CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-962

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 1

2. ANDA # 74-962

3. NAME AND ADDRESS OF APPLICANT
Upsher-Smith Laboratories
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 5544-4709

4. LEGAL BASIS FOR SUBMISSION
Trental® (Pentoxifylline Tablets 400 mg) Hoechst-Roussel, NDA 18-631

Patent Certification:

Upsher-Smith certifies that the patents which cover the listed drug Trental® Tablets 400 mg, Hoechst-Roussel NDA 18-631 including patent #4189469 and #3737433 will expire on February 2, 1997 and April 3, 1997 respectively.

5. SUPPLEMENT(s): N/A

6. Proprietary Name: Pentoxil™ Tablets

7. NONPROPRIETARY NAME: Pentoxifylline

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: September 17, 1996
Amendment: February 12, 1997

FDA:
Acknowledgement: December 10, 1996

10. PHARMACOLOGICAL CATEGORY
Treatment of intermittent claudication

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

i)

s)

:)

(Drug Fax 1011 - Reynolds)

The following excipient DMFs were referenced:

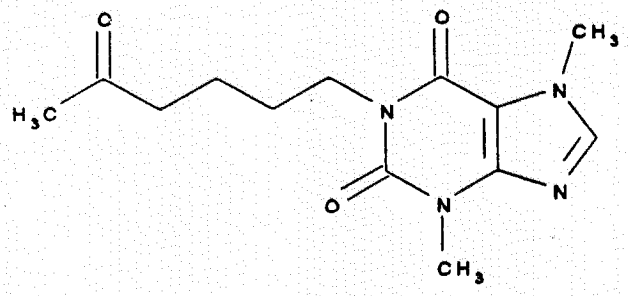
LOAs were included for each referenced DMF

13. DOSAGE FORM
Extended-release tablet

14. POTENCY: 400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline
$C_{13}H_{18}N_4O_3$; M.W. = 278.31



3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.
CAS [6493-05-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. Chemistry, manufacturing and controls deficiencies remain
b. Label review is unsatisfactory 2/21/97
c. Methods validation is required but is deferred - see item 32
d. Bio review is pending
e. EIR is pending

18. CONCLUSIONS AND RECOMMENDATIONS

This Application is NOT APPROVABLE. The amendment is MAJOR.

19. REVIEWER: Donald Shostak
DATE COMPLETED: February 26, 1997

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1. CHEMISTRY REVIEW NO 2

2. ANDA # 74-962

3. NAME AND ADDRESS OF APPLICANT
Upsher-Smith Laboratories
Attention: Mark B. Halvorsen, Pharm.D.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

4. LEGAL BASIS FOR SUBMISSION
Trental® (Pentoxifylline Tablets 400 mg) Hoechst-Roussel, NDA 18-631

Patent Certification:

Upsher-Smith certifies that the patents which cover the listed drug Trental® Tablets 400 mg, Hoechst-Roussel NDA 18-631 including patent #4189469 and #3737433 will expire on February 2, 1997 and April 3, 1997 respectively.

5. SUPPLEMENT(s): N/A

6. Proprietary Name: Pentoxil™ Tablets

7. NONPROPRIETARY NAME: Pentoxifylline

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: September 17, 1996
Amendment: February 12, 1997
Amendment: April 30, 1997 (Subject of this review)
New Correspondence (Bio): July 18, 1997
New Correspondence (Bio): September 8, 1997

FDA:
Acknowledgment: December 10, 1996
Letter, C.R. # 1: March 27, 1997
Letter (Bio): July 10, 1997

10. PHARMACOLOGICAL CATEGORY
Treatment of intermittent claudication

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

The following excipient DMFs were referenced:

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LOAs were included for each referenced DMF

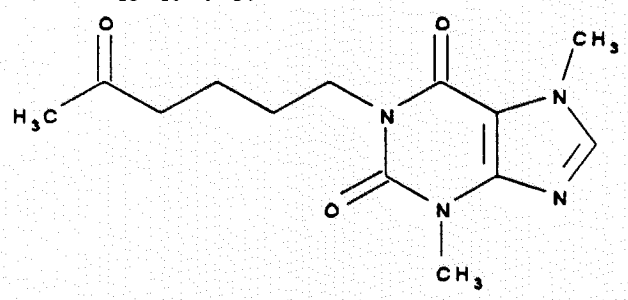
13. DOSAGE FORM
Extended-release tablet

14. POTENCY: 400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline

$C_{13}H_{18}N_4O_3$; M.W. = 278.31



3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.
CAS [6493-05-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. A minor deficiency remains regarding a specification for related compounds in the drug substance.
b. Label review is unsatisfactory 9/2/97.
c. Methods validation request issued 10/14/97.
d. Bio correspondence of 9/8/97 pending review as of 10/28/97. The review of this correspondence will determine the dissolution method and specifications to be used for this drug product.
e. EIR acceptable 7/15/97.

18. CONCLUSIONS AND RECOMMENDATIONS

This Application is NOT APPROVABLE. The amendment will be a FACSIMILE.

19. REVIEWER: Donald Shostak

DATE COMPLETED: October 9, 1997
(Revised 10/28/97 - Bio)

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Chemistry

1. CHEMISTRY REVIEW NO 4

2. ANDA # 74-962

3. NAME AND ADDRESS OF APPLICANT

Upsher-Smith Laboratories
Attention: Mark B. Halvorsen, Pharm.D.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

4. LEGAL BASIS FOR SUBMISSION

Trental® (Pentoxifylline Tablets 400 mg) Hoechst-Roussel, NDA 18-631

Patent Certification:

Upsher-Smith certifies that the patents which cover the listed drug Trental® Tablets 400 mg, Hoechst-Roussel NDA 18-631 including patent #4189469 and #3737433 will expire on February 2, 1997 and April 3, 1997 respectively.

5. SUPPLEMENT(s): N/A

6. Proprietary Name: Pentoxil™ Tablets

7. NONPROPRIETARY NAME: Pentoxifylline

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Submitted: September 17, 1996
Amendment: February 12, 1997
Amendment: April 30, 1997 (Subject of this review)
New Correspondence (Bio): July 18, 1997
New Correspondence (Bio): September 8, 1997
Facsimile amendment: November 26, 1997
Amendment: January 15, 1999

FDA:
Acknowledgment: December 10, 1996
Letter, C.R. # 1: March 27, 1997
Letter (Bio): July 10, 1997
Chem. Rev # 2 (Facsimile): October 30, 1997
Letter (Bio): January 13, 1998
Telephone Memo: January 6, 1999

10. PHARMACOLOGICAL CATEGORY — 11. Rx or OTC

Treatment of intermittent claudication — Rx

12. RELATED IND/NDA/DMF(s)

The following excipient DMFs were referenced:

[redacted].

LOAs were included for each referenced DMF

13. DOSAGE FORM

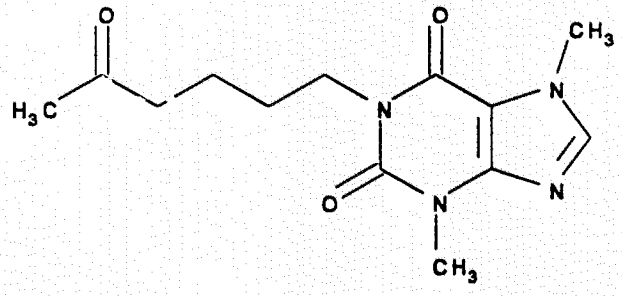
Extended-release tablet

14. POTENCY: 400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline

$C_{13}H_{18}N_4O_3$; M.W. = 278.31



3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.
CAS [6493-05-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

Status:

a. EER status: Acceptable

Acceptable 7/15/97.

b. Method Validation status: acceptable with comments

Not compendial.

Since the drug substance and finished drug product are not USP items, methods validation for both is required.

Method validation for samples of the active ingredient and finished product were sent to Detroit District Laboratory on 10-14-97 by Don Shostak and found acceptable with comments on 1-25-99.

c. Bio-review status: Acceptable

Acceptable per telephone memo by L. Sancheze (CSO) & J. Chaney (Chemist) on 1-6-99.

d. Labeling review status: Satisfactory

Satisfactory A Vezza reviewed on 12/5/97

e.

was reviewed and found acceptable by L. Tang, on 1-25-99.

18. CONCLUSIONS AND RECOMMENDATIONS

This application can be approved upon receipt of satisfactory: Methods validation

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang January 25, 1999, revised 2-10-99

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Chemistry

1. CHEMISTRY REVIEW NO 5

2. ANDA # 74-962

3. NAME AND ADDRESS OF APPLICANT

Upsher-Smith Laboratories
Attention: Mark B. Halvorsen, Pharm.D.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

4. LEGAL BASIS FOR SUBMISSION

Trental® (Pentoxifylline Tablets 400 mg) Hoechst-Roussel, NDA 18-631

Patent Certification:

Upsher-Smith certifies that the patents which cover the listed drug Trental® Tablets 400 mg, Hoechst-Roussel NDA 18-631 including patent #4189469 and #3737433 will expire on February 2, 1997 and April 3, 1997 respectively.

5. SUPPLEMENT(s): N/A

6. Proprietary Name: Pentoxil™ Tablets

7. NONPROPRIETARY NAME: Pentoxifylline

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
- Submitted: September 17, 1996
- Amendment: February 12, 1997
- Amendment: April 30, 1997 (Subject of this review)
- New Correspondence (Bio): July 18, 1997
- New Correspondence (Bio): September 8, 1997
- Facsimile amendment: November 26, 1997
- Amendment: January 15, 1999
- Amendment: March 12, 1999

FDA:
- Acknowledgment: December 10, 1996
- Letter, C.R. # 1: March 27, 1997
- Letter (Bio): July 10, 1997
- Chem. Rev # 2 (Facsimile): October 30, 1997
- Letter (Bio): January 13, 1998
- Telephone Memo: January 6, 1999
- NA letter (Chem Rev# 4 - Minor): 3-2-99
- Detroit District Laboratory OK for MV: 3-15-99

10. PHARMACOLOGICAL CATEGORY	11. Rx or OTC
Treatment of intermittent claudication	Rx

12. RELATED IND/NDA/DMF(s)

The following excipient DMFs were referenced:

DMF for contract lab:

LOAs were included for each referenced DMF

13. DOSAGE FORM

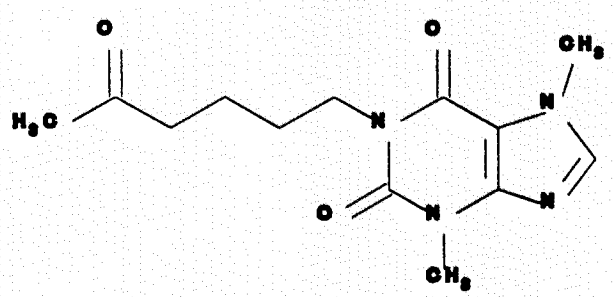
Extended-release tablet

14. POTENCY: 400 mg

15. CHEMICAL NAME AND STRUCTURE

Pentoxifylline

$C_{13}H_{18}N_4O_3$; M.W. = 278.31



3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.
CAS [6493-05-6]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

Status:

a. EER status: **Acceptable with one of contract Labs (pending)**

Acceptable 2/1/99 for drug substance manufacturer and finished product manufacturer except one of contract Lab , **Inc. - pending**). All acceptable, 3/22/99.

b. Method Validation status: Acceptable

Not compendial.

Since the drug substance and finished drug product are not USP items, methods validation for both is required.

Method validation for samples of the active ingredient and finished product were sent to Detroit District Laboratory on 10-14-97 by Don Shostak and found acceptable on 3-15-99.

c. Bio-review status: Acceptable

Acceptable per J. Chaney (Chemist) on 1-28-99.

d. Labeling review status: Satisfactory

Satisfactory A Vezza reviewed on 12/5/97

e. Acceptable

was reviewed and found acceptable by L. Tang, on 1-25-99.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 3-17-99

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