

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-168/S-004

CHEMISTRY REVIEW(S)

NDA 20-782

Depakote ER (divalproex sodium) Tablets, 250 & 500 mg

Abbott Laboratories

Thomas A. Broadbent, Ph.D.

Division of Neuropharmacological Drug Products

APR 22 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-782

CHEM REVIEW: #1

REVIEW DATE: 4/17/98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE /ACTION
ORIGINAL	6/16/97	6/18/97	9/2/97
N(BC) Amendment	10/13/97	10/14/97	10/20/97 / NAI on 4/17/98
N(BC) Amendment	10/23/97	10/24/97	10/27/97
N(BC) Amendment	1/29/98	1/30/98	2/5/98 / NAI on 2/5/98
N(GC)Amendment	2/5/98	2/6/98	2/10/98 / NAI on 2/10/98
N(BC)Amendment	2/9/98	2/10/98	2/18/98 / NAI on 2/18/98

NAME AND ADDRESS OF APPLICANT

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

DRUG PRODUCT NAME

Proprietary:
Non proprietary/USAN:
Code Name/Number:
Chem. Type/Ther. Class:

DEPAKOTE® _____ Tablets
Divalproex Sodium
None
3S

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

DISPENSED:

Epilepsy
Tablets
500mg
Oral
 RX OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: Pentanoic acid, 2-propyl-, sodium salt (2:1)

USAN Name: Divalproex Sodium

Chemical Formula: $C_{16}H_{31}O_4Na$

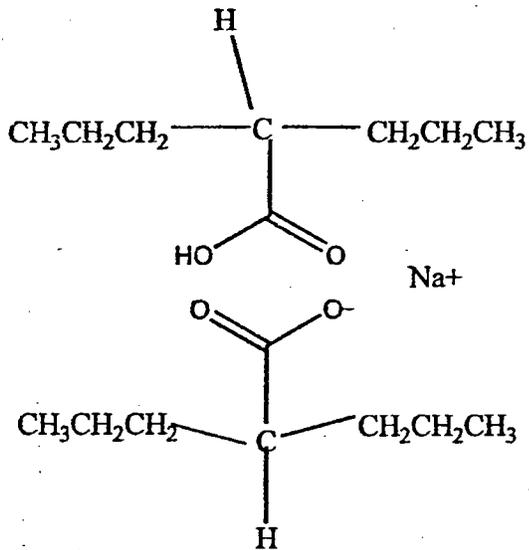
Molecular Weight: 310.41

CAS Registry Number: 76584-70-8

Laboratory code: A-50711

Synonyms: Valproic acid semisodium salt; Sodium hydrogen divalproate

APPEARS THIS WAY
ON ORIGINAL



SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER/ SPONSOR	STATUS	REVIEW DATE	LETTER DATE
IND 47,714	DEPAKOTE® Tablets	Abbott Laboratories	CMC reviews up to date	Not Applicable	Not Applicable
NDA 18-723	Depakote® Tablets (divalproex sodium delayed-release tablets)	Abbott Laboratories	Approved; referenced for the drug substance divalproex sodium.	Approved 3/10/97	Approved 3/10/97
DMF — (Type III)				Reviewed by Don Klein, Ph.D. and found adequate on 10/24/97.	Reviewed by Don Klein, Ph.D. and found adequate on 10/24/97.
DMF — (Type III)				Reviewed by Don Klein, Ph.D. and found adequate on 10/24/97.	Reviewed by Don Klein, Ph.D. and found adequate on 10/24/97.
DMF — (Type III)				Reviewed by Don Klein, Ph.D. and found adequate on 12/23/97.	Reviewed by Don Klein, Ph.D. and found adequate on 12/23/97.
DMF — (Type III)				Reviewed by Don Klein, Ph.D. and found adequate on 4/8/98.	Reviewed by Don Klein, Ph.D. and found adequate on 4/8/98.
DMF — (Type III)				Reviewed by Don Klein, Ph.D. and found adequate on 4/8/98.	Reviewed by Don Klein, Ph.D. and found adequate on 4/8/98.
DMF — (Type III)				Reviewed by Don Klein, Ph.D. and found adequate on 4/8/98.	Reviewed by Don Klein, Ph.D. and found adequate on 4/8/98.

DMF (Type III)	[Handwritten bracket]	Not necessary to review; CBE should be submitted which will cite DMF	Not Applicable	Not Applicable
DMF (Type I)		NDA 18-723 approved on 3/10/97.	Not Applicable	Not Applicable
DMF (Type I)		Not required to review Type I DMF.	Not Applicable	Not Applicable
DMF (Type I)		Not required to review Type I DMF.	Not Applicable	Not Applicable
DMF (Type I)		Not required to review Type I DMF.	Not Applicable	Not Applicable

a. **PACKAGING DMFs:** The following DMFs were referenced in this application. Refer to Section 7: Container/Closure system in this review: DMF — (Type III); DMF — (Type III).

RELATED DOCUMENTS:

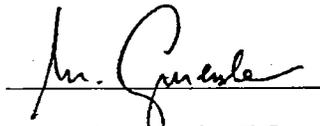
- NDA 18-081; Depakene® Capsules: Abbott Laboratories; Approved 2/28/78; drug substance is valproic acid.
- NDA 18-082; Depakene® Syrup: Abbott Laboratories; Approved 2/28/78; drug substance is valproic acid.
- NDA 18-723; Depakote Tablets(divalproex sodium delayed-release tablets): Abbott Laboratories; Approved 3/10/83; drug substance is divalproex sodium.
- NDA 20-320; Depakote® Tablets(divalproex sodium delayed-release tablets): Abbott Laboratories; Approved 5/26/95; drug substance is divalproex sodium.
- NDA 20-593; Depacon® Valproate Sodium Injection; Abbott Laboratories; Approved 12/30/96; drug substance is valproate sodium.
- NDA 19-680; Depakote® Sprinkle Capsule: Abbott Laboratories; Approved 9/10/89; drug substance is divalproex sodium.
- NDA 19-794; Depakote® CP Tablets: Abbott Laboratories; Currently not distributing but the NDA file remains open.

CONCLUSIONS & RECOMMENDATIONS: With regards to the chemistry, manufacturing, and controls, NDA 20-782 is not approvable. The Applicant must address the deficiencies before the NDA can be approved.

See draft deficiency letter.

 4/17/98

Donald N. Klein, Ph.D.
Review Chemist



Maryla Guzewska, Ph.D.
Chemistry Team Leader

cc:

Orig. NDA 20-782

HFD-120/Division File

HFD-810/CHoiberg

HFD-810/JSimmons

HFD-120/DKlein

HFD-120/MGuzewska

HFD-120/RSeevers

HFD-120/JWare

File: C:\hfd120\n20782\N20782 Review

MG 4.22.98

A. DRUG SUBSTANCE

1. NDA 18-723, DEPAKOTE® Tablets (divalproex sodium delayed-release tablets) is referenced for the drug substance divalproex sodium. NDA 18-723 was approved on March 10, 1983. The drug substance is divalproex sodium which is a stable co-ordination compound comprised of sodium valproate and valproic acid(1:1) molar relationship and formed during the _____

_____ On pages 105 and 106 in Volume 1.4 are the COAs for the respective drug substance lot 10-213-AC and lot 09-066-CA that were used in the manufacturing stability batches 10-263-AR-04, 10-264-AR-04, 10-265-AR-04.

2. DESCRIPTION & CHARACTERIZATION:

- a. Solid, essentially white
- b. Solubility in Water: 1.27mg/L
- c. pKa : 4.6
- d. Melting point: 98 - 100°C.

3. MANUFACTURER:

The drug substance is manufactured at the following location:
Abbott Laboratories
1401 Sheridan Road
North Chicago, IL 60064
(DMF 1617, Type I)

4. REGULATORY SPECIFICATIONS:

Below in Table 1 are the current specifications for the drug substance. These specifications were included in NDA 18-723 CBE Supplement(S-024) which was approved on 12/24/97.

Table 1

SPECIFICATIONS	LIMIT

EVALUATION: Acceptable

Redacted 32

Page(s) of trade

secret and /or

confidential

commercial

information

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-782

CHEM. REVIEW # 2

REVIEW DATE

14-OCT-99

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

ORIGINAL

16-JUN-97

18-JUN-97

02-SEP-97

AMENDMENT N(BC)

07-OCT-99

10-OCT-98

25-AUG-99

NAME AND ADDRESS OF APPLICANT

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/Number:

Chem. Type

Depakote ER

Divalproex Sodium

A-50711

3S

PHARMACOLOGICAL CATEGORY/INDICATION

Epilepsy

DOSAGE FORM

Tablets

STRENGTHS

500 mg

ROUTE OF ADMINISTRATION

oral

DISPENSED

XXX RX

 OTC

SPECIAL PRODUCTS

 YES

XX NO

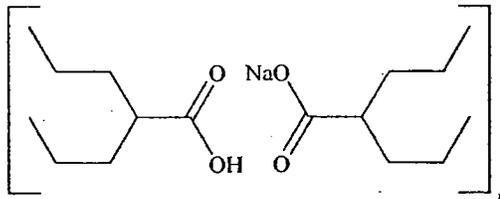
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

Sodium hydrogen bis(2-propylvalerate), oligomer

(C₁₆H₃₁NaO₄)_n

F.W. 310.41

CAS Registry # [76584-70-8]



SUPPORTING DOCUMENTS: NDA 18-723 (Depakote Tablets, provides CMC for drug substance) IND 18,827; DMF (all Type 3)

RELATED DOCUMENTS: NDA 19-680 (Depakote Sprinkle Capsules), 19-794 (Depakote Dispartab CP Tablets), 20-320 (Depakote Tablets), 20-321 (Depakote Sprinkle Caps), 21-168 (Depakote ER, Migraine)

CONSULTS: Trademark (See Attachment 1)

REMARKS/COMMENTS: This NDA amendment provides responses to the CMC questions contained in the June 17, 1998 Action Letter (NA) for NDA 20-782. The action letter cited 23 deficiencies regarding the drug product, 3 deficiencies regarding labeling and 13 recommendations regarding the drug product. This review evaluates the responses provided by the sponsor. The responses are adequate. The expiration dating for the product is determined to be 24 months. The dissolution specifications (page 11) remain a matter of review by the Division of Pharmaceutical Evaluation I because of the Division's NA filing.

CONCLUSIONS & RECOMMENDATIONS: NDA 20-782 is APPROVABLE. Methods validation and acceptable establishment evaluation are pending.

cc: Orig. NDA 20-782
HFD-120/Division File
HFD-120/TBroadbent
HF-120/MGuzewska
HFD-120/JWare
R/D Init by: MEG

T. Broadbent, Ph.D., Chemist

Filename: N20782.002.doc

Review Notes

Deficiencies, Responses and Evaluations of Responses to NDA 20-782

Deficiency # 1, Drug Product

"Please provide the purity of _____ used in the manufacture of the drug product."

Response to Deficiency # 1, Drug Product

"For drug product lots 10-263-AR-04, 10-264-AR-04 and 10-265-AR-04, the _____ (Abbott lot 82-172-AC. _____ Lot G20614) assay result was _____, (by _____). A copy of the vendor's certificate of analysis is attached."

Evaluation of Response # 1, Drug Product

Adequate. The COA is noted.

Deficiency # 2, Drug Product

"The table on page 94 in Volume 4 shows that the drug substance lot 10-213-AC and lot 09-066-CA were both used in the manufacturing of the stability batches 10-263-AR-04, 10-264-AR-04 and 10-265-AR-04. Were these _____, 10-263-AR-04, 10-264-AR-04 and 10-265-AR-04?"

Response to Deficiency # 2, Drug Product

"As noted by the asterisks at the bottom of page 094 of volume 4, drug substance used to manufacture the stability batches was synthesized by the Abbott Chemical and Agricultural Products Division (CAPD) under lot number 09-066-CA. When this lot was delivered to the drug product manufacturing plant (Abbott Barceloneta, Puerto Rico), it was assigned a new lot number of 10-213-AC-00. Thus, this is the same lot of drug substance that was assigned two different lot number designations by the drug substance manufacturer and the drug product manufacturer. There was no mixing of bulk drug lots."

Evaluation of Response # 2, Drug Product

Adequate.

Deficiency # 3, Drug Product

"Please define the acronym "BOP" in the sentence, "The procedures and limits for tablet weight are controlled by an in-plant BOP" which is on page 133 in Volume 4."

Response to Deficiency # 3, Drug Product

"The acronym "BOP" refers to "Basic Operating Procedure.""

Evaluation of Response # 3, Drug Product

Adequate. This reviewer assumes this is synonymous with "SOP" (Standard Operating Procedure), a more common term.

**APPEARS THIS WAY
ON ORIGINAL**

Deficiency # 4, Drug Product

"Please clarify: Are uncoated or printed tablets tested for hardness in the Document S41.07126 (pg. 19, Volume 6) and Standard Test Method S42P.0067 for Tablet Hardness (pg. 79-80 in Volume 6)? Please correct this Standard Test Method S42P.0067 such that the type of tablet tested is clearly stated."

Response to Deficiency # 4, Drug Product

"Tablet hardness is tested on uncoated tablets (pg. 24, vol. 6).

The sampling plan document (S05.07126, pg. 23, vol. 6) identifies how the final product will be sampled for testing during its manufacture. It provides the sampling instructions relative to the manufacturing stage at which the sample is taken (eg. _____ vs. uncoated vs. coated tablets), sample amount needed for the testing, the test location to where the sample is sent for testing and the actual test to be performed. In view of the modular structure of our current specification document system, the specification document (S41.07126) needs to be reviewed along with the sampling plan document (S05.07126) to be able to associate sample and testing requirements. Standard Test Methods (S42) typically do not reference the type of sample used in the method because the manufacturing stage at which the test is performed and the type of sample is identified in the S05 document. Standard Test Methods could potentially be used across products and multiple sample types. Again this is inherent in the modular nature of our specification documentation system and the linkages are via cross-reference to the related documents."

Evaluation of Response # 4, Drug Product

Adequate.

Deficiency # 5, Drug Product

"Please clarify: Are uncoated or printed tablets tested for thickness in the in Document S41.07126 (pg. 19, Volume 6) and Standard Test Methods S42P.0066 (pg. 77-78, Volume 6)? Please correct the Standard Test Method S42P.0066 such that the type of tablet tested is clearly stated."

Response to Deficiency # 5, Drug Product

"Tablet thickness is tested on uncoated tablets (pg 24, vol. 6).

Please refer to the response to number 4 above for an explanation of our modular document system."

Evaluation of Response # 5, Drug Product

Adequate.

Deficiency # 6, Drug Product

"The in-process control on page 28 in Volume 5 in the batch record should be consistent with the Loss on Drying (LOD) description of the in-process control on pages 133-134 in Volume 4. Please change future batch records such that it states "The target value for LOD is not more than _____ for the average of three samples with not more than _____ for any individual sample"."

Response to Deficiency # 6, Drug Product

"To be consistent with the Loss on Drying description, the text in future batch records will read: "The target value for LOD is not more than _____ for the average of three samples with not more than _____ for any individual sample.""

Evaluation of Response # 6, Drug Product

Adequate.

Deficiency # 7, Drug Product

"Please clarify: Are uncoated or printed tablets LOD tested in the in Document S41.07126 (pg. 12, Volume 6) and Standard Test Method S42C.0341 (pg. 39-40, Volume 6). Please correct the Standard Test Method S42C.0341 such that the type of tablet tested is clearly stated."

Response to Deficiency # 7, Drug Product

"LOD testing is performed on the _____ pg 24, vol. 6).

Please refer to the response to number 4 above for an explanation of our modular document system."

Evaluation of Response # 7, Drug Product

Adequate.

Deficiency # 8, Drug Product

"Please clarify: Are uncoated or printed tablets tested for aerobic microbial count in the Document S41.07126 (pg. 22, Volume 6) and Standard Test Method S42C.0003 (pg. 74-76, Volume 6). Please correct the Standard Test Method S42C.003 such that the type of tablet tested is clearly stated."

Response to Deficiency # 8, Drug Product

"Aerobic Microbial Count (AMC) testing is performed on _____ (pg. 25, vol. 6).

Please refer to the response to number 4 above for an explanation of our modular document system."

Evaluation of Response # 8, Drug Product

Adequate.

Deficiency # 9, Drug Product

"Does the recoating procedure start with Section IV followed by Section V and finally Section VI, as described on page 127 in Volume 4?"

Response to Deficiency # 9, Drug Product

"This operation is conducted only on lots that require it (for physical inspection) and would be performed after either the _____ step (Section V, pg. 127, vol. 4) or after the _____, step (Section VI, pg. 127, vol. 4) based on the appearance at each stage."

Evaluation of Response # 9, Drug Product

Adequate.

Deficiency # 10, Drug Product

"Please explain why the reference document S43D.07126 on page 74 in Volume 5 is "(PENDING)." Is this reference document S43D.07126 incomplete?"

Response to Deficiency # 10, Drug Product

"The S43D.07126 document is complete. The term "pending" by the document title indicates that the document is pending approval of the NDA."

Evaluation of Response # 10, Drug Product

Adequate.

Deficiency # 11, Drug Product

"It is stated in the Table of Contents on page 11 in Volume 1 that Lot 10-263-AR-04 was used in the pivotal bioavailability study. Please provide the identification number of the pivotal bioavailability study to which this statement refers."

Response to Deficiency # 11, Drug Product

"M95-376 is the pivotal bioavailability study referred to in the Table of Contents on page 11 of volume 1."

Evaluation of Response # 11, Drug Product

Adequate.

Deficiency # 12, Drug Product

"Please provide an _____ of the Divalproex Sodium _____ placebo, of the Sodium Hydrogen Divalproex (referenced standard), and of the drug product."

Response to Deficiency # 12, Drug Product

"Enclosed are the _____ for the Depakote _____ placebo, the Sodium Hydrogen Divalproate reference standard, and the drug product. The attached _____ were generated using Standard Test Method (STM) S421.0617 (10/14/96P). The _____ a provided are _____ dispersions containing portions of a Depakote _____ 500 mg tablet (lot 10-263-AR-23), a placebo of the Depakote _____ 500 mg tablet (lot 39-898-AR-03), a subtraction of the Depakote _____ 500 mg tablet (lot 10-263-AR-23) minus the placebo of the Depakote _____ 500 mg tablet (lot 39-898-AR-03), and a Sodium Hydrogen Divalproate reference standard (lot 23-497-CA). The _____ was determined to be qualitatively similar to the Sodium Hydrogen Divalproate _____. This is indicative of the presence of Sodium Hydrogen Divalproate in Depakote _____ Tablets."

Evaluation of Response # 12, Drug Product

Adequate. The _____ are attached to this review in Attachment 2. The _____ are plotted as _____ vs. _____ rather than the more common ' _____ vs. _____. This provides a plots that are inverted _____ images of the common format. The combined _____ produced from the drug product _____ and the subtracted placebo _____ closely matches the _____ the drug substance reference material.

Deficiency # 13, Drug Product

"Please clarify: Are uncoated or printed tablets used in the Document S42C.1705 (pg. 41, Volume 6) and Document S42C.1706 (pg. 45, Volume 6). Please correct Document S42C.1705 and Document S42C.1706 such that the type of tablets tested are clearly stated."

Response to Deficiency # 13, Drug Product

"The assay for the determination of valproic acid by _____ is conducted on _____ (pg. 24, vol. 6). Please refer to the response to number 4 above for an explanation of our modular document system."

Evaluation of Response # 13, Drug Product

Adequate.

Deficiency # 14, Drug Product

"Please clarify: Are uncoated or printed tablets tested to determine the Content Uniformity? Please refer to the Standard Test Method S42C.1708 on pages 48-51 in Volume 6."

Response to Deficiency # 14, Drug Product

"Content uniformity testing is conducted on _____ (pg. 24, vol. 6).

Please refer to the response to number 4 above for an explanation of our modular document system."

Evaluation of Response # 14, Drug Product

Adequate.

Deficiency # 15, Drug Product

"Please clarify: In the Release Testing Requirement table provided by facsimile on 7/28/97 from Mr. Steven Townsend, Project Manager to Maryla Guzewska, Ph.D., it states that the Drug Release testing is conducted _____ . However, in Document S41.07126 on page 15 in Volume 6, it states that the Drug Release is _____

Response to Deficiency # 15, Drug Product

"Drug release testing is conducted on coated tablets as stated in Document S41.07126 (pg. 15, vol.6). The facsimile of 7/28/97 from Mr. Steven Townsend to Maryla Guzewska, Ph.D. was in error on this point, and we apologize for the resulting confusion."

Evaluation of Response # 15, Drug Product

Adequate. The correction of contradictory information is noted.

Deficiency # 16, Drug Product

"Please refer to Document S41.07126 pages 15-17 in Volume 6: Why are there two Standard Test Methods listed for Drug Release?"

Response to Deficiency # 16, Drug Product

"Test method S42C.1955 refers to the ~~an~~ analytical method. Test method S42C.1957 refers to the ~~an~~ analytical method. These assays provide equivalent results (Ref 2, R&D/96/603, pg. 162, vol. 6). ~~an~~ technology is an Abbott proprietary assay used primarily during development and maintained as an alternative procedure for marketed products."

Evaluation of Response # 16, Drug Product

Adequate.

Deficiency # 17, Drug Product

"Please refer to page 12 in Volume 8: Please explain why there are two different dissolution methods, initial and final, being applied."

Response to Deficiency # 17, Drug Product

"During formulation development work, the *in vitro* dissolution method referred to as "initial" (DLP-93-032) was used. This method used very standard dissolution conditions and showed extended release of drug. Release profiles generated with the initial method did not correlate with the *in vivo* performance of the product, therefore several studies were carried out to investigate the effects of various *in vitro* testing variables on drug release. The variables tested included _____ including: _____ concentration. The method referred to as "final" (DLP-96-072) resulted from these studies, and release profiles generated with the final method do correlate with *in vivo* performance."

All stability studies were switched from the initial to the final dissolution method at the 9 month sample point, except for the bottles of 6 tablets packaged at Abbott Park (study no. 121-00E-027-8, 121-00E-028-6, and 121-00E-29-4), which were switched at the 6 month sample point. Two stability studies were continued with both the initial and final dissolution methods, for purposes of linking the two methods. These are lot 10-263-AR-04 in bottles of 500 (study no. 121-00E-001-2) and lot 10-264-AR-04 in _____ blisters with Child-Resistant (CR) push through foil backing (study no. 121-00E-016-1)."

Evaluation of Response # 17, Drug Product

Adequate. The explanation for different dissolution methods is duly noted. The reviewer notes that this application is no longer under PK review, having been found deficient. A request for methods validation for dissolution (test methods 1955 & C0181) is being submitted to Agency laboratories.

Deficiency # 18, Drug Product

"Please provide a list of all the container/closure systems that are currently being planned to be marketed. Also, include all the professional sample container/closure systems."

Response to Deficiency # 18, Drug Product

"The following are the container/closure systems being considered for market launch:

No. of Tablets	Packaging Site	Packaging Commodity/ Number	Description
6 Count (Sample)	AP ¹ & PR ²	Bottle Cap Desiccant	1 oz white plastic bottle 1 gm desiccant
10 Count (Sample)	PR	Bottle Cap Desiccant	1 oz white plastic bottle 1 gm desiccant
60 Count	PR	Bottle Cap Desiccant	4 oz white plastic bottle 2 gm canister
100 Count	PR	Bottle Cap Desiccant	5 oz white plastic bottle 2 gm canister
500 Count	PR	Bottle Cap Desiccant	32 oz white plastic bottle cap 2 gm canister (x2)
HUD ³ Abbo-Pac®	PR	Blister Foil	Clear
Blister Package (Sample)	AP	Blister Foil	Clear Push Thru Foil 8"

- 1. Abbott Park
- 20. Puerto Rico
- 21. Child-Resistant/Tamper Evident
- 22. _____
- 23. Hospital Unit Dose"

Evaluation of Response # 18, Drug Product

Adequate. The "white plastic bottle" should be identified as HDPE. The reviewer has examined bottle samples and notes the plastic is HDPE.

**APPEARS THIS WAY
ON ORIGINAL**

Deficiency # 19, Drug Product

"Are all the following blister packaging which are referred to on pages 35-38 and pages 42-43 in Volume 12 comprised of the same materials: Single tablet blister; 100 tablet ABBO-PAC®; 10 tablet professional sample blister; 6 tablet professional sample blister?"

Response to Deficiency # 19, Drug Product

"In all packaging configurations, the blister film is the same. ~~clear:~~ clear: ~~_____~~. There are two specifications because they run on different machines and require different roll widths. The sample blister will be packaged at Abbott Park, while the Abbo-Pacs (HUD) will run at our Puerto Rico facility.

The foil lidding are two different materials. The Abbo-Pac (HUD) is a Peelable foil lidding stock where the lidding material is adhered to the forming stock and is allowed to be peeled apart for use. This material is preferred for hospital use.

The sample packages are Push Thru foils where the lidding material is permanently adhered to the forming material and the product is pushed through the lidding material at time of use. This is the material of choice for general market sampling purposes."

Evaluation of Response # 19, Drug Product

Adequate. The consistency of blister packaging materials is noted.

Deficiency # 20, Drug Product

"Does the modified ~~_____~~ described in Document S01.985359 (peelable blister packaging) on page 191 in Volume 5 comply with the 21 CFR, section 175.300?"

Response to Deficiency # 20, Drug Product

~~_____~~ complies with 21 CFR § 175.300. ~~_____~~
(See attached letter)."

Evaluation of Response # 20, Drug Product

Adequate.

Deficiency # 21, Drug Product

"Does the modified ~~_____~~ described in Document S01.985360 (push-thru blister packaging) on page 196 in Volume 5 comply with the 21 CFR, section 175.300?"

Response to Deficiency # 21, Drug Product

~~_____~~ complies with 21 CFR § 175.300. ~~_____~~ (See attached letter)."

Evaluation of Response # 21, Drug Product

Adequate.

Deficiency # 22, Drug Product

"Refer to Document S01.633004 on page 160 in Volume 5: Why are two different ~~_____~~ clear and gold, listed for the inside of the ~~_____~~ cap?"

Response to Deficiency # 22, Drug Product

"Commodity 63-3003. ~~_____~~ cap, has ~~_____~~ available from the supplier. Both function as a protective ~~_____~~ for the ~~_____~~ cap."

Evaluation of Response # 22, Drug Product

Adequate.

Deficiency # 23, Drug Product

"Please explain the dissolution specification "DLP-93-032: Mean of 6 tablets release NMT LC in 5 hours" which is located in the stability section of the NDA application."

Response to Deficiency # 23, Drug Product

"Please refer to our response to question # 17 above regarding development of dissolution test methodology. The dissolution specification for DLP-93-032 which was used at the start of the stability studies was "NMT LC in 5 hours" for the "final" dissolution method, DLP-96-072, the dissolution specification was changed to "3 hours - NMT released, 9 hours released, 12 hours released, and 18 hours NLT released" based on our *in vitro/in vivo* correlation. Stability studies monitored the amount of drug released at 1, 3, 5, 9, 12, 18, and 24 hours for both dissolution methods in order to characterize the drug release profile."

Evaluation of Response # 23, Drug Product

Adequate.

Deficiency # 1, Labeling

"Please explain why the following inactive ingredients are listed in the Inactive Ingredient section in the draft labeling on page 7 of Volume 2. These inactive ingredients are not listed in the table on page 58 of Volume 2 (FD&C Blue No. 1: iron oxide; polydextrose; polyethylene glycol; propylene glycol; titanium dioxide and triacetin)."

Response to Deficiency # 1, Labeling

"The items listed in the draft labeling that are not shown in the drug product formula are components of the proprietary coloring and ink formulations supplied by (Please refer to DMF, referenced on page 92 of volume 4.)."

Evaluation of Response # 1, Labeling

Adequate.

Deficiency # 2, Labeling

"Please clarify pages 44-45 of Volume 12. Are there 100 tablets in the 6 x 6 professional sample or 36 tablets?"

Response to Deficiency # 2, Labeling

"There are 36 tablets in the 6 x 6 professional sample."

Evaluation of Response # 2, Labeling

Adequate.

Deficiency # 3, Labeling

"Please clarify pages 46-47 of Volume 12. Are there 100 tablets in the 3 x 10 professional sample or 30 tablets?"

Response to Deficiency # 3, Labeling

"There are 30 tablets in the 3 x 10 professional sample."

Evaluation of Response # 3, Labeling

Adequate.

Recommendation # 1, Drug Product

"In future applications the Agency recommends that the drug product's regulatory specification be provided in tabular form. This table should contain the drug product's tests, specifications, and the location of the test methods."

Response to Recommendation # 1, Drug Product

"Abbott Laboratories is currently developing this type of documentation for future submissions."

Evaluation of Response # 1, Drug Product

Adoption of recommendation noted.

Recommendation # 2, Drug Product

"In future applications the Agency recommends that the content of the application is consistent with the listing in the Table of Contents. For example, on page 14, Volume 2 Document S42C.1706 pertains to Content Uniformity however, in Document S41.07126, page 13-14, Volume 6, Document S42C.1706 isn't listed as one of the Standard Test Methods."

Response to Recommendation # 2, Drug Product

"The referenced Table of Contents Listing was a typographical error. The "Content Uniformity, List 7126" was inadvertently transposed into the title of S42C. 1706. It should have been part of the next document title (S42C. 1708)."

Evaluation of Response # 2, Drug Product

Correction noted.

Recommendation # 3, Drug Product

"In regards to the alternative packaging information on pages 231-274 in Volume 5, the FDA recommends that after NDA 20-782 is approved, a Special-Supplement-Changes Being Effected for NDA 20-782 be submitted that contains all the information as recommended in the June 20, 1997 letter from Dr. Eric Sheinin and Dr. Douglas Sporn pertaining to the implementation of bottles."

Response to Recommendation # 3, Drug Product

"Following approval we will submit a Special Supplement: Changes-Being-Effectuated in accordance with the documentation recommended in the June 20, 1997 letter referenced above. Our plan is to launch to market with as described in our response to question # 18 above."

Evaluation of Response # 3, Drug Product

Adoption of recommendation noted.

Recommendation # 4-13, Drug Product

"The following statement should be used...

- in the HOW SUPPLIED SECTION of the package insert:" (4)
- on the label of the bottles containing 60,100, and 500 tablets respectively:" (5)
- on the label of the single tablet blister:" (6)
- on the label of the 100 tablet unit dose carton containing the ABBO-PAC@:" (7)
- on the label of the 10 tablet professional sample bottle:" (8)
- on the label of the 6 tablet professional sample bottle:" (9)
- on the label of the 10 tablet professional sample bottle:" (10)
- on the label of the 6 tablet professional sample bottle:" (11)
- on the label of the 100 tablets 6 x 6 professional sample carton:" (12)
- on the label of the 100 tablets 3 x10 professional sample carton:" (13)

(Recommendation 10 is identical to # 8.)

(Recommendation 11 is identical to # 9.)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]"

Response to Recommendation # 4-13, Drug Product

"The storage statement will be adopted as requested."

Evaluation of Response # 4-13, Drug Product

Adoption of recommendation noted.

Additional Review Notes

B.6.B. Regulatory Specifications and Methods for Drug Product

The dissolution tests and specifications are:

Tests:

Test Method C01818 "Dissolution, USP Apparatus 2" See submission volume 9, pp 66-69.

Test Method 1955 "Release Test by ~~the~~ Divalproex Sodium ~~Tablets~~" See submission V9, pp 83-91.

Specifications:

L-1 (6 tablets): 3 hrs NMT ~~_____~~
 9 hrs ~~_____~~
 12 hrs ~~_____~~
 18 hrs NLT ~~_____~~

(If these conditions are not met, test 6 additional tablets)

L-2 (12 tablets): 3 hrs NMT ~~_____~~ (average limits)
 NMT ~~_____~~ (individual limits)
 9 hrs ~~_____~~ (average limits)
~~_____~~ (individual limits)
 12 hrs ~~_____~~ (average limits)
~~_____~~ (individual limits)
 18 hrs NLT ~~_____~~ (average limits)
 NLT ~~_____~~ (individual limits)

(If these conditions are not met, test 12 additional tablets)

L-3 (24 tablets): 3 hrs NMT ~~_____~~ (average limits)
 3 hrs NMT 2 tablets release MT ~~_____~~, and no individual tablet releases MT ~~_____~~
 9 hrs ~~_____~~ (average limits)
 9 hrs NMT 2 tablets are outside the range of ~~_____~~, and no individual tablet MT ~~_____~~
 12 hrs ~~_____~~ (average limits)
 12 hrs NMT 2 tablets are outside the range of ~~_____~~, and no individual tablet is outside the range of ~~_____~~
 18 hrs NLT ~~_____~~ (average limits)
 18 hrs NMT 2 tablets release LT ~~_____~~ and no individual tablet releases LT ~~_____~~

The requirements are met if the results for the 24 individual tablets and the average of the 24 tablets for each time period meet their respective limits.

Evaluation: None. Because N 20-782 has been filed NA by the Division of Pharmaceutical Evaluation I, the dissolution tests and specifications remain subject to review.

An editorial change is needed for Test 1955, reflecting the name change from Depakote ~~_____~~ to Depakote ER.

Table of Contents

Chemistry Review Data Sheet	3
The Executive Summary	5
I. Recommendations	5
A. Recommendation and Conclusion on Approvability	5
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	5
II. Summary of Chemistry Assessments	5
A. Description of the Drug Product and Drug Substance	5
B. Description of How the Drug Product is Intended to be Used	5
C. Basis for Approvability or Not-Approval Recommendation	5
III. Administrative	6
A. Reviewer's Signature	6
B. Endorsement Block	6
C. CC Block	6
Chemistry Assessment	7
I. DRUG SUBSTANCE	7 (Section A)
II. DRUG PRODUCT	7 (Section B)
III. INVESTIGATIONAL FORMULATIONS	Review # 1, p 32
IV. ENVIRONMENTAL ASSESSMENT	Review # 1, p 32
V. METHODS VALIDATION	Review # 2, p 12
VI. LABELING	7 (Section F)
VII. ESTABLISHMENT INSPECTION	7

Chemistry Review Data Sheet

1. NDA # 20-782
2. REVIEW #: 3
3. REVIEW DATE: 16-DEC-2002
4. REVIEWER: Thomas A. Broadbent, Ph.D.
5. PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
Original	16-JUN-1997
Amendment N(BC)	13-OCT-1997
Amendment N(BC)	23-OCT-1997
Amendment N(BC)	29-JAN-1998
Amendment N(GC)	05-FEB-1998
Amendment N(BC)	09-FEB-1998
Review #1	17-APR-1998
Amendment N(BC)	07-OCT-1999
Review # 2	14-OCT-1999
T-Con	27-OCT-1999
T-Con	01-NOV-1999

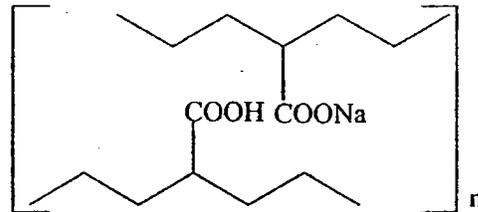
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment AZ	26-JUN-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Abbott Laboratories
Address: 200 Abbott Park Road
D491 AP30
Abbott Park, IL 60064-6157

Representative: Steven Townsend
Telephone: (847) 938-9547



divalproex sodium

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Depakote ER Tablets, 250 & 500 mg
- b) Non-Proprietary Name (USAN): Divalproex Sodium
- c) Code Name/# A-50711
- d) Chem. Type/Submission Priority
Chem. Type = 3
Submission Priority = S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b) of the Federal Food, Drug, and Cosmetic Act

10. PHARMACOL. CATEGORY: anticonvulsant

11. DOSAGE FORM: tablet
12. STRENGTH / POTENCY: 250 and 500 mg (Refer to 21-168 / S-001 (AP 5/31/02) for 250 mg)
13. ROUTE OF ADMINISTRATION: oral
14. Rx / OTC DISPENSED: XXX Rx ___ OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) – Not Applicable
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: sodium hydrogen bis(2-propylvalerate), oligomer

Formula: $(C_{16}H_{31}NaO_4)_n$

Formula Weight: 310.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
—	3	[1	Adequate	10/24/97	Reviewed by Don Klein
—	3			1	Adequate	10/24/97	
—	3			1	Adequate	12/23/97	
—	3			1	Adequate	4/8/98	Reviewed by Don Klein
—	3			1	Adequate	4/8/98	Reviewed by Don Klein
—	3			1	Adequate	3/13/96	Also provided for 18-081 & 18-723

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	36,945	DS/DP development – indication for migraine
IND	47,714	Tablets - Indication for epilepsy
NDA	18-081	Provides valproic acid (drug substance precursor)
NDA	18-723	Provides drug substance (divalproex sodium)
NDA	21-168	Provides drug product (Depakote ER Tablets)

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Not Applicable	--	--
EES	Acceptable	12/13/02	Shirnette Ferguson
Pharm/Tox	Adequate (NDA 21-168)	8/01/00	Ed Fisher
Biopharm	Acceptable	11/26/02	Veneta Tandon
LNC	Adequate	11/3/97 & 4/6/98	Dan Boring
Methods Validation	Adequate	8/22/00	James Brower
OPDRA	Not Applicable	--	--
EA	Categorical exclusion	10/13/97	--
Microbiology	Adequate	4/17/98	Don Klein (chemist)

The Chemistry Executive Summary

I. Recommendations

- A. Recommendation and Conclusion on Approvability**
Recommend approval.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
Not applicable

II. Summary of Chemistry Assessments

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

Drug substance: The drug substance is provided by NDA 18-723. Divalproex sodium is the semisodium salt of valproic acid. The provided systematic name is sodium hydrogen bis(2-propylpentanoate). The sponsor also identifies the substance as sodium hydrogen divalproate (SHD). The substance is a white powder having a characteristic odor. The melting point is 85° C. It is not hygroscopic. The retest period for bulk drug substance is 24 months.

Drug product: Depakote ER tablets are ovaloid in shape with embossed markings for the corporate logo and codes, HF for the 250 mg strength and HC for the 500 mg strength. The 250 mg tablets are white and the 500 mg tablets are gray. (The 250 mg strength tablets are provided by NDA 21-168 / S-001, approved 5/31/02.) This is an extended release product, hence the name "ER." Tablet excipients include FD&C Blue No. 1, hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, polyethylene glycol, potassium sorbate, propylene glycol, silicon dioxide, titanium dioxide, and triacetin. Excipient iron oxide and polydextrose are exclusive to the 500 mg strength. The ingredient hydroxypropyl methylcellulose. Recommended storage: Store tablets at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. The expiration dating of the 250 mg strength is 18 months.

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

Depakote ER Tablets (250 mg & 500 mg) are taken orally once daily. Because it is an extended release product, the tablets should be swallowed whole and not crushed or chewed. The approved indication for Depakote ER is migraine prophylaxis (NDA 21-168). For migraine, the starting dose is 500 mg, then 1000 mg for maintenance. This application provides for use of Depakote ER Tablets for a once-daily dosing regimen for sole and adjunctive therapy for simple and complex absence seizures and as adjunctive therapy for multiple seizure types including absence seizures. An increase in the dose is recommended for patients converting from Depakote DR Tablets (NDA 18-723) to Depakote ER Tablets. The strength of the dose as an anticonvulsant ranges incrementally from 500 mg to 6500 mg.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is the same as that provided in an approved NDA (21-168, approved 04-AUG-00). No significant changes in the labeling related to CMC were submitted. The EER recommends the manufacturing and analysis sites as acceptable. Therefore, approval is recommended.

III. Administrative

- A. Reviewer's Signature** (signature is electronic in DFS.)
- B. Endorsement Block**
In DFS
- C. CC Block**

Thomas Broadbent, CMC Reviewer, HFD-120
Maryla Guzewska, Neurology CMC Team Leader, HFD-120
Jackie Ware, Project Manager, HFD-120

**APPEARS THIS WAY
ON ORIGINAL**

Review Notes – Chemistry Assessment

A. Drug Substance

The drug substance is divalproex sodium. It is provided by NDA 18-723 (approved March 10, 1983). The precursor of divalproex sodium is valproic acid. Valproic acid is provided by NDA 18-081.

Evaluation: Adequate.

B. Drug Product

The drug product is provided by NDA 21-168 (approved August 4, 2000).

Evaluation: Adequate.

F. Labeling

CMC labeling for the product insert and the packaging remain essentially unchanged from that approved in NDA 21-168. Formatting changes (addition of blank lines) have been made in the *How Supplied* section of the insert.

Evaluation: Adequate.

G. Establishment Inspection

The Detroit District Office and the Office of Compliance have recommended all facilities provided in the application as acceptable. See EER report as follows.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

TO: NDA 20-782 Division File
DATE: 22-APR-98
SUBJECT: Supervisory Review of NDA 20-782 for DEPAKOTE® _____ Tablets

Dr. Klein, the chemistry reviewer of NDA 20-782, completed his review listing numerous deficiencies and recommended that this NDA be NOT APPROVED. I concur with his conclusions.

In view of the fact that NDA 20-782 is deemed to be NOT APPROVED by the clinical Division HFD-120 for the lack of equivalence to the already marketed delayed tablets, I recommend that the CMC deficiencies listed in Dr. Klein's review be not included in the Not Approvable letter to be sent to the Applicant.

Since the majority of these deficiencies consist of requests for further clarification of the CMC information, I consider them as minor deficiencies which could be communicated to the Applicant at a later time in the event of a resubmission.


Maryla Guzewska, Ph.D., Chemistry TL

cc: Orig. NDA 20-782
HFD-120/MGuzewska *MG 4.22.98*
HFD-120/DKlein
HFD-120/JWare
HFD-810/JSimmons
HFD-810/CHOiberg

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

/s/

Thomas Broadbent
12/18/02 09:45:41 AM
CHEMIST

Maryla Guzewska
12/18/02 09:52:10 AM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**