control pain. Patients should be advised to take the medication as directed.

2. Morphine may cause constipation, which may be managed by taking a stool softener or laxative. Patients should be advised to take stool softeners or laxatives as directed.

3. Morphine may cause dizziness, which may be managed by avoiding driving or other activities that require alertness. Patients should be advised to avoid driving or other activities that require alertness.

4. Morphine may cause respiratory depression, which may be managed by taking deep breaths or using a nebulizer. Patients should be advised to take deep breaths or use a nebulizer as directed.

5. Morphine may cause nausea and vomiting, which may be managed by taking anti-nausea medication. Patients should be advised to take anti-nausea medication as directed.

6. Morphine may cause constipation, which may be managed by taking a stool softener or laxative. Patients should be advised to take stool softeners or laxatives as directed.

7. Morphine may cause dizziness, which may be managed by avoiding driving or other activities that require alertness. Patients should be advised to avoid driving or other activities that require alertness.

8. Morphine may cause respiratory depression, which may be managed by taking deep breaths or using a nebulizer. Patients should be advised to take deep breaths or use a nebulizer as directed.

9. Morphine may cause nausea and vomiting, which may be managed by taking anti-nausea medication. Patients should be advised to take anti-nausea medication as directed.

10. Morphine may cause constipation, which may be managed by taking a stool softener or laxative. Patients should be advised to take stool softeners or laxatives as directed.

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12. Morphine may cause respiratory depression, which may be managed by taking deep breaths or using a nebulizer. Patients should be advised to take deep breaths or use a nebulizer as directed.

13. Morphine may cause nausea and vomiting, which may be managed by taking anti-nausea medication. Patients should be advised to take anti-nausea medication as directed.

14. Morphine may cause constipation, which may be managed by taking a stool softener or laxative. Patients should be advised to take stool softeners or laxatives as directed.

15. Morphine may cause dizziness, which may be managed by avoiding driving or other activities that require alertness. Patients should be advised to avoid driving or other activities that require alertness.

16. Morphine may cause respiratory depression, which may be managed by taking deep breaths or using a nebulizer. Patients should be advised to take deep breaths or use a nebulizer as directed.

17. Morphine may cause nausea and vomiting, which may be managed by taking anti-nausea medication. Patients should be advised to take anti-nausea medication as directed.

18. Morphine may cause constipation, which may be managed by taking a stool softener or laxative. Patients should be advised to take stool softeners or laxatives as directed.

19. Morphine may cause dizziness, which may be managed by avoiding driving or other activities that require alertness. Patients should be advised to avoid driving or other activities that require alertness.

20. Morphine may cause respiratory depression, which may be managed by taking deep breaths or using a nebulizer. Patients should be advised to take deep breaths or use a nebulizer as directed.

21. Morphine may cause nausea and vomiting, which may be managed by taking anti-nausea medication. Patients should be advised to take anti-nausea medication as directed.

22. Morphine may cause constipation, which may be managed by taking a stool softener or laxative. Patients should be advised to take stool softeners or laxatives as directed.

23. Morphine may cause dizziness, which may be managed by avoiding driving or other activities that require alertness. Patients should be advised to avoid driving or other activities that require alertness.

24. Morphine may cause respiratory depression, which may be managed by taking deep breaths or using a nebulizer. Patients should be advised to take deep breaths or use a nebulizer as directed.

25. Morphine may cause nausea and vomiting, which may be managed by taking anti-nausea medication. Patients should be advised to take anti-nausea medication as directed.
Patients are advised to refer to published redrafting guidelines keeping in mind that such drugs are only approved in general for the treatment of primary hyperparathyroidism due to the lack of data on the use of morphine sulfate extended-release tablets in elderly patients. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

Conversion from Parenteral or Oral Morphine (or Other Opioids) to Morbaine Sulfate Extended-Release Tablets

Conversion tables from intravenous to oral morphine sulfate tablets can be used to achieve effective morphine sulfate oral maintenance dosing. The following table provides conversion factors that can be used to convert parenteral morphine sulfate to oral equivalent doses. These conversion factors are based on the assumption that morphine sulfate is equally effective to parenteral morphine sulfate.

DOSAGE AND ADMINISTRATION:

[Details from text]
1. CHEMISTRY REVIEW NO. #5

2. ANDA #74-862

3. NAME AND ADDRESS OF APPLICANT
   AB Generics L.P.,
   Attention: James H. Conover, Ph.D.
   100 Connecticut Avenue,
   Norwalk, CT 06850-3590

4. LEGAL BASIS FOR SUBMISSION
   The reference listed drug for this ANDA submission is MS
   Contin® (morphine sulfate controlled-release) Tablets, 15 mg
   30 mg and 60 mg; Holder: Purdue Frederick Company.

   Marketing exclusivity for reference drug MS Contin® Tablets,
   15 mg, 30 mg and 60 mg, the reference drug for this ANDA
   submission is not entitled to marketing exclusivity under

   The patent information regarding Patent No. 4,235,870 (exp
   11-25-95) and Patent No. 4,366,310 (exp 12-28-99) has not
   been submitted to FDA. A.B Generics L.P certifies that
   Patent No. 4,235,870 and Patent No. 4,366,310 will not be
   infringed by the manufacture, use or sale of Morphine
   Sulfate Controlled-Release 15 mg, 30 mg and 60 mg Tablets
   for which this application is submitted.

   The subject product and its use in the treatment of pain in
   opioid tolerant patients was the subject of United States

   The applicant has been granted a patent license by the
   patent owner.

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   Morphine Sulfate Extended-Release Tablets

7. NONPROPRIETARY NAME
   Morphine Sulfate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
   NA

9. AMENDMENTS AND OTHER DATES:
Firm:
February 23, 1996: Original submission (30 mg)
November 14, 1995: Amendment
February 16, 1996: Amendment
March 11, 1996: Amendment for 30 mg tablets
March 11, 1996: Amendment Submission) for 60 mg tablets
April 2, 1996: Amendment to March 18, 1996 letter for 30 mg tablets.
April 9, 1996: Submitted one copy of the Department Statement (page 283 for 30 mg tablets).
May 3, 1996: Amendment (submission) for 15 mg Tablets
May 8, 1996: Bioavailability correspondence
February 12, 1997: Amendment
December 3, 1997: Minor Amendment
February 9, 1998: Facsimile deficiencies
March 11, 1998: Telephone conversation

FDA:
March 18, 1996: Not sufficient letter for 30 mg
April 24 1996: Acknowledgment and correspondence letter for 30 mg and 60 mg tablets.
July 31, 1996: Bio. deficiency letter for 30 mg and 60 mg tablets.
November 8, 1996: Deficiency letter
October 21, 1997: Minor Deficiency letter
March 6, 1998: Facsimile amendment
March 11, 1998: Telephone amendment

10. PHARMACOLOGICAL CATEGORY
   Opioid analgesic

11. Rx or OTC
   Rx

12. RELATED IND/NDA/DMF(s)
   NDA#19-516/S-003 and S-004
13. **DOSAGE FORM**
   Controlled-release Tablet

14. **POTENCY**
   15 mg, 30 mg and 60 mg

15. **CHEMICAL NAME AND STRUCTURE**
   Morphine Sulfate USP

\[
(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O; \quad M.W. = 758.85
\]

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\text{N} - \text{CH}_3 \\
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\text{OH}
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\]

\[
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\cdot 5H_2O
\end{array}
\]

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\]

7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate. CAS [6211-15-0]

16. **RECORDS AND REPORTS**
   Generic drug enforcement act Certifications are provided in Section XX for drug substance manufacturer, contract firms and AB Generics L.P.
March 19, 1996: Memo from Bill Russell to Keith Chan.
A phone conversation between FDA and the firm regarding Patent Certification on 11-13-95.

Replacement page is being submitted to correct the Patent Certification Statement covering Patent Nos. 4,235,870 and 4,366,310 which were noted under a Paragraph IV Certification rather than Paragraph I Certification on November 14, 1995 amendment.

Control document#P 94-043; September 30, 1994.
Control document#B 93-61; February 17,1994.
July 1,1993 letter from R.L. Williams to the firm, submitting an ANDA for MS Contin controlled-release tablets.

Telephone conversation on 3-11-98.

17. COMMENTS
The following deficiencies are found:

None

18. CONCLUSIONS AND RECOMMENDATIONS
This application can be approved. A Approval will be issued.

19. REVIEWER:        DATE COMPLETED:
S.Basaran, Ph.D.     4-6-98
38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-862  APPLICANT: AB Generics L.P.

DRUG PRODUCT: Morphine Sulfate Extended-Release Tablets, 15 mg, 30 mg and 60 mg.

The deficiencies presented below represent Facsimile deficiencies.

Deficiencies:

1. Your individual and total impurities limits for Morphine sulfate USP are high based upon available data. The data from the drug substance lots showed that the highest total impurities and maximum individual impurity were respectively. Please tighten your limits and resubmit.

2. Your dissolution sampling time has been changed from 1,2,6 hrs to 1,2,9 hrs for 15, 30 and 60 mg tablets in your revised finished product specifications and COAs. Please provide explanation and clarify.

3. Please incorporate the following dissolution testing and tentative specifications into your stability and finished product testing and resubmit.

The dissolution testing should be conducted in 900 mL of Water at 37°C using USP 23 apparatus I (basket) at 50 rpm. The tentative recommended specifications are followings:

1 hr
2 hr
4 hr
8 hr

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research