APPLICATION NUMBER:
21-341

CHEMISTRY REVIEW(S)
NDA 21-341

Bextra (Valdecoxib) Tablets

G.D. Searle & Co.

Rao Puttagunta, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs (HFD-550)
# Table of Contents

Table of Contents .................................................................................................................. 2

Chemistry Review Data Sheet ................................................................. 4

The Executive Summary ....................................................................................... 8

1. Recommendations ......................................................................................... 8
   A. Recommendation and Conclusion on Approvability .......................... 8

   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
      Management Steps, if Approvable ......................................................... 8

II. Summary of Chemistry Assessments .......................................................... 8
   A. Description of the Drug Product(s) and Drug Substance (s) ............... 8

   B. Description of How the Drug Product is Intended to be Used: ............ 9

   C. Basis for Approvability or Not-Approval Recommendation: ............. 9

III. Administrative ................................................................................................. 10
   A. Reviewer's Signature .............................................................................. 10

   B. Endorsement Block ............................................................................... 10

   C. CC Block ............................................................................................... 10

Chemistry Assessment ....................................................................................... 11

A. DRUG SUBSTANCE ....................................................................................... 11

1. DESCRIPTION ................................................................................................. 11

   a. Physical and Chemical Characteristics ............................................. 11

   b. Elucidation of Structure ................................................................... 13

2. MANUFACTURER ............................................................................................ 15

3. SYNTHESIS AND METHOD OF MANUFACTURE ..................................... 16

   a. Flow Chart (Commercial Process) ..................................................... 16

   b. Description ......................................................................................... 17

   c. Starting Materials .............................................................................. 17

4. PROCESS CONTROLS ..................................................................................... 19

   a. Synthesis Reagents and Solvents ....................................................... 19

   b. Reaction Completion and Other In-Process Tests ............................ 19

   c. Intermediate Specifications and Tests .............................................. 19

5. LABORATORY CONTROLS FOR THE DRUG SUBSTANCE ....................... 20

   a. Specification and Batch Analysis data ............................................. 20

   b. Analytical Methods .......................................................................... 22

   c. Purity Profile .................................................................................... 31

   d. Microbiology ................................................................................... 33

6. CONTAINER ....................................................................................................... 33

7. REFERENCE STANDARD .............................................................................. 33
Chemistry Review Data Sheet

1. NDA #: 21-341

2. REVIEW #: 1

3. REVIEW DATE: 14-NOV-2001

4. REVIEWER: Rao Puttagunta

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>15-JAN-2001</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>19-JUL-2001</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>31-AUG-2001</td>
</tr>
<tr>
<td>Amendment 3</td>
<td>26-OCT-2001</td>
</tr>
<tr>
<td>Amendment 4</td>
<td>02-NOV-2001</td>
</tr>
<tr>
<td>Amendment 5</td>
<td>09-NOV-2001</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

- Name: G.D. Searle & Co.
- Address: 4901 Searle Parkway, Skokie, IL 60077
- Representative: Peter East, Associate Director, Regulatory Affairs
- Telephone: 847-982-8606

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Bextra
- b) Non-Proprietary Name: Valdecoxib Tablets
- c) Code Name/#: SC-65872
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg and 20 mg per Tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

_____SPOTS product – Form Completed

_X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

![Chemical structure image]

Chemical name: 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide
Molecular Formula: C_{16}H_{14}N_{2}O_{3}S  Molecular Weight: 314.36
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

1. Action codes for DMF Table:
   1 – DMF Reviewed.
   Other codes indicate why the DMF was not reviewed, as follows:
   2 – Type I 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 6 of 60
### B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td></td>
<td>Valdecoxib</td>
</tr>
<tr>
<td>IND</td>
<td></td>
<td>Valdecoxib</td>
</tr>
</tbody>
</table>

### 18. STATUS:

<table>
<thead>
<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>Acceptable</td>
<td>24-SEP-2001</td>
<td>J.D. Ambrogio</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopharm</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td>USAN</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Pending</td>
<td>Initiated on 02-NOV-2001</td>
<td>Marci Lee</td>
</tr>
<tr>
<td>OPDRA</td>
<td>Acceptable</td>
<td>10-OCT-2001</td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>FONSI recommended</td>
<td>24-OCT-2001</td>
<td>Melissa J. Maust</td>
</tr>
<tr>
<td>Microbiology</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-341

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry standpoint this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Valdecoxib (SC-65872), an isoxazole derivative, is a selective inhibitor of cyclooxygenase-2 (COX-2). The drug substance (valdecoxib) is a white to off white solid. Valdecoxib has very low solubility in water (10 mcg/mL at 25°C, pH 7.0). It is more soluble in organic solvents such as methanol (51-77 mg/mL), acetone (136-181 mg/mL), dimethyl sulfoxide (>283 mg/mL) and tetrahydrofuran (229-413 mg/mL) at ambient temperature.

Details of the drug substance manufacturing process are included. The drug substance specification was considered adequate after the acceptance criteria for
CHEMISTRY REVIEW

Executive Summary Section

A description of the drug product manufacturing process is included. were established to achieve consistency in product quality.

The drug product specification was considered adequate after the applicant included the test for in response to a request for justification for omission of the test.

The tablets are packaged in The packaging materials used were found adequate. The submitted drug product stability data include long-term stability data for The applicant initially proposed an expiration date. Based on the submitted data it was decided to allow a 36-month expiration period for the bottles and a 30-month expiration period for the blister package. The applicant agreed to these expiration dates.

The proposed dissolution acceptance criterion (Q ≥ at 45 minutes) is acceptable to the Biopharm reviewer Dr. Veneeta Tandon (discussed on 10/18/01).

The original application proposed a total of 10, 20 mg. Firm did not seek approval for At the time of this review the medical reviewers indicated that only the 10 mg and 20 mg tablet strengths will be approved.

B. Description of How the Drug Product is Intended to be Used:

Bextra (valdecoxib) tablets are intended to be used orally for the relief of osteoarthritis and adult rheumatoid arthritis. The recommended maximum dose is 20 mg/day. Bextra tablets will be supplied in bottles in 100 and 500 counts, and in a carton of 100 unit doses.

The expiration period for the drug product in bottle is 36 months, and for the drug product in the unit dose package is 30 months.

Recommended storage conditions: 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation:

N/A
III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

Chemist Name/Date: Rao Puttagunta/19-OCT-2001
Chemistry Team Leader Name/Date: John Smith/
Project Manager Name/Date: Carmen DeBellas/

C. CC Block

Orig. NDA # 21-341
HFD-550/Division File
HFD-550/Chem./R.Puttagunta
HFD-550/T.L./J.Smith
HFD-550/CSO/C.DeBellas
HFD-830/Dir./C.Chen
50 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

11-60