CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-006

CHEMISTRY REVIEW(S)

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.			
BC (Withdrawn by former sponsor)	24-AUG-2000	25-AUG-2000	25-AUG-2000
BC (Partial CMC response to AE letter)	03-OCT-2000	04-OCT-2000	04-OCT-2000
BC (Partial CMC response to AE letter)	27-OCT-2000	01-NOV-2000	02-NOV-2000
AZ (Partial response to AE letter)	07-MAY-2001	08-MAY-2001	N/A
BL (PI—response to AE letter "complete")	07-MAY-2001	10-MAY-2001	21-MAY-2001
BL (Revised container labels)	01-JUN-2001	04-JUN-2001	06-JUN-2001
Submissions reviewed in current review.			
BC	09-AUG-2001	10-AUG-2001	10-AUG-2001
BC	12-SEP-2001	14-SEP-2001	04-OCT-2000

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**

DESI/PATENT STATUS: U.S. Patent Nos. 5,464,864 (07-NOV-2102), 5,827,871 (27-OCT-2015), 5,637,611 (10-JUN-2014), 5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2104) cover composition of matter, synthesis, formulation and/or use in treatment of migraine.

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

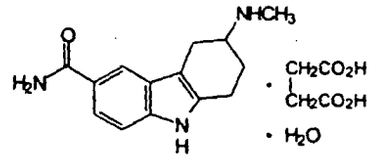
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

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

CAS No.: 158930-17-7

Mol. Formula: $C_{14}H_{17}N_3O \cdot C_4H_6O_4 \cdot H_2O$

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:

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 **CHEMISTRY REVIEW: # 4** **DATE REVIEWED:** 17-JUL-2001

SUBMISSION TYPE	Letter Date	Stamp Date	Assigned Date
BC (Withdrawn by former sponsor)	24-AUG-2000	25-AUG-2000	25-AUG-2000
BC (Partial CMC response to AE letter)	03-OCT-2000	04-OCT-2000	04-OCT-2000
BC (Partial CMC response to AE letter)	27-OCT-2000	01-NOV-2000	02-NOV-2000
AZ (Partial response to AE letter)	07-MAY-2001	08-MAY-2001	N/A
BL (PI—response to AE letter "complete")	07-MAY-2001	10-MAY-2001	21-MAY-2001
BL (Revised container labels)	01-JUN-2001	04-JUN-2001	06-JUN-2001

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: ~~[redacted]~~
Nonproprietary/Established/USAN: frovatriptan succinate
Code Name/#: VML251
Chem. Type/Therapeutic Class: **1 S**

DESI/PATENT STATUS: U.S. Patent Nos. 5,464,864 (07-NOV-2102), 5,827,871 (27-OCT-2015), 5,637,611 (10-JUN-2014), 5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2104) cover composition of matter, synthesis, formulation and/or use in treatment of migraine.

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

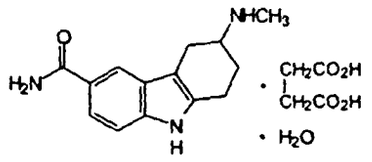
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

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

CAS No.: 158930-17-7

Mol. Formula: $C_{14}H_{17}N_3O \cdot C_4H_6O_4 \cdot H_2O$

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 ~~[redacted]~~ consulted to OPDRA by project manager. Tradename is acceptable pending final OPDRA review.

REMARKS / COMMENTS:

This NDA was originally submitted by [redacted] 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 [redacted] laboratories on 22-MAR-2000. Based on information received from [redacted] 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: [redacted]

Review completed:

APPEARS THIS WAY
ON ORIGINAL

MAR 22 2000

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

NDA#: 21-006 **CHEMISTRY REVIEW: # 3** **DATE REVIEWED: 22-MAR-2000**

Submission Type	Document Date	CDER Stamp Date	Assigned Date
N(BC) Response to IR letter #2	27-JAN-2000	28-JAN-2000	31-JAN-2000
N(BC) Correction to 27-JAN-2000 amendment	02-FEB-2000	03-FEB-2000	04-FEB-2000
N(BC) Methods Validation package	28-FEB-2000	29-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™ ——— are proposed
Nonproprietary/Established/USAN: frovatriptan succinate (USAN letter dated 27-OCT-1997)
Code Name/#: VML251
Chem. Type/Therapeutic Class: 1 S

DESI/PATENT STATUS: U.S. Patent Nos. 5,464,864 (07-NOV-2102), 5,827,871 (27-OCT-2015), 5,637,611 (10-JUN-2014), 5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2104) cover composition of matter, synthesis, formulation and/or use in treatment of migraine. Patents are assigned to SmithKline Beecham and licensed to Vanguard.

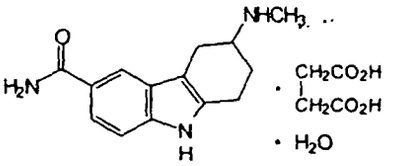
PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 2.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx __ OTC
SPECIAL PRODUCTS: No

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: $C_{14}H_{17}N_3O \cdot C_4H_6O_4 \cdot H_2O$

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. 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 acceptable recommendation for manufacturing facilities on 09-NOV-1999.

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

/S/ 3/22/2000
Martha R. Heimann, Ph.D., Review Chemist
Filename: ———

/S/ 3/24/00

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

NOV 30 1999

NDA#: 21-006 | **CHEMISTRY REVIEW: # 2** | **DATE REVIEWED:** 30-NOV-1999

Submission Type	Document Date	CDER Date	Assigned Date
N(BC)	29-SEP-99	30-SEP-99	01-OCT-99

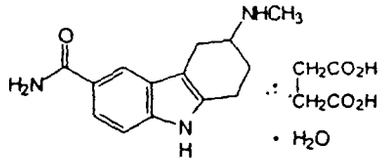
NAME AND ADDRESS OF APPLICANT: Vanguard Medica Limited
Chancellor Court, Surrey Research Park
Guilford, Surrey GU2 5SF, UK

DRUG PRODUCT NAME:
Proprietary: MIGUARD™; ——— are proposed
Nonproprietary/Established/USAN: frovatriptan succinate (USAN letter dated 27-OCT-1997)
Code Name/#: VML251
Chem. Type/Therapeutic Class: **1 S**

DESI/PATENT STATUS: U.S. Patent Nos. 5,464,864 (07-NOV-2102), 5,827,871 (27-OCT-2015), 5,637,611 (10-JUN-2014), 5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2104) 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: $C_{14}H_{17}N_3O \cdot C_4H_6O_4 \cdot H_2O$ 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/MGuzewska/R/D Init.by: MG
HFD-810/JSimmons /S/ 11.30.99

/S/ 11/30/99
Martha R. Heimann, Ph.D., Review Chemist
Filename: ———

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

JUN 30 1999

NDA#: 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**

DESI/PATENT STATUS: U.S. Patent Nos. 5,464,864 (07-NOV-2102), 5,827,871 (27-OCT-2015), 5,637,611 (10-JUN-2014), 5,618,947 (08-APR-2014), 5,618,948 (08-APR-2014), and 5,616,603 (01-APR-2104) cover composition of matter, synthesis, formulation and/or use in treatment of migraine. Patents are assigned to SmithKline Beecham and licensed to Vanguard.

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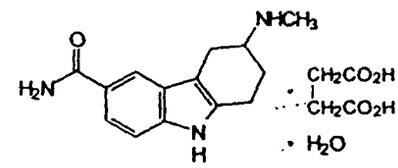
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

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: $C_{14}H_{17}N_3O \cdot C_4H_6O_4 \cdot H_2O$ 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: All drug substance and tablet manufacturing and control functions to will be [redacted] 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/CHoiberg

/S/ 6.30.99

/S/ 6/28/99
Martha R. Heimann, Ph.D., Review Chemist
Filename: ———