CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74862

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-862** Date of Submission: **February 12, 1997**

Applicant's Name: **AB Generics L.P.**

Established Name: **Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg**

Labeling Deficiencies:

1. CONTAINER 15 mg, 30 mg, 60 mg - 100s

   We acknowledge your comments regarding the differentiation of your product strengths. In particular we recognize your statement that the use of black print on a white background enhances the readability of the labels. We encourage you to prominently differentiate the different strengths to reduce the possibility of medication errors. The differentiation might be accomplished through use of boxing, or other means without compromising your preference for black print on a white background.

2. INSERT

   a. GENERAL COMMENTS

      i. We encourage you to revise your package insert labeling to combine all information for the three strengths (15 mg, 30 mg, and 60 mg). In addition, we encourage you to include the 100 mg and the 200 mg tablets (subjects of ANDA 74-769), as does the labeling for the reference listed drug, MS CONTIN.

      ii. Delete the strength from the established name throughout the package inserts.

      iii. The following comments refer to all 3 inserts (15 mg, 30 mg, 60 mg) unless otherwise specified.

b. DESCRIPTION

i. Include the route of administration.

ii. Revise the molecular weight to read 758.85.

iii. Delete the third paragraph (**Morphine Sulfate Extended-Release Tablets __mg.**)

iv. Include the molecular formula; $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

v. Last paragraph

A). First line - Tablet (singular - for 15 mg and 60 mg inserts)

B). Revise to read:

... U.S.P. In addition each tablet also contains the following inactive ...

c. CLINICAL PHARMACOLOGY

Pharmacodynamics, Plasma Level- Analgesia Relationships

i. ... non-tolerant ... (hyphen - 3 instances),

ii. ... 20 ng/mL. (Upper case "L")

d. INDICATIONS AND USAGE

They are intended ... (rather than "It is intended ...")

e. WARNINGS

Interactions with other CNS Depressants, First sentence

Morphine Sulfate, like all opioid ... (for the 30 mg insert only)

f. PRECAUTIONS

i. Drug Interactions, last sentence

... including morphine, may enhance ...

ii. Pregnancy (Teratogenic Effects - CATEGORY C)

Replace the first paragraph with the following text:

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus.

Morphine sulfate extended-release tablets should be used in pregnant women only when clearly needed. (See also: PRECAUTIONS: Labor and Delivery, and DRUG ABUSE AND DEPENDENCE.).

iii. Pediatric Use - Revise to read:

Use of extended-release morphine sulfate has not been evaluated systematically in pediatric patients.

g. OVERDOSAGE

i. Second paragraph - delete the trailing zero in ..."2 mg"...

ii. Indent the fourth paragraph (Note: ...)

h. DOSAGE AND ADMINISTRATION

i. General Comments

A). To facilitate the dosing of this drug product we feel that this section should contain mention of the availability of other dosage strengths as well as reference to the dosing information for the other strengths (as does the innovator). See comments below.

B). The DOSAGE AND ADMINISTRATION section should be the same for all three proposed inserts to facilitate the dosing of this drug.

ii. Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-Release Tablets

The following text should appear as the last 3 sentences in this subsection:

A 15 mg extended-release morphine sulfate tablet should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. Morphine sulfate extended-release tablets of 30 mg strength are recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

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

Add the following text as the last 2 sentences in the first paragraph:

In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, morphine sulfate extended-release tablets of 30 mg strength are recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 100 mg morphine sulfate extended-release tablets, or an appropriate combination of tablet strengths, if desired.

iv. Use of Morphine Sulfate Extended-release Tablets as the First Opioid Analgesic

A). Note upper case letters in title for "First Opioid Analgesic".

B). Replace the first two sentences with the following text:

There has been no systematic evaluation of morphine sulfate extended-release tablets as an initial opioid analgesic in the management of pain.

v. Considerations in the Adjustment of Dosing Regimens

A). Second paragraph - (N.B. extended-release morphine sulfate tablets are a controlled-release formulation which do not ...

B). The third paragraph should appear as follows:

For patients with low daily morphine requirements, morphine sulfate extended-release tablets of 15 mg strength should be used.

vi. Conversion from Morphine Sulfate Extended-release Tablets to Parenteral Opioids

A). Note the upper case letters in the title (see above).

B). Fourth sentence

Replace the word "morphine" with "morphine sulfate" throughout the sentence (3 instances).

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/ [redacted]

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-862** Date of Submission: **December 3, 1997**

Applicant's Name: **AB Generics L.P.**

Established Name: **Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg**

Labeling Deficiencies:

1. CONTAINER 15 mg, 30 mg, 60 mg

   Satisfactory, in FPL - However 12 copies of each label in FPL are needed prior to approval. Please submit. In addition, at time of next printing:

   i. Revise to replace the "Caution: Federal law..." statement with "Rx only". See section 126 of the FDA Modernization Act of 1997. Also revise your carton and insert labeling in the same manner.

   ii. This Act also allows for the deletion of the statement "Warning: May be habit forming." from the labels and labeling of controlled substances. To simplify the labeling requirements for controlled substances all that is required is the controlled substance symbol.

   iii. The changes listed in (i) and (ii) may be submitted in an annual report providing that the changes are described in full.

2. INSERT 15 mg, 30 mg, 60 mg

   a. DESCRIPTION

      i. Include the route of administration (30 mg tablet only) - **Each morphine sulfate extended-release oral tablet contains...**

      ii. Revise the first sentence of the third paragraph as follows (60 mg tablet only) - **Each morphine sulfate extended-release oral tablet contains...** (delete the capital

letters)

b. PRECAUTIONS

i. Drug Interactions, last sentence (30 mg and 60 mg tablet)

... including morphine, may enhance ... (delete "sulfate")

ii. Pregnancy (Teratogenic Effects - CATEGORY C) [15 mg, 30 mg, and 60 mg tablet]

First paragraph, last sentence

Although there is no clearly... (add "no")

c. DOSAGE AND ADMINISTRATION

i. Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-release Tablets

Fourth sentence (15 mg tablet) -

The 15 mg extended-release morphine sulfate tablet...

ii. Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets (15 mg tablet)

Delete "15 mg" from the title.

iii. Use of Morphine Sulfate Extended-release Tablets as the First Opioid Analgesic (15 mg tablet)

Delete "15 mg" from the title.

iv. Considerations in the Adjustment of Dosing Regimens (30 mg and 60 mg tablet)

Second paragraph, last sentence -

...formulation; which do not release...

Please revise your insert labeling, as instructed above, and submit in 12 final printed container labels and insert labeling for each piece.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/ [redacted]

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research