DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-006 CHEMISTRY REVIEW: #5 DATE REVIEWED: 09-OCT-2001

SUBMISSION TYPE Letter Date Stamp Date Assigned Date

Refer to CMC reviews #1-3 for documents reviewed prior to April 28, 2001 "Approvable" (AE) Letter.

Previous submissions reviewed in CMC review # 4.

AZ (Partial response to AE letter) 07-MAY-2001 08-MAY-2001 N/A
BL (Revised container labels) 01-JUN-2001 04-JUN-2001 06-JUN-2001

Submissions reviewed in current review:


NAME AND ADDRESS OF APPLICANT: Elan Pharmaceuticals
800 Gateway Boulevard
South San Francisco, CA 94080

Note sponsor change from Vanguard/Vernalis to Elan.

DRUG PRODUCT NAME:
Proprietary:
Nonproprietary/Established/USAN: frovatriptan succinate
Code Name/#: VML251
Chem. Type/Therapeutic Class: 1 S


PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 2.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(R) (+)-3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate monohydrate;
CAS No.: 158930-17-7
Mol. Formula: C_{14}H_{17}N_{2}O \cdot C_{4}H_{8}O_{4} \cdot H_{2}O
Mol. Weight: 379.41 - succinate monohydrate
243.31 - base

SUPPORTING DOCUMENTS:

IND (Vernalis Limited, for frovatriptan succinate). Refer to Section A.7 of CMC Review #2 and Section B.7 of CMC Review #3 for this NDA for information regarding container closure DMFs cited.
RELATED DOCUMENTS: N/A

CONSULTS:

Proposed tradename —— consulted to OPDRA by project manager. Tradename is acceptable pending final OPDRA review.

REMARKS / COMMENTS:

Frovatriptan succinate was developed by Vernalis under license from SmithKline Beecham. The NDA was originally submitted on 29-JAN-1999 by ——— acting as agent for Vernalis Limited (formerly Vanguard Medica Limited). Ownership of the NDA was transferred to Elan Pharmaceuticals effective 09-FEB-2001.

An "approvable" letter, which cited minor CMC deficiencies, was issued by the Agency on 28-APR-2000. Refer to CMC review #4 for review of the firm's response to the approvable letter. Additional comments regarding labeling, and analytical methods validation that were communicated in a Chemistry Discipline Review Letter on 17-JUL-2001. These were addressed in the 09-AUG-2001 and 12-SEP-2001 amendments.

The NDA is generally adequate for CMC controls on frovatriptan succinate bulk API, and the dosage form. Minor problems with a proposed regulatory analytical procedure (Identification of Frovatriptan in Tablets by ——— ) were noted by an Agency analyst during methods validation. The firm has submitted preliminary data to demonstrate the suitability of a slightly modified procedure (12-SEP-2001 amendment). The firm provides a Phase IV commitment ———

CONCLUSIONS AND RECOMMENDATIONS:

Adequate CMC information to support approval of the application.

The following Phase IV commitment should be noted in action letter:

Revise ——— identification method ——— to improve method specificity and submit revised method, with supporting validation data, within three months.

Action letter should contain paragraph regarding completion of methods validation.

Electronic copy of package insert should be revised as follows (revisions acceptable to firm):

Delete the word ——— from Description section.
Delete the ——— statement from How Supplied section.

———

Martha R. Heimann, Ph.D., Review Chemist

cc: Orig. NDA 21-006
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/R/D Init by: MG
HFD-810/Simmons

Filename: ———

Review completed: 10/5/2001
**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**
Review of Chemistry, Manufacturing, and Controls

**NDA#: 21-006**

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<th>DATE REVIEWED: 17-JUL-2001</th>
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**NAME AND ADDRESS OF APPLICANT:**
Elan Pharmaceuticals
800 Gateway Boulevard
South San Francisco, CA 94080

Note sponsor change from Vanguard/Vernalis to Elan.

**DRUG PRODUCT NAME:**

- Proprietary:
- Nonproprietary/Established/USAN: frovatriptan succinate
- Code Name/#: VML251
- Chem. Type/Therapeutic Class: 1 S


**PHARMACOLOGICAL CATEGORY / INDICATION:** Migraine

**DOSE FORM:** Tablets

**STRENGTH(S):** 2.5 mg

**ROUTE OF ADMINISTRATION:** Oral

**DISPENSED:** RX

**SPECIAL PRODUCTS:** No

**CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:**

(R) (+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate monohydrate;

- CAS No.: 158930-17-7
- Mol. Formula: C_{14}H_{17}N_2O \cdot C_4H_6O_4 \cdot H_2O
- Mol. Weight: 379.41 - succinate monohydrate
  243.31 - base

**SUPPORTING DOCUMENTS:**

IND —— (Vernalis Limited, for frovatriptan succinate). Refer to Section A.7 of CMC Review #2 and Section B.7 of CMC Review #3 for this NDA for information regarding container closure DMFs cited.

**RELATED DOCUMENTS: N/A**

**CONSULTS:**

Proposed tradename —— consulted to OPDRA by project manager. Tradename is acceptable pending final OPDRA review.
REMARKS / COMMENTS:

This NDA was originally submitted by ——— as agent for Vernalis Limited (formerly Vanguard Medica Limited). Frovatriptan succinate was developed by Vernalis under license from SmithKline Beecham. Ownership of the NDA was transferred to Elan Pharmaceuticals effective 09-FEB-2001.

NDA is generally adequate for CMC controls on frovatriptan succinate bulk API, and the dosage form, but minor deficiencies remain as noted below. Refer to review notes for specific details. Acceptable Compliance recommendation for manufacturing facilities (originally issued 09-NOV-1999) was updated on 07-JUN-2001.

Specifications/Method Validation

Methods validation assignments were forwarded to ———— laboratories on 22-MAR-2000. Based on information received from ———— laboratory, the proposed regulatory methods for frovatriptan succinate bulk drug substance and frovatriptan succinate tablets are not adequate. The sponsor should address MV deficiencies, detailed in Section E of this review, prior to approval of the application.

Labeling/Container Labels

The sponsor should address deficiencies detailed in Section F prior to approval of the application.

CONCLUSIONS AND RECOMMENDATIONS:

Approvable pending resolution of minor deficiencies and methods validation.

Martha R. Heimann, Ph.D., Review Chemist

cc: Orig. NDA 21-006
    HFD-120/Division File
    HFD-120/MHeimann
    HFD-120/LChen
    HFD-120/MGuzewska/R/D Init by: MG
    HFD-810/Simmons

Filename: ————

Review completed:

APPEARS THIS WAY ON ORIGINAL
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-006

CHMISTRY REVIEW: #3

DATE REVIEWED: 22-MAR-2000

Submission Type
N(BC) Response to IR letter #2
N(BC) Correction to 27-JAN-2000 amendment
N(BC) Methods Validation package

Document Date
27-JAN-2000
02-FEB-2000
28-FEB-2000

CDER Stamp Date
28-JAN-2000
03-FEB-2000
29-FEB-2000

Assigned Date
31-JAN-2000
04-FEB-2000
29-FEB-2000

NAME AND ADDRESS OF APPLICANT:
Vanguard Medica Limited
Chancellor Court, Surrey Research Park
Guilford, Surrey GU2 5SF, UK

DRUG PRODUCT NAME:
Proprietary: MIGUARD™
Code Name/#: VML251
Chem. Type/Therapeutic Class: 1 S

5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2004) cover composition of matter, synthesis,
formulation and/or use in treatment of migraine. Patents are assigned to SmithKline Beecham and licensed to Vanguard.

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine

DOSAGE FORM: Tablets
STRENGTH(S): 2.5 mg
ROUTE OF ADMINISTRATION: Oral

DISPENSED: XX Rx OTC

SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(R) (+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole
succinate monohydrate; CAS No.: 158930-17-7
Mol. Formula: C_{18}H_{17}N_{3}O \cdot C_{4}H_{8}O_{4} \cdot H_{2}O
Mol. Weight: 379.41 - succinate monohydrate; 243.31 - base

SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS: N/A

CONSULTS: Proposed tradename —— consulted to LNC by project manager. Unacceptable to LNC.

REMARKS / COMMENTS: NDA is adequate for CMC controls on frovatriptan succinate bulk API, and the dosage
form but some minor deficiencies remain. [Refer to review notes.] Methods validation is pending; package
was forwarded to —— laboratories on 22-MAR-2000. OCPB reviewers have established
a dissolution specification that the firm will be asked to adopt. [Refer to section B.6.b) Compliance issued

CONCLUSIONS AND RECOMMENDATIONS:

Approvable pending resolution of minor deficiencies and methods validation.

cc: Orig. NDA 21-006
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/R/D Init.by: MG
HFD-810/JSimmons

Martha R. Heimann, Ph.D., Review Chemist

Filename: 

S/ 2/22/2000
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-006
Submission Type: N(BC)

CHEMISTRY REVIEW: #2
Document Date: 29-SEP-99
CDER Date: 30-SEP-99
Assigned Date: 01-OCT-99

DATE REVIEWED: 30-NOV-1999

NAME AND ADDRESS OF APPLICANT:
Vanguard Medica Limited
Chancellor Court, Surrey Research Park
Guilford, Surrey GU2 5SF, UK

DRUG PRODUCT NAME:
Proprietary:
Nonproprietary/Established/USAN: MIGUARD™, __________ are proposed
Code Name/#:
Chem. Type/Therapeutic Class: VML251 1S


PHARMACOLOGICAL CATEGORY / INDICATION:
Migraine

DOSAGE FORM:
Tablets

STRENGTH(s):
2.5 mg

ROUTE OF ADMINISTRATION:
Oral

 dispensed: XX Rx __ OTC

SPECIAL PRODUCTS:
No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:
(R) (+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate monohydrate

CAS No.: 158930-17-7

Mol. Formula: C_{14}H_{17}N_{3}O  \cdot C_4H_6O_4  \cdot H_2O

Mol. Weight: 379.41 - succinate monohydrate 243.31 - base

SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS: N/A

CONSULTS: Proposed tradename __________ consulted to LNC by project manager.

REMARKS / COMMENTS: The 29-SEP-1999 amendment is a response to CMC questions and deficiencies communicated in an information request (IR) letter sent on 02-JUL-1999. NDA is adequate for CMC controls on frovatriptan succinate bulk API, but remains deficient for drug product packaging, stability and labeling issues. Methods validation has been not initiated since the tablet dissolution specification has not been established by OCPB reviewers. Compliance issued acceptable recommendation for manufacturing facilities on 09-NOV-1999 (EER attached).

CONCLUSIONS AND RECOMMENDATIONS:

Approvable pending resolution of remaining CMC deficiencies

cc: Orig. NDA 21-006
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewsk/R/O Init.by: MG
HFD-810/JSimmons

_________________________
MaRTHA R. HEIMANN, Ph.D., Review Chemist

Filename: _______________

[Signature]
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

ND&D: 21-006

Chemistry Review: #1

Date Reviewed: 28-Jun-99

Submission Type

Document Date  CDER Date  Assigned Date

ORIGINAL
29-JAN-99  29-JAN-99  05-FEB-99
N(BL) revised annotated label
25-MAR-99  01-MAR-99  02-MAR-99
N(BC)
08-JUN-99  10-JUN-99  10-JUN-99

NAME AND ADDRESS OF APPLICANT:
Vanguard Medica Limited
Chancellor Court, Surrey Research Park
Guilford, Surrey GU2 5SF, UK

DRUG PRODUCT NAME:
Proprietary: MIGUARD™ are proposed
Nonproprietary/Established/USAN: frovatriptan succinate – USAN status is unclear.
Code Name/#: VML251
Chem. Type/Therapeutic Class: 1 S

5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2004) cover composition of matter, synthesis, formulation
and/or use in treatment of migraine. Patents are assigned to SmithKline Beecham and licensed to Vanguard.

PHARMACOLOGICAL CATEGORY / INDICATION:
Migraine

DOSSAGE FORM:
Tablets

STRENGTH(S):
2.5 mg

ROUTE OF ADMINISTRATION:
Oral

DISPENSED:
XX Rx  OTC

SPECIAL PRODUCTS:
No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:
(R) (+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole
succinate monohydrate
CAS No.: 158930-17-7
Mol. Formula: C_{14}H_{17}N_{3}O • C_{4}H_{6}O_{4} • H_{2}O
Mol. Weight: 379.41 - succinate monohydrate
243.31 - base

SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS: N/A

CONSULTS: Proposed tradename consulted to LNC by project manager.

REMARKS / COMMENTS: All drug substance and tablet manufacturing and control functions to will be
NDA is deficient with respect to drug substance characterization,
manufacturing controls for bulk drug substance and tablets, regulatory specifications and analytical
methodology. Additional information is need to allow review of packaging documentation. [Refer to Review
Notes and List of Deficiencies.] Establishment evaluations are pending. Methods validation will be initiated
when all deficiencies in regulatory methods have been corrected.

CONCLUSIONS AND RECOMMENDATIONS:

Not approvable at this time. Recommend Information Request letter to sponsor.

cc: Orig. NDA 21-006
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/R/D Init by: MG
HFD-810/CHolberg

/S/

Martha R. Heimann, Ph.D., Review Chemist

Filename: