

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-951

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3
2. ANDA #: 74-951
3. NAME AND ADDRESS OF APPLICANT
Jerome Stevens Pharmaceuticals, Inc.
Sixty DaVinci Drive
Bohemia, NY 11716
4. LEGAL BASIS FOR SUBMISSION
The reference Listed Drug is Fiorinal® with Codeine Capsules (Sandoz Pharmaceutical Corp.) The applicant certified that there are no relevant patents for the listed drug and that the period of marketing exclusivity for the listed drug expired on October 26, 1993.
5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME:
Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules USP
8. SUPPLEMENT(s) PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: August 29, 1996
New Corresp. (Environmental): September 30, 1996
New Corresp. (CGMP): October 16, 1996
Amendment: (Field Copy): November 26, 1996
New Corresp. (Bio): April 2, 1997
New Corresp. (Bio): April 10, 1997
Major Amendment: September 29, 1997 (Subject of this review)
Minor amendment: June 4, 1998 (Subject of this review)

FDA:
Telecon (A. Weikel): September 30, 1996
Telecon (C. Parise): October 16, 1996
Refusal to File Letter: November 20, 1996
Acceptance Letter: December 27, 1996
Method Verification: January 6, 1997
Label Review: April 21, 1997
Bio Letter & Review: May 2, 1997
Letter, C.R. # 1: June 9, 1997
Letter; C.R. # 2: May 4, 1998
Memo (Dissolution testing): May 18, 1998
Telecon (T. Ames/J. Stevens): May 20, 1998
10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

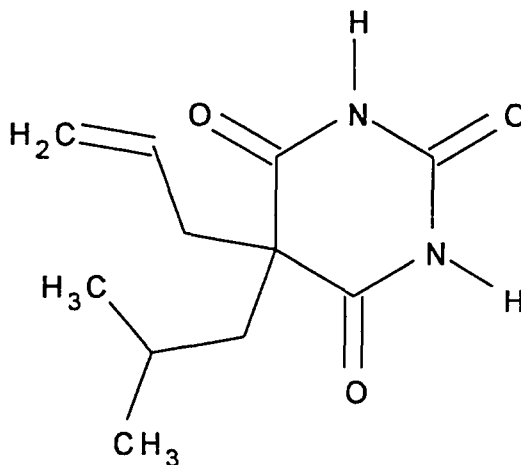
DMF 4164 Cotton (Personna Medical)
 LOAs included

13. DOSAGE FORM
 Capsule (Hard Gelatin)

14. POTENCY
 Butalbital: 50 mg
 Aspirin: 325 mg
 Caffeine: 40 mg
 Codeine Phosphate: 30 mg

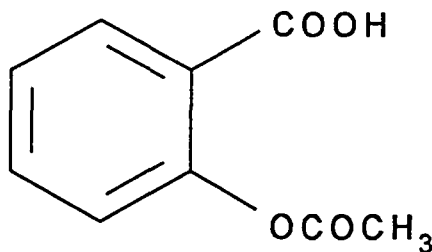
15. CHEMICAL NAME AND STRUCTURE

Butalbital USP
 $C_{11}H_{16}N_2O_3$; M.W. = 224.26



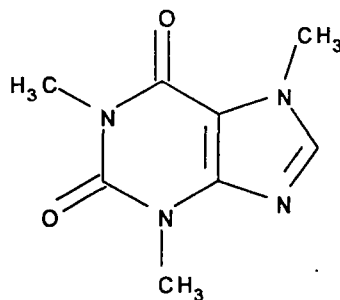
5-Allyl-5-isobutyl barbituric acid. CAS [77-26-9]

Aspirin USP
 $C_9H_8O_4$; M.W. = 180.16



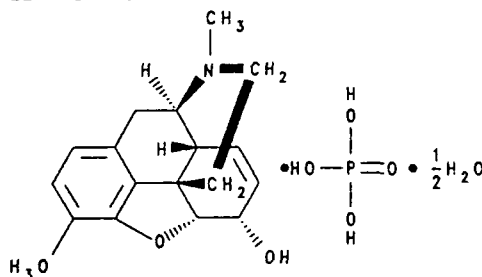
Salicylic acid acetate. CAS [50-78-2]

Caffeine USP
 $C_8H_{10}N_4O_2$; M.W. = 194.19



1,3,7-Trimethylxanthine. CAS [58-08-2]

Codeine Phosphate USP
 $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol
 phosphate (1:1) (salt) hemihydrate. CAS [41444-62-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

- a. CMC issues are satisfactory
- b. Label review acceptable; A. Vezza 8/4/98.
- c. Bio review is satisfactory - 5/2/97.
- d. Drug substances and product are USP - methods validation not required. Methods verification performed on drug product 1/6/97 by the New York Regional Laboratory and is satisfactory.
- e. There is currently only one generic approval for this drug product - ANDA 74-359 (Watson Labs, approved ca. 8/95).
- f. EIR acceptable 8/3/98.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is approved

19. <u>REVIEWER:</u>	<u>DATE COMPLETED:</u>
Donald Shostak	July 20, 1998

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Information and are not

releasable.

Chem Rev 3

7/20/98

ANDA 74-951

1. CHEMISTRY REVIEW NO. 2
2. ANDA #: 74-951
3. NAME AND ADDRESS OF APPLICANT
Jerome Stevens Pharmaceuticals, Inc.
Sixty DaVinci Drive
Bohemia, NY 11716
4. LEGAL BASIS FOR SUBMISSION
The reference Listed Drug is Fiorinal® with Codeine Capsules (Sandoz Pharmaceutical Corp.) The applicant certified that there are no relevant patents for the listed drug and that the period of marketing exclusivity for the listed drug expired on October 26, 1993.
5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME:
Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules USP
8. SUPPLEMENT(s) PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
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New Corresp. (Bio): April 10, 1997
Major Amendment: September 29, 1997 (Subject of this review)

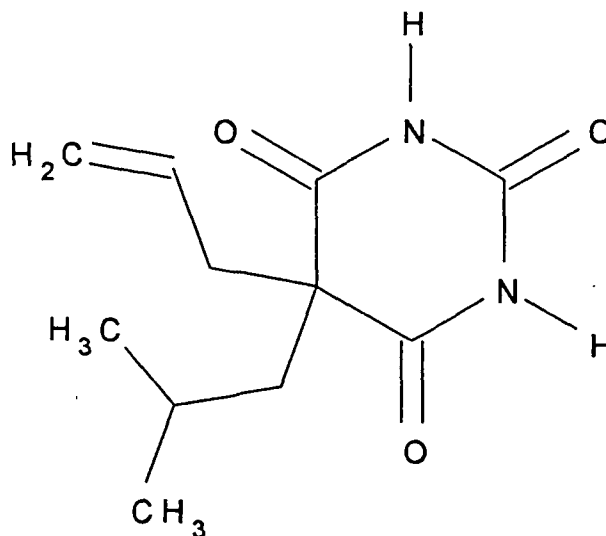
FDA:
Telecon (A. Weikel): September 30, 1996
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10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule (Hard Gelatin)

14. POTENCY
Butalbital: 50 mg
Aspirin: 325 mg
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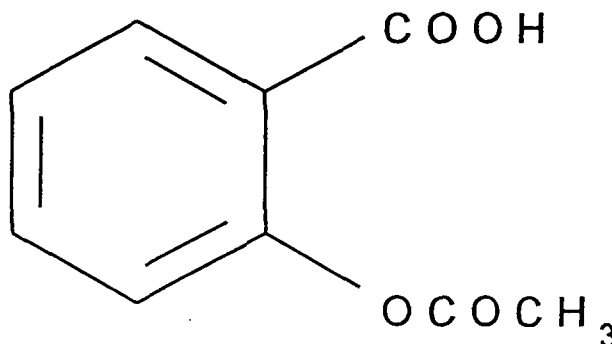
15. CHEMICAL NAME AND STRUCTURE

Butalbital USP
C₁₇H₁₆N₂O₃; M.W. = 224.26



5-Allyl-5-
isobutyl
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CAS [77-26-9]

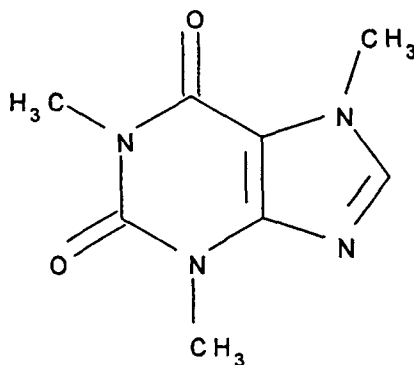
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Salicylic acid acetate. CAS [50-78-2]

Caffeine USP

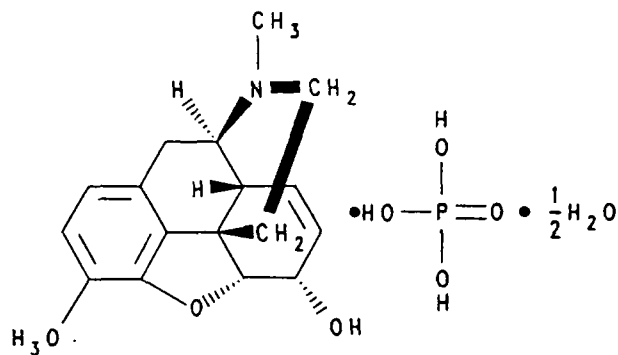
$C_8H_{10}N_4O_2$; M.W. = 194.19



1,3,7-Trimethylxanthine. CAS [58-08-2]

Codeine Phosphate USP

$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol phosphate (1:1) (salt) hemihydrate. CAS [41444-62-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

- a. Minor deficiencies remain regarding the container/closure system.
- b. Label review pending for 9/29/97 amendment.
- c. Bio review is satisfactory - 5/2/97.
- d. EIR pending for Jerome Stevens; satisfactory for all other firms per EES 3/16/98.
- e. Drug substances and product are USP - methods validation not required. Methods verification performed on drug product 1/6/97 by the New York Regional Laboratory and is satisfactory.
- f. There is currently only one generic approval for this drug product - ANDA 74-359 (Watson Labs, approved ca. 8/95).

18. CONCLUSIONS AND RECOMMENDATIONS

This application is NOT APPROVABLE. The amendment will be ^{AJ}MINOR.

19. REVIEWER:

Donald Shostak

DATE COMPLETED:

March 20, 1998

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Chem Rev 2

3/20/98

ANDA 74-951

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DMF
DMF
DMF
DMF
DMF
DMF
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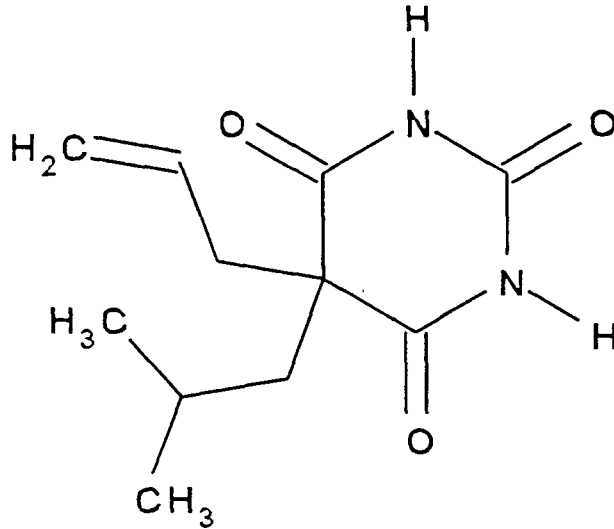
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15. CHEMICAL NAME AND STRUCTURE

Butalbital USP

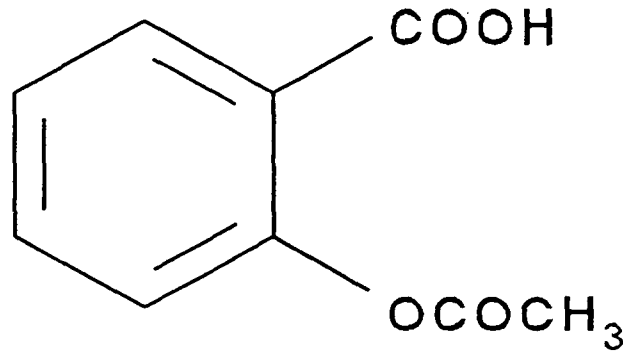
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5-Allyl-5-isobutyl barbituric acid. CAS [77-26-9]

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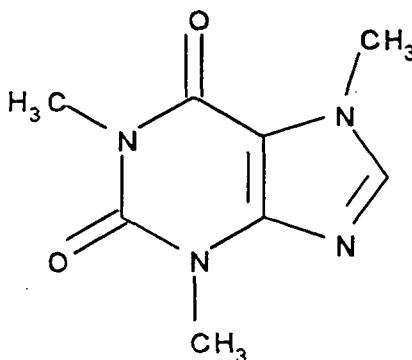
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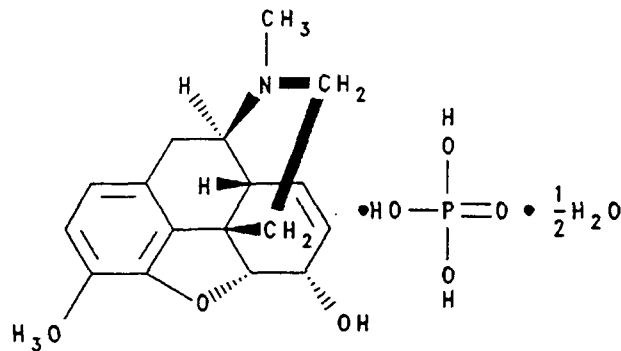
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16. RECORDS AND REPORTS: N/A17. COMMENTS

- a. ANDAs 74-951 contains significant deficiencies regarding chemistry, manufacturing and controls procedures, container/closure issues and stability testing and protocol procedures.
- b. Label review is unsatisfactory - 4/21/97.
- c. Bio review is satisfactory - 5/2/97.
- d. EIR unsatisfactory for Jerome Stevens; satisfactory for all other firms 4/30/97.
- e. Drug substances and product are USP - methods validation not required. Methods verification performed on drug product 1/6/97 by the New York Regional Laboratory and is satisfactory.
- f. There is currently only one generic approval for this drug product - ANDAs 74-359 (Watson Labs, approved ca. 8/95).

18. CONCLUSIONS AND RECOMMENDATIONS

ANDAs 74-951 is NOT APPROVABLE. The amendment will be MAJOR.

19. REVIEWER:

Donald Shostak

DATE COMPLETED:

May 13, 1997

Page(s)

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Chem Rev 1

5/13/97