CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74879

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY

ANDA #: 74-879

FIRM: Elan Pharmaceutical Research Corporation **DRUG:** Keto(profen
DOSAGE: Extended release capsules **STRENGTH:** 200 mg
cGMP STATEMENT/EIR UPDATE STATUS:
cGMP: Satisfactory per Review #1.
EER: satisfactory dated March 12, 1997.

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:

Satisfactory per letter dated 8/27/97. The approved dissolution specs are interim.

METHODS VALIDATION(Including dosage form description):

Pending, MV submitted 5/12/97.
STABILITY(Conditions, Containers, methods):
Bio batch?

Stability containers are the same as containers section and stability studies were conducted on the bio batch.

Test	Specifications
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity.
Assay	mg/capsule
Related compounds	3-acetylbenzophenone: nmt % Individual: nmt % Total: nmt %
Dissolution (interim)	1 Hours not less than % and not more than % 2 Hours not less than % and not more than % 4 Hours not less than % and not more than % 8 Hours not less than % and not more than % 16 Hours not less than %

LABELING REVIEW STATUS: Satisfactory dated May 28, 1997.

STERILIZATION VALIDATION(If Applicable): N/A

BATCH SIZES:

BIO BATCH(identity #, DS source)

Manufacturing process: production procedures

Manufacturing site: production facility
Equipment: Is comparable for bio and production batches.

Proposed Batch Size: [ ] kg

Batch #: C5J1932/ DB3497
DS source: [ ]
- -Units of dosage form: 40 kg [ ] capsules)

STABILITY BATCHES(different from BIO BATCH, manuf. site, process)

Same as the bio batch

PROPOSED PRODUCTION BATCH(same manuf. process, #s, quant.)

COMMENTS: Approvable (MV pending; dissolution specs interim)

DSG: 11
9/30/97

APPEARS THIS WAY
ON ORIGINAL

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-879

3. NAME AND ADDRESS OF APPLICANT

Elan Pharmaceutical Research Corporation
Attention: Sharon L. Hamm, Pharm. D.
1300 Gould Dr.
Gainesville, GA 30504-3947

4. LEGAL BASIS FOR ANDA SUBMISSION:
Listed drug: NDA #19,816
Exclusivity until September 24, 1996
Active ingredient, route of administration, dosage form, and strength are the same for ANDA and NDA.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME
Ketoprofen

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

9. AMENDMENTS AND OTHER DATES:
April 1, 1996: Date of submission
September 5, 1997: Amendment
September 9, 1997: Bio correspondence
October 7, 1997: Bio correspondence

10. PHARMACOLOGICAL CATEGORY	11. Rx or OTC
NSAID	Rx

12. RELATED IND/NDA/DMF(s)
See checklist

13. DOSAGE FORM	14. POTENCY
Extended-Release Capsules	200 mg

16. RECORDS AND REPORTS: None

18. CONCLUSIONS AND RECOMMENDATIONS : Approvable
((MV pending; dissolution specs interim)

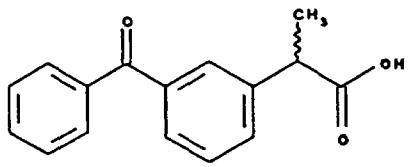
19. REVIEWER:	DATE COMPLETED:
Devinder S. Gill	September 30, 1997

cc: ANDA 74-879
Division File
Field Copy

Endorsements:
HFD-623/D.Gill/9-30-97/10-15-97
HFD-623/V. Sayeed/
X:\new\firmsam\elan\ltrs&rev\74879ap.dg
F/T by: bc/10-21-97

15. CHEMICAL NAME AND STRUCTURE

Ketoprofen $C_{16}H_{14}O_3$; M.W. = 254.28



m-Benzoylhydratropic acid. CAS [22071-15-4]

17. COMMENTS

Q.1. Please be advised that DMF [illegible] is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the DMF deficiencies is required prior to the approval of this ANDA.

Reply: The above DMF was reviewed by me and is currently adequate.

Comment: O.K.

Q.2. Please revise your dissolution specification for release and stability to comply with the recommendation made by Division of Bio-Equivalence in the letter date October 31, 1996.

Reply: Firm is in touch with the Division of Bioequivalence. Bio has approved the following interim specs per letter dated 8/27/97.

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test should meet the following interim specifications:

Amount Dissolved

1 Hours	not less than [illegible] % and not more than [illegible] %
2 Hours	not less than % and not more than %
4 Hours	not less than [illegible] % and not more than [illegible] %

8 Hours not less than % and not more than %
16 Hours not less than %

Comment: O.K.

B. Additional Comments

Q.1. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval. We have requested the Division of Manufacturing and Product Quality for an evaluation report.

Reply: Firm did not respond; assumed it to be informational.

Comment: EER is satisfactory dated March 12, 1997.

Q.2. Since this drug product is not covered by an official monograph in the USP, the analytical methods must be validated by an FDA field laboratory. Samples for the methods validation will be requested up by the FDA at the appropriate time.

Reply: Firm did not respond; assumed it to be informational.

Comment: **MV report is pending.**

Note: In addition, firm has submitted slightly modified analytical methods. Changes are not significant. Also, the firm submitted stability data. The data are adequate within the specified limits.

20. COMPONENTS AND COMPOSITION: satisfactory Per Review #2

Ingredient	Per ANDA mg/capsule	Scale-up mg/capsule
Ketoprofen	200.00	200
Starch & sucrose(non-pareil seeds)		
Colloidal silicon dioxide		
Talc		
Ethyl cellulose		
Polyvinylpyrrolidone		
Isopropyl alcohol	%	%

21. FACILITIES AND PERSONNEL: satisfactory per Review # 1.

22. SYNTHESIS: satisfactory

NDS: Ketoprofen

Manufacturer: [ ]

DMF #: [ ]

DMF Referral Letter: Satisfactory

The amendment was reviewed by me recently and is adequate.

23. RAW MATERIAL CONTROLS

A. NEW DRUG SUBSTANCE: satisfactory per this review

SPECIFICATIONS

Test	Specification
Appearance	A white or almost white color
Identification	a. melting point [ ] b. (maxima at]nm)
Melting range	[
LOD	nmt __ %
Specific rotation	[/
ROI	nmt __ %
Heavy metals	__ %
Chromatographic purity	nmt [% individual nmt __ % total
OVI	compendial
Assay	98.5% to 101.0% on dried basis
Particle size	nlt [% under [μ nlt % under __ μ
Bulk density	[g/ml
Tapped density	]g/ml
Residual solvents	toluene nmt ppm cyclohexane nmt ppm

B. OTHER INGREDIENTS: satisfactory per previous reviews

24. OTHER FIRM(s): Satisfactory per Review # 1

25. MANUFACTURING AND PROCESSING: satisfactory per Review # 1

Proposed Batch Size: kg
Manufacturing process: production procedures
Manufacturing site: production facility
Equipment: Is comparable for bio and production batches.

26. CONTAINER: Satisfactory per this review.

27. PACKAGING AND LABELING: Satisfactory per Review # 1.

The packaging reconciliation is satisfactory.

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM):

Satisfactory

BIO BATCH:

Batch #: C5J1932/ DB3497
DS source: [ ]
Units of dosage form:40 kg [ ]capsules)
Reconciliation: The manufacturing and packaging yields are satisfactory.

Release Specifications

Test	Specification
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity
Color	Cap: Powder blue opaque Print: "Ketoprofen ER' 200 mg Body: white opaque Printed: "Schein"
Physical appearance	complies with description
Identification	Positive for Ketoprofen [ ] [ ]
Uniformity of dosage units	Within USP requirements
Assay	[ ] % of label claim
Related Compounds	3-acetylbenzophenone: nmt ___ % Individual: nmt ___ % Total: nmt ___ %

Dissolution(interim)	1 Hours not less than % and not more than % 2 Hours not less than % and not more than % 4 Hours not less than % and not more than % 8 Hours not less than % and not more than % 16 Hours not less than %

29. STABILITY: satisfactory

Stability Specifications

Test	Specifications
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity.
Assay	(mg/capsule (%)
Related compounds	3-acetylbenzophenone: nmt % Individual: nmt % Total: nmt %
Dissolution (interim)	1 Hours not less than % and not more than % 2 Hours not less than % and not more than % 4 Hours not less than % and not more than % 8 Hours not less than % and not more than % 16 Hours not less than %

In addition the bulk packages are tested for moisture and color.

Stability Lot: DB3497

Expiry Date: 3 months for the bulk packaging and 24 months for the market containers.

30. CONTROL NUMBERS : N/A

31. SAMPLES AND RESULTS: **Pending, MV submitted 5/12/97.**

32. LABELING : Satisfactory dated May 28, 1997.

33. ESTABLISHMENT INSPECTION: EER is satisfactory dated March 12, 1997.

34. BIOEQUIVALENCY STATUS:

Satisfactory per letter dated 8/27/97. The approved dissolution specs are interim.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory per Review # 1.

36. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes_____x____
No _____

If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

Table 1 : Batch composition of the bio-study lot and the scale-up composition ranges sought by the firm

Ingredient	Bio-Study lot Composition as Presented in the ANDA (mg/capsule)	Revised Compositions sought for the Scale-Up (mg/capsule)
Ketoprofen	200	200
[redacted]	[redacted]	[redacted]
Talc	[redacted]	[redacted]
Colloidal Silicon Dioxide	[redacted]	[redacted]
Ethylcellulose	[redacted]	[redacted]
Polyvinylpyrrolidone	[redacted]	[redacted]
Isopropyl Alcohol	NMT [redacted] %	NMT [redacted] %

Table 2 : Newly sought target composition compared to the closely resembling lot composition.

Ingredient	New Target Batch Composition Sought by the firm (mg/capsule)	Target Composition of Lot #DD1212 (mg/capsule)
Ketoprofen	200	200
[redacted]	[redacted]	[redacted]
Talc	[redacted]	[redacted]
Colloidal Silicon Dioxide	[redacted]	[redacted]
Ethylcellulose	[redacted]	[redacted]
Polyvinylpyrrolidone	[redacted]	[redacted]
Isopropyl Alcohol	NMT [redacted] %	NMT [redacted] %

As seen from Table 2, lot #DD1212 composition differs from the target composition only in [redacted] mg Polyvinylpyrrolidone.

37. **DMF CHECKLIST FOR ANDA # 74-879 REVIEW # 3 __**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[ ]	[ ]	1	adequate	9-29-97

__Comments: Draft review

[ ] FACILITY/[ ] 2

Comments:

[ ] 4

Comments:

[ ] Containers, [ ] 4

Comments:

[ ] packaging mat/ [ ] 4

Comments: The DMF is currently adequate.

[ ] closures [ ] 4

Comments:

[ ] liner [ ] 4

Comments:

[ ] Statpak [ ] 4

Comments:

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) [ ] DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Page 1 of 1 . Devinder S. Gill /S/ 10-03-97

Reviewer Signature Date

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-879

3. NAME AND ADDRESS OF APPLICANT

Elan Pharmaceutical Research Corporation
Attention: Sharon L. Hamm, Pharm. D.
1300 Gould Dr.
Gainesville, GA 30504-3947

4. LEGAL BASIS FOR ANDA SUBMISSION:
Listed drug: Oruvail®, NDA #19,816
Exclusivity until September 24, 1996
Active ingredient, route of administration, dosage form, and strength are the same for ANDA and NDA.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME
Ketoprofen

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

9. AMENDMENTS AND OTHER DATES:
April 1, 1996: Date of submission
November 8, 1996:Amendment in response to deficiency letter
December 20, 1996: Amendment, additional information
March 12,1997: Amendment for change in method of synthesis of DS
Amendments are the subject of this review.

10. PHARMACOLOGICAL CATEGORY

NSAID

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)
See checklist

13. DOSAGE FORM

Extended-Release Capsules

14. POTENCY

200 mg

16. RECORDS AND REPORTS: None

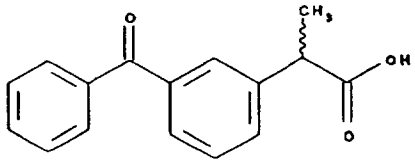
18. CONCLUSIONS AND RECOMMENDATIONS : Not Approvable
DMF is deficient.

19. REVIEWER: Devinder S. Gill

DATE COMPLETED: May 12, 1997

15. CHEMICAL NAME AND STRUCTURE

Ketoprofen $C_{16}H_{14}O_3$; M.W. = 254.28



m-Benzoylhydratropic acid. CAS [22071-15-4]

17. COMMENTS

Q.1. You have proposed ranges for excipients for the manufacture of production batches. Please justify the proposed ranges.

In addition, we note that the composition of the product is listed up to the second significant number for the ANDA batch but not for the scale-up batch. Please clarify.

Response: Firm is using [ ] manufacturing approach and the approach has been employed for four NDA marketed products. Firm provided a lengthy reasoning for the desirability of this approach. Based on the review of a number of batches, the firm has revised the composition for the scale up batch slightly (see components and composition section)

Firm uses rounding practice, and the values were incorrectly rounded for the ANDA batch.

Comment: O.K. I am not a proponent of [ ] manufacturing approach, but for the sake of consistency with Elan's approved applications and other similar applications issue will not be pressed further.

Q.2. Please provide the composition of the gelatin capsules and provide references to appropriate CFRs that the components of the capsules meet the requirements of food additives.

Response: Firm submitted a copy of the letter from [ ] which contains the composition (see

components and composition section) and specifications. In addition, the firm provided appropriate CFR citations for the components of gelatin capsules.

Comment: O.K.

Q.3. The specifications for the sugar spheres do not fully conform to compendial specifications. Please submit updated specifications.

Response: Firm reported the particle size specification to conform to USP.

Comment: O.K.

Q.4. We recommend that you add the specifications for [content and particle size to your specifications for ethyl cellulose.

Response: [content of [% is reported under assay and particle size specifications are not required because it is dissolved in isopropanol prior to application.

Comment: O.K.

Q.5. Please provide specifications for particle size, bulk density, and OVI/residual solvents for the drug substance.

Response: Firm provided the requested specs and in addition revised the specs in accordance with supplement 4.

Comment: O.K.

Q.6. The packaging description indicates that [and a [are used for the packaging of the drug product in market containers. Please provide specifications, technical information and appropriate DMF reference for these materials.

Response: Firm states that neither [nor] was used. Any mention of these materials in the ANDA was in error.

Comment: O.K.

Q.7. The bio batch is listed as C5J1932 and DB3497 at different places and C5J1932 is assigned as a control number at some places and batch number at other places. Please clarify this discrepancy and provide the batch numbering system for the manufactured batches.

Response: Firm states that the product is manufactured at Elan's manufacturing facility and the bulk product is given a control number according to Elan's procedures. The bulk is then shipped to Shein Pharmaceuticals for packaging and the second number for the batch was assigned at that stage. In fact, it is the same batch with two different numbers.

Comment: O.K.

Q.8. The composition and in-process controls provide for the solvent residue of nmt[% for the test batch and[% for production batch. These values are high and should be revised in conformity with the observed value of [%.

Response: Firm has reduced the isopropanol levels to[%.

Comment: O.K.

Q.9. The [ ]method alone is not adequate for the identification test for the drug product. Please provide an additional spectroscopic identification test.

Response: Firm has added[ ]as an additional ID test.

Comment: O.K.

Q.10. You have not submitted analytical methods validation data for the analysis of the related compound, 2-(3-carboxyphenyl)propionic acid in the drug product. Please provide this information.

Response: Firm provided the methods validation data for the analysis of the related compound, 2-(3-carboxyphenyl)propionic acid.

Comment: The method has been adequately validated for LOD, LOQ, accuracy, linearity, precision, and ruggedness.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

a. Since this drug product is not covered by an official monograph in the USP, the analytical methods must be validated by an FDA field laboratory. Samples for the

methods validation will be requested by the FDA at the appropriate time.

Response: Acknowledged

Comment: O.K.

b. The dissolution specifications for the drug products will be reviewed and established by the Division of Bioequivalence.

Response: Acknowledged

Comment: O.K.

c. All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality. Any unsatisfactory review/evaluation will delay the approval of the ANDA.

Response: Acknowledged

Comment: O.K.

d. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

Response: Acknowledged

Comment: O.K.

20. COMPONENTS AND COMPOSITION: satisfactory

Ingredient	Per ANDA mg/capsule	Scale-up mg/capsule
Ketoprofen	200.00	200
Starch & sucrose Colloidal silicon dioxide Talc Ethyl cellulose Polyvinylpyrrolidone Isopropyl alcohol	nmt %	nmt %

21. FACILITIES AND PERSONNEL: satisfactory per Review # 1.

The finished product is manufactured at the following

address and is the proposed alternate site for packaged finished product release testing:

Elan Pharma Ltd.
Monksland Industrial Estate
Athlone Co. Wesmeath, Ireland

The bulk product is packaged, labeled , and tested for release and stability at the following site:

Schein Pharmaceutical
1033 Stoneleigh Ave
Carmel, NY 10512

GMP Certification (v.1.2 page 162): Satisfactory

22. SYNTHESIS: Unsatisfactory

NDS: Ketoprofen

Manufacturer: [ ]

DMF #: [ ]

DMF Referral Letter: Satisfactory

The amendment was reviewed by me and is inadequate.

23. RAW MATERIAL CONTROLS

A. NEW DRUG SUBSTANCE: satisfactory per this review

SPECIFICATIONS

Test	Specification
Appearance	A white or almost white color
Identification	a. melting point [ ] b. [ ] (maxima at 255 nm)
Melting range	[ ]
LOD	nmt [ ] %
Specific rotation	[ ]
ROI	nmt [ ] %
Heavy metals	[ ] %
Chromatographic purity	nmt [ ] % individual nmt [ ] % total

OVI	compendial
Assay	[ ]
Particle size	nlt [ ] % under [ ] µ nlt [ ] % under [ ]
Bulk density	[ ] g/ml
Tapped density	[ ] g/ml
Residual solvents	toluene nmt [ ] ppm cyclohexane nmt [ ] ppm

certificate of analysis for lot # 45105 complies with the firm's specs. The specs of the manufacturer are the same and COA complies.

B. OTHER INGREDIENTS: satisfactory per this review

24. OTHER FIRM(s): Satisfactory per Review # 1

1. [ ]

   Functions: micro testing
   GMP Certification:Satisfactory

2. Schein Pharmaceuticals
   1033 Stoneleigh Ave
   Carmel, NY 10512
   Functions: packaging, labeling, release and stability testing
   GMP Certification:Satisfactory

3. [ ]

   Functions: trace analysis and nitrogen testing
   GMP Certification:Satisfactory

4. [ ]

   Functions: HDPE container/closure testing
   GMP Certification:Satisfactory

25. MANUFACTURING AND PROCESSING: satisfactory per Review # 1

[ ]

Proposed Batch Size: [ ]kg
Manufacturing process: production procedures
Manufacturing site: production facility
Equipment: Is comparable for bio and production batches. No procedures have been investigated for reprocessing. If need be, the firm will follow appropriate procedures.

Unexecuted batch records are provided for the bio (40kg) and production batches.

26. CONTAINER: Satisfactory per this review.

Tablet Count	Bottle Size	Bottle Manuf	Cap size	Cap manuf
100s	120 cc		38/40	
500s	500 cc		53/400	
1000s	950 cc		53/400	

Appropriate referral letters are provided.

The diagrams and physical data are provided for the containers and closures. Testing data per USP chapters <661> and <671> are also provided. Appropriate certifications are provided which state that the packaging materials are suitable as indirect food additives.

Firm has also specifications and adequate test data per USP test data for 6 and 88 liter HDPE bulk containers containing polyethylene bags.

27. PACKAGING AND LABELING: Satisfactory per Review # 1.

The packaging reconciliation is satisfactory.

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM): Unsatisfactory per this review.

BIO BATCH:
Batch #: C5J1932/ DB3497

DS source: [ ]
Units of dosage form:40 kg [ ]capsules)
DS source:[ ]

Reconciliation: The manufacturing and packaging yields are satisfactory.

Release Specifications

Test	Specification
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity
Color	Cap: Powder blue opaque Print: "Ketoprofen ER' 200 mg Body: white opaque Printed: "Schein"
Physical appearance	complies with description
Identification	Positive for Ketoprofen
Uniformity of dosage units	Within USP requirements
Assay	% of label claim
Related Compounds	Individual: nmt % Total: nmt %
Dissolution	Proposed limit are not in concurrance with the bio's recommendation

Must revise release and stability specification for dissolution to meet the bio's recommendation.

29. STABILITY: Unsatisfactory

Stability Specifications

Test	Specifications
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity.
Assay	(mg/capsule (%)
Related compounds	Individual: nmt % Total: nmt %
Dissolution	Proposed limit are not in concurrence with the bio's recommendation.

In addition the bulk packages are tested for moisture and color.

Stability Lot: DB3497

Schedule: Conforms to CDER Stability Guideline

Expiry Date: 3 months for the bulk packaging and 24 months for the market containers.

Elan's Reported Results

Firm has submitted three months stability data at % RH. for the 6 kg bulk package. The data meets the above specifications. Three months expiration is requested for bulk packaging based on this data.

Schein's Reported Results

Stability data are submitted under accelerated and room temperature conditions for three months. The data conforms to the proposed specifications.

Postapproval Commitments: Conform to CDER Stability Guideline.

30. CONTROL NUMBERS : N/A

31. SAMPLES AND RESULTS: **Pending**, MV submitted 5/12/96

32. LABELING : Deficiant 12/6/96.

33. ESTABLISHMENT INSPECTION : Pending

34. BIOEQUIVALENCY STATUS: **Tentative ok 10/31/96.**

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory per Review # 1.

Categorical exclusion is requested and a certificate of compliance with environmental laws is provided.

36. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes_____x____
No _____

If no, explain reason(s) below:

37. **DMF CHECKLIST FOR ANDA # 74-879 REVIEW # 2 __**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[	DS,]	1	Inadequate	5-12-97
Comments:				
[	/FACILITY]	2		
Comments:				
[	]	3	ADE	6.21.96
Comments:				
[	Containers]	3	ADE	5.29.95
Comments:				
[	packaging mat]	4		
Comments: The DMF is currently adequate.				
[	closures]	3	ADE	5.6.96
Comments:				
[	liner]	4		
Comments:				
[	Statpak,]	4		
Comments:				

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

Page 1 of 1 . Devinder S. Gill /S/ 5-15-97

Reviewer Signature Date

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 74-879

3. NAME AND ADDRESS OF APPLICANT

Elan Pharmaceutical Research Corporation
Attention: Sharon L. Hamm, Pharm. D.
1300 Gould Dr.
Gainesville, GA 30504-3947

4. LEGAL BASIS FOR ANDA SUBMISSION:
Listed drug: Oruvail®, NDA #19,816
Exclusivity until September 24, 1996
Active ingredient, route of administration, dosage form, and strength are the same for ANDA and NDA.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME
Ketoprofen

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

9. AMENDMENTS AND OTHER DATES:
April 1, 1996: Date of submission
April 4, 1996: New correspondence

10. PHARMACOLOGICAL CATEGORY	11. Rx or OTC
NSAID	Rx

12. RELATED IND/NDA/DMF(s)
See checklist

13. DOSAGE FORM	14. POTENCY
Extended-Release Capsules	200 mg

16. RECORDS AND REPORTS: None

18. CONCLUSIONS AND RECOMMENDATIONS : Not Approvable
See Comments

19. REVIEWER:	DATE COMPLETED:
Devinder S. Gill	August 16, 1996

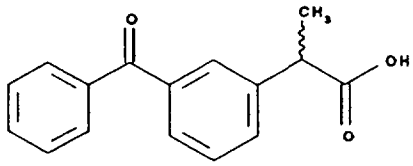
cc: ANDA
Division File
DUP File
Field Copy

Endorsements:

HFD-623/D.Gill/8-16-96 DSGill 9.3.96
HFD-623/V.Sayeed, Ph.D./8-21-96 for Dr. Sayeed 9/3/96
X:\new\firmsam\elan\ltrs&rev\74879na1.d
F/T by: bc/8-29-96

15. CHEMICAL NAME AND STRUCTURE

Ketoprofen $C_{16}H_{14}O_3$; M.W. = 254.28



m-Benzoylhydratropic acid. CAS [22071-15-4]

17. COMMENTS

Excipient ranges are proposed for the production batches.

The composition of the product is listed up to second decimal for the ANDA batch, but decimals are missing for the scale-up batch.

Firm did not provide the composition of the gelatin capsules.

The specifications (v.1.2, page 63) for sugar spheres do not fully conform to compendial specifications.

Firm will be asked to provide specifications for[ ] content and particle size for Ethylcellulose.

Particle size, bulk density, and OVI/residual solvent specifications and methods for the drug substance are not provided.

Packaging description indicates that [ ] are used for packaging. Firm has not provided any DMF reference or technical data.

The bio batch is listed as C5J1932 and as DB3497 at different places and C5J1932 is listed as control number at some places and lot number at other places. Firm will be asked to clarify and provided the batch numbering system.

The composition and in-process controls provide for solvent residue of nmt [ ]% for ANDA and [ ] % for production batch. Either number is high. The observed numbers are [ ]%.

Identification test for the drug product is by [ ] alone.

Validation data is not submitted for the analysis of the related compound, 2-(3-carboxyphenyl)propinic acid.

20. COMPONENTS AND COMPOSITION: Unsatisfactory

Ingredient	Per ANDA mg/capsule	Scale-up mg/capsule
Ketoprofen	200.00	200
Starch & sucrose	[	[
Colloidal silicon dioxide		
Talc		
Ethylcellulose		
Polyvinylpyrrolidone		
Isopropyl alcohol	**nmt** [ ]%	**nmt** [ ]%

The composition of the product is listed up to second decimal for the ANDA batch, but decimals are missing for the scale-up batch.

Firm did not provide the composition of the gelatin capsules.

21. FACILITIES AND PERSONNEL: satisfactory

The finished product is manufactured at the following address and is the proposed alternate site for packaged finished product release testing:

Elan Pharma Ltd.
Monksland Industrial Estate
Athlone Co. Wesmeath, Ireland

The bulk product is packaged, labeled , and tested for release and stability at the following site:

Schein Pharmaceutical
1033 Stoneleigh Ave
Carmel, NY 10512

GMP Certification (v.1.2 page 162): Satisfactory

22. SYNTHESIS: Satisfactory

NDS: Ketoprofen

Manufacturer: [ ]

DMF #: [ ]

DMF Referral Letter: Satisfactory

23. RAW MATERIAL CONTROLS

A. NEW DRUG SUBSTANCE: Unsatisfactory

SPECIFICATIONS

Test	Specification
Appearance	A white or almost white color
Identification	a. melting point b. (maxima at 255 nm) c. comparison with reference d. (must comply)
Appearance of solution	clear solution, and not intensely colored
Related substances	2-(3-carboxyphenyl)propinic acid: nmt % 3-acetylbenzophenone: nmt % other individual: nmt % total otherS: nmt %
Heavy metals	nmt ppm
LOD	nmt %
Sulphated ash	nmt %
Assay	
Particle size	- - -
Bulk density	- - -
OVI/residual solvents	- - -

certificate of analysis for lot # 45105 complies with the firm's specs. The specs of the manufacturer are the same and COA complies.

B. OTHER INGREDIENTS: Unsatisfactory

The specifications (v.1.2, page 63) for sugar spheres do not fully conform to compendial specifications.

Firm will be asked to provide specifications for content and particle size for Ethylcellulose.

The COAs conform to specifications, which are compendial.

24. OTHER FIRM(s): Satisfactory

1. [redacted]

Functions: micro testing
GMP Certification:Satisfactory

2. Schein Pharmaceuticals
1033 Stoneleigh Ave
Carmel, NY 10512
Functions: packaging, labeling, release and stability testing
GMP Certification:Satisfactory

3. [redacted]

Functions: trace analysis and nitrogen testing
GMP Certification:Satisfactory

4. [redacted]

Functions: HDPE container/closure testing
GMP Certification:Satisfactory

25. MANUFACTURING AND PROCESSING: satisfactory

[redacted]

Proposed Batch Size: [redacted] kg
Manufacturing process: production procedures
Manufacturing site: production facility
Equipment: Is comparable for bio and production batches.
No procedures have been investigated for reprocessing. If need be, the firm will follow appropriate procedures.

Unexecuted batch records are provided for the bio (40kg) and production batches.

26. CONTAINER: Unsatisfactory

Tablet Count	Bottle Size	Bottle Manuf	Cap size	Cap manuf
100s	120 cc		38/40	
500s	500 cc		53/400	
1000s	950 cc		53/400	

Packaging description indicates that [ ] are used for packaging. Firm has not provided any DMF reference or technical data.

Appropriate referral letters are provided.

The diagrams and physical data are provided for the containers and closures. Testing data per USP chapters <661> and <671> are also provided. Appropriate certifications are provided which state that the packaging materials are suitable as indirect food additives.

Firm has also specifications and adequate test data per USP test data for 6 and 88 liter HDPE bulk containers containing polyethylene bags.

27. PACKAGING AND LABELING: Satisfactory

The packaging reconciliation is satisfactory.

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM): Unsatisfactory

BIO BATCH:
Batch #: C5J1932/ DB3497

The bio batch is listed as C5J1932 and as DB3497 at different places ; C5J1932 is listed as control number at some places and lot number at other places. Firm will be asked to clarify and provide the batch numbering system.

DS source: [
Units of dosage form:40 kg [capsules)
DS source: [
Reconciliation: The manufacturing and packaging yields are satisfactory.

In-Process Specifications

[

Release Specifications

Test	Specification
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity
Color	Cap: Powder blue opaque Print: "Ketoprofen ER' 200 mg Body: white opaque Printed: "Schein"
Physical appearance	complies with description
Identification	**Positive for Ketoprofen**
Uniformity of dosage units	Within USP requirements
Assay	% of label claim
Related Compounds	Individual: nmt % Total: nmt %
Dissolution	2 hr: % 6 hr: % 24: nlt %

Method Validation (DS):

(

29. STABILITY: Satisfactory

Stability Specifications

Test	Specifications
Appearance	Hard gelatin capsules containing roughly spherical pellets free from visible impurity.
Assay	mg/capsule %)
Related compounds	Individual: nmt % Total: nmt %
Dissolution	2 hr: % 6 hr: % 24: nlt %

In addition the bulk packages are tested for moisture and color.

Stability Lot: DB3497

Schedule: Conforms to CDER Stability Guideline

Expiry Date: 3 months for the bulk packaging and 24 months for the market containers.

Elan's Reported Results

Firm has submitted three months stability data at % RH. for the 6 kg bulk package. The data meets the above specifications. Three months expiration is requested for bulk packaging based on this data.

Schein's Reported Results

Stability data are submitted under accelerated and room temperature conditions for three months. The data conforms to the proposed specifications.

Postapproval Commitments: Conform to CDER Stability Guideline.

30. CONTROL NUMBERS : N/A

31. SAMPLES AND RESULTS

Since the review contains a deficiency related to methods validation, it will be requested at the time of next review.

32. LABELING : Pending

33. ESTABLISHMENT INSPECTION : Pending

34. BIOEQUIVALENCY STATUS: Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Satisfactory

Categorical exclusion is requested and a certificate of compliance with environmental laws is provided.

36. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes_____x____
No _____

If no, explain reason(s) below:

37. **DMF CHECKLIST FOR ANDA # 74-879 REVIEW # 1 __**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[	/DS/]	1	ADE	10.25.96
__Comments:				
[	/FACILITY)	2		
Comments:				
[	]	3	ADE	6.21.96
Comments:				
[	Containers]	3	ADE	5.29.95
Comments:				
[	packaging mat]	4		
Comments: The DMF is currently adequate.				
[	/closures]	3	ADE	5.6.96
Comments:				
[	liner]	4		
Comments:				
[	Statpak]	4		
Comments:				

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

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Reviewer Signature Date

ANDA # 74-879

Addendum to the Review (Review of Amendment dated November 13, 1997

In response to the agency's concern for ranges in formulation, the firm submitted the following target composition on November 13, 1997:

Ingredient	Per ANDA mg/capsule
Ketoprofen	200
Starch & sucrose	
Colloidal silicon dioxide	
Talc	
Ethyl cellulose	
Polyvinylpyrrolidone	
Isopropyl alcohol	nmt 5%

The revised composition is satisfactory.

/s/
11-21-97

APPEARS THIS WAY
ON ORIGINAL