CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-606

CHEMISTRY REVIEW(S)

NDA 21-606

Zemplar®
(Paricalcitol) Capsules

Abbott Laboratories

David B. Lewis, Ph.D.
Division of Metabolic and Endocrine Drug Products
(HFD-510)

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Chemistry Review Data Sheet

1. NDA 21-606

2. REVIEW #: 1

3. REVIEW DATE: April 7th, 2005

4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
ORIGINAL NDA	28-Jul-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL NDA	28-Jul-2004
AMENDMENT	26-Jan-2005
AMENDMENT	2-Mar-2005
AMENDMENT	11-May-2005

- The amendment of January 26th, 2005 included clarification regarding drug substance specifications (reference to USP monograph), method validation reports for the drug product, and a comparability protocol (for future changes in drug product manufacture).
- The amendment of March 2nd provided revised labeling for the drug product.
- The amendment of May 11th, 2005 provided responses to information requests communicated to the applicant by the FDA; these request items were reiterated in the amendment. Among the provisions of the May 11th amendment was the withdrawal of the comparability protocol. This amendment was submitted in response to the teleconference of May 9th, 2005 (see official meeting minutes dated May 16th, 2005).

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Abbott Laboratories
Address:	200 Abbott Park Road – AP34-3S Abbott Park, Illinois 60064-6133
Representative:	Mary O'Sullivan, M.Ph.
Telephone:	(847) 935-9183

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zemplar®
b) Non-Proprietary Name (USAN) Paricalcitol
c) Code Name/# (ONDC only): ABT-358, Abbott-122358, Abbott Drug Code 49510
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease, Stages 3 and 4.

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 1, 2, and 4 mcg per capsule

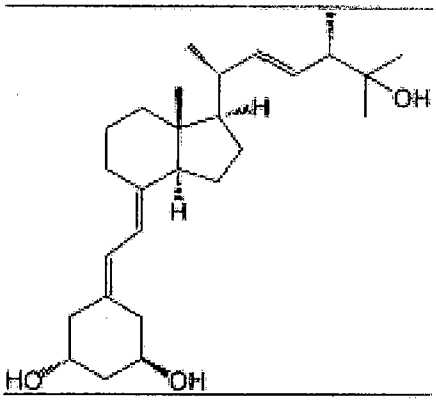
13. ROUTE OF ADMINISTRATION: oral

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:



- Molecular Weight = 416.64
- Molecular Formula = $C_{27}H_{44}O_3$

Nomenclature

- USAN Name: Paricalcitol
- INN Name: Paricalcitol
- Chemical Name: 19-nor-1α, 3β, 25-trihydroxy-9,10-secoergosta-5(Z), 7(E), 22(E)-triene
- Other Names: 19-nor-1α, 25-dihydroxyvitamin D_2; 19-nor-1, 25$(OH)_2$ D_2; Paracalcin; —— (proposed trade name, replaced by Zemplar®)
- Trade name: Zemplar®
- Compound Codes: ABT-358, Abbott-122358, Abbott Drug Code 49510
- Chemical Abstracts Services (CAS) Registry Number: 131918-61-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	3	Adequate	23-Jan-2002 by Y. Yang, Ph.D.	No significant changes since last review
/	II	/	/	1	Adequate	11-May-2005 by S. Ding, Ph.D.	Minor information request (IR) communicated to DMF holder
/	II	/	/	1	Adequate	11-May-2005 by S. Ding, Ph.D.	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Comment: DMF — was evaluated by S. Ding (April-May 2005), at which time it was determined that no significant changes had been affected since the latest review (January 23rd, 2005).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-819	Zemplar® injection, approved on April 17th, 1998
IND	60,672	Zemplar® capsules (Abbott)
NDA	21-606	Teleconference held on May 9th, 2005 (official minutes dated May 16th, 2005).

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	28-Mar-2005	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	APPROVAL	17-May-2005	W. Qiu, Ph.D.
LNC	N/A		
Methods Validation	ACCEPTABLE*		
ODS (DMETS)	ACCEPTABLE**	19-Jan-2005 06-May-2005	D. Toyer
EA	Acceptable (categorical exclusion)		D. Lewis, Ph.D.
Microbiology	N/A		

* The analytical methods are suitable for release and stability studies.

** The nomenclature was accepted (proprietary name already approved for NDA 20-819, established name is USAN/INN). Some labeling revisions were recommended; these will be discussed with the applicant at the final labeling meeting after completion of all discipline reviews. Two DMETS reviews were performed because the applicant submitted revised labeling in the March 2nd, 2005 amendment.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-606

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from the standpoint of chemistry, manufacturing and controls (CMC).

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

In the original submission, the applicant stated their intent to re-evaluate the drug product specifications, regarding related substances after the 1st three marketed lots.

II. Summary of Chemistry Assessments

NDA 21-606 provides CMC information for Zemplar® (paricalcitol) capsules, a solid oral dosage form. This NDA was filed electronically, but not in CTD format. Paricalcitol has previously been approved as the drug substance for the related NDA 20-819, Zemplar® (paricalcitol) injection. All chemistry, manufacturing and controls (CMC) information regarding paricalcitol is adequate to support this NDA by reference to NDA 20-819. The manufacturing processes for Zemplar® capsules is described in DMF's , which have been reviewed, and found adequate to support this NDA.

Note: *DMF contains CMC information for Zemplar® 2 and 4 µg capsules, while DMF concerns the 1-µg dosage strength.* CMC information, regarding the drug substance paricalcitol is contained in DMF The CMC review of DMF indicated that no significant changes have been made to the manufacture of paricalcitol since the last review, which found DMF adequate to support NDA 20-819. Thus, CMC information for paricalcitol is adequate to support this NDA. The facilities involved with the manufacture, testing, and packaging of the drug substance and drug product were submitted to the Office of Compliance (OC), and were found acceptable per EER dated March 28th, 2005.

Executive Summary Section

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

- The proprietary name for the drug product, Zemplar® was approved for the related NDA, Zemplar® (paricalcitol) injection (NDA 20-819), and is acceptable for this NDA. The established name, paricalcitol, is USAN.
- The drug product consists of soft gelatin capsules containing either 1, 2, or 4 mcg of paricalcitol — medium-chain triglycerides. The capsules contain BHT as an — The capsule shells are formulated from gelatin and glycerin and are colored with mixtures of titanium dioxide and iron oxide; each dosage strength has a different color. The drug product is manufactured by — , as described in DMF's — which were reviewed and found adequate to support this NDA (S. Ding, reviews dated May 11th, 2005). **Note**: *DMF — concerns the manufacture of the 2 and 4-mcg dosage strengths, while DMF — addresses the 1-mcg capsules.*
- Zemplar capsules are packaged in plastic high-density polyethylene (HDPE) bottles, and are intended for use in the treatment of secondary hyperparathyroidism associated with chronic kidney disease.
- The applicant provided a comparability protocol (CP) regarding future changes to manufacturing process parameters (amendment of January 26th, 2005), which was found to be deficient. However, based on a teleconference between the applicant and the Agency (May 9th, 2005, official minutes dated May 16th, 2005), the applicant withdrew the CP in the amendment dated May 11th, 2005.
- Paricalcitol is synthesized by — CMC information regarding paricalcitol was found adequate to support Zemplar® injection (NDA 20-819) by review of DMF — (review dated March 24th, 1998, S. Markofsky), and remains adequate to support this NDA. A subsequent review of DMF — (January 23rd, 2002, Y. Yang) indicated that the CMC information for paricalcitol remained adequate to support this NDA (no significant changes since last adequate review). ***Note**: Paricalcitol also meets the requirements of the current USP monograph.*

  — The retest date for paricalcitol is — (DMF — review of October 15th, 1997, S. Markofsky).

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

- The drug product is intended for three times-per-week dosing, or, alternatively, once daily, and is proposed for marketing in 30-count plastic bottles. Additionally, the product is to be supplied as physician samples in — bottles. The recommended daily dose is based on intact parathyroid hormone levels, and ranges from 7 to 14 mcg per WEEK, with daily or three-times-per-week dosing.
- The proposed shelf life is 24 months with storage at *room temperature*. The expiry is adequately supported by stability data and statistical analysis, and is deemed acceptable for all three dosage strengths.

C. Basis for Approvability or Not-Approval Recommendation

The NDA may be approved pending minor revisions to the labeling, which will be discussed with the applicant at the final labeling meeting.

Approval is based on the following criteria:

- Adequate CMC information for the drug substance, paricalcitol (DMF —,
- Adequate manufacturing process for the drug product (DMF's —
- Bioequivalence between the clinical trial drug product formulation(s) and the NDA drug product formulation. **Note**: *The formulations used in clinical trials were practically identical to those proposed for the NDA.*
- Adequate cGMP profile for the manufacturing and testing facilities for the drug substance and drug product (see EER Summary report attached to the end of this review).
- Adequate stability data, which supports the proposed expiration dating periods for the drug product (24 months)
- Adequate specifications for the drug product, including method validation data for the analytical methods.

III. Administrative

A. Reviewer's Signature

David B. Lewis, Ph.D., CMC reviewer, DNDCII, ONDC, co-located with DMEDP (HFD-510)

B. Endorsement Block

N/A (required for OGD only)

C. CC Block

N/A (required for OGD only)

34 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Lewis
5/18/05 11:02:20 AM
CHEMIST
The application may be approved from the standpoint of CMC.
Made requested edits

Sheldon Markofsky
5/18/05 01:32:36 PM
CHEMIST
Concur. Signed by S. Markofsky (Acting Team Leader) for Mamta Gautam-Basak. Project Manager: See labeling commentson pp. 46 of the review