

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 20-789**

**CHEMISTRY REVIEW(S)**

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

JAN 29 1998

SUMMARY REVIEW

**NDA 20-789**

REVIEW DATE 28-JAN-98

SUBMISSION TYPE ORIGINAL DOCUMENT DATE 19-MAR-97 CDER DATE 19-MAR-97 ASSIGNED DATE N/A

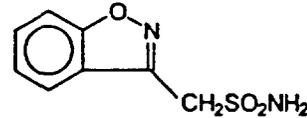
NAME AND ADDRESS OF APPLICANT DAINIPPON Pharmaceuticals, Ltd.  
c/o Athena Neurosciences  
800 Gateway Blvd.  
South San Francisco, CA 94080

DRUG PRODUCT NAME  
Proprietary: Not designated  
USAN [1985]: zonisamide  
Code Name/Number: AD-810, CI-912  
Chem. Type/Ther. Class: 1 S

PHARMACOLOGICAL CATEGORY/INDICATION Anticonvulsant  
DOSAGE FORM Capsules  
STRENGTHS 100 mg  
ROUTE OF ADMINISTRATION Oral  
DISPENSED  RX  OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA  
2-Benzisoxazole-3-methanesulfonamide

C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S Mol. Wt. 212.23  
CAS Registry #: 68291-97-4



SUPPORTING DOCUMENTS: IND [redacted]

RELATED DOCUMENTS: U.S. Patent No. 4,172,896 (Expires June 5, 1998)

CONSULTS: The proposed trademark choices (i.e., Zonegran, Actizure, Promtrol) are currently being evaluated by the CDER Nomenclature and Labeling Committee. The CGMP compliance status of the manufacturing facilities is acceptable as of 02-MAY-97 [redacted]. The MV package needs to be prepared.

REMARKS/COMMENTS: The Biopharmaceutics Division recommends [redacted]

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-789 be APPROVED. The 24 months expiration dating period is acceptable. Recommend that the storage statement in the "How Supplied" section of the labeling be revised to read:

[redacted] We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-789  
HFD-120/Division File  
HFD-120/MGuzewska  
HFD-120/JWare  
HFD-810/CHoiberg  
HFD-810/JSimmcons  
**51**.28.98

**/S/**  
M. Guzewska Ph.D., Chemistry TL (acting)

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

NDA 20-789

CHEM. REVIEW #7

REVIEW DATE 06-DEC-99

SUBMISSION TYPE  
AMENDMENT .N(BL)

DOCUMENT DATE  
24-NOV-99

CDER DATE  
29-NOV-99

ASSIGNED DATE  
30-NOV-99

NAME AND ADDRESS OF APPLICANT

Dainippon Pharrnaceutical U S.A. Corporation  
c/o Elan Pharmaceuticals  
800 Gateway Blvd  
South San Francisco, CA 94080

DRUG PRODUCT NAME

Proprietary: Zonegran™  
Nonproprietary/USAN [1985]: Zonisamide  
Code Name/Number: AD-810, CI-912  
Chem. Type/Ther. Class: 1S

PHARMACOLOGICAL CATEGORY/INDICATION

Anti-Convulsants

DOSAGE FORM

Capsules

STRENGTHS

100 mg

ROUTE OF ADMINISTRATION

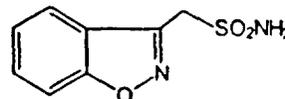
Oral

DISPENSED

XXX RX \_\_\_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

1,2-Benzisoxazole-3-methanesulfonamide  
C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S; Mol. Wt. 212.23; CAS Registry #: 68291-97-4



SUPPORTING DOCUMENTS: DMF

IND

RELATED DOCUMENTS: None

CONSULTS: The proposed trademark "Zonegran" was found acceptable by the CDER Labeling and Nomenclature Committee. The EER was found acceptable June 23, 1999. The MV package is in preparation.

REMARKS/COMMENTS: The sponsor plans to initially market the 100ct [redacted] bottle (100 cc) and the [redacted] blister pack (professional sample). The [redacted] bottle (950 cc) and the [redacted] blister pack will be introduced post-approval. The labels for the [redacted] bottle and the [redacted] blister pack (professional sample) were provided. The labels contain the agreed upon storage statement ("Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature], in a dry place and protected from light") and they provide a spot for the lot # and expiration date. The labels for the 1000ct bottle and the 100ct blister have not been designed yet, however, the sponsor expects a layout similar to the 100ct bottle and 28ct blister. Bottles (100 cc and 950cc) and [redacted] blisters have a 36-month tentative expiration date. The [redacted] blister professional sample has a recommended tentative 18-month expiration date. The recommended dissolution specification is 0 [redacted]

CONCLUSIONS & RECOMMENDATIONS: Recommend approval.

cc: Orig. NDA 20-789  
HFD-120  
HFD-120/TOliver  
HFD-120/JWare  
HFD-120/MGuzewska  
R/D Init by: M.E.

6/126.95

/S/  
Thomas F. Oliver, Ph.D., Chemist

Filename: N20-789.N(BC).04



**Division of Neuropharmacological Drug Products****NDA: 20-789**

Review of Chemistry, Manufacturing, and Controls

**JAN 29 1998**

	<u>Letter Date</u>	<u>Stamp Date</u>	<u>Rec'd by Chemist</u>	<u>Completed</u>
Initial Submission	19-Mar-97	19-Mar-97	28-Mar-97	23-Jun-97
Amendment N(BZ)	27-Mar-97	27-Mar-97	01-Apr-97	23-Jun-97

<b>Chemistry Review</b>	<b>#1</b>	<b>Sponsor</b>	Dainippon Pharmaceuticals Ltd
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<b>Review Chemist</b>	D. Scarpetti	<b>Address</b>	c/o IBRD Rostrum Global Gwynedd Hall, Ste 100 Blue Bell, PA 19422
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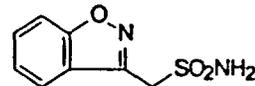
**Product Name**

<b>Proprietary:</b>	no designation at this time
<b>Nonproprietary/USAN:</b>	Zonisamide
<b>Code Name/#:</b>	AD-810, CI-912

**Chemical Name, Structural and Molecular Formula** 1,2-Benzisoxazole-3-methanesulfonamide  
 $C_8H_8N_2O_3$ , MW 212.23

**Dosage Form/Route of Administration**

Gelatin Capsule/Oral

**Pharmacological Category/Indication**

Anticonvulsant

**Supporting Documents**

Type	Number	Subject	Manufacturer	LoA Date
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Type	Number	Subject	Manufacturer	LoA Date
[Empty table area for supporting documents]				

Remarks

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**Conclusions and Recommendations**

Status: NDA 20-789 is approvable with respect to chemistry, manufacturing and controls.

Expiration Dating, Requested 24 months with 18 months submitted in blisters and [redacted] bottles, We agree.

Site Inspections: All sites acceptable with compliance as of 02-May-97.

Environmental Assessment: Still under review as of 23-Jun-97.

Methods Validation: Methods in good shape, will be sent out upon initial sign off of review.

cc:

- Original NDA 20-789
- HFD-120/Division File
- HFD-120/DScarpetti
- HFD-120/JWare
- HFD-120/SWBlum
- Init by: SWB/

*[S]* 1-28-98

*[S]*

David Scarpetti, Chem Reviewer

APPEARS THIS WAY  
ON ORIGINAL

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

JUN 30 1999

NDA 20-789

CHEM. REVIEW #5

REVIEW DATE 25-JUN-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	19-MAR-97	19-MAR-97	
AMENDMENT .N(BZ)	19-AUG-98	20-AUG-98	26-OCT-98
AMENDMENT .N(BL)	28-DEC-98	29-DEC-98	04-JAN-99
AMENDMENT .N(BC)	21-APR-99	23-APR-99	23-APR-99

NAME AND ADDRESS OF APPLICANT

Dainippon Pharmaceutical U.S.A. Corporation  
c/o Elan Pharmaceuticals  
800 Gateway Blvd  
South San Francisco, CA 94080

DRUG PRODUCT NAME

Proprietary: Zonegran™  
Nonproprietary/USAN [1985]: Zonisamide  
Code Name/Number: AD-810, CI-912  
Chem. Type/Ther. Class: 1S

PHARMACOLOGICAL CATEGORY/INDICATION

Anti-Convulsants

DOSAGE FORM

Capsules

STRENGTHS

100 mg

ROUTE OF ADMINISTRATION

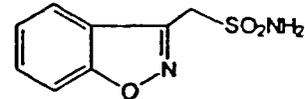
Oral

DISPENSED

XXX RX \_\_\_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

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C<sub>8</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub>S; Mol. Wt. 212.23; CAS Registry #: 68291-97-4



SUPPORTING DOCUMENTS: DMF  
IND. DMF  
RELATED DOCUMENTS: None

CONSULTS: The proposed trademark "Zonegran" was found acceptable by the CDER Labeling and Nomenclature Committee. The EER was found acceptable June 23, 1999.

REMARKS/COMMENTS: The proposed 36-month expiration date was found acceptable for : 100 cc bottles, 950 cc bottles, and blisters. The blister professional sample has a recommended 12-month expiration date. The recommended

CONCLUSIONS & RECOMMENDATIONS: Recommend approval. CMC Input for the Draft Action Letter is as follows: 1) The proposed expiration date of 36 months is acceptable for the drug product packaged in the bottles and blisters. However, it is recommended that the professional sample blisters have an expiration date not to exceed 12 months, based on the provided stability results. This 12 month expiration can be extended, if additional stability data (submitted post-approval) demonstrate comparability to the stability data generated with the blister. 2) The removal of the phrase from the label (as shown in the approvable letter, 5/19/98) is unacceptable for the blister and blister professional sample. The storage should read

The bottles (100 cc and 950 cc)

storage should read

cc: Orig. NDA 20-789  
HFD-120  
HFD-120/TOliver  
HFD-120/JWare  
HFD-120/MGuzewska  
R/D Ini by: MEG

TS/ 6.30.99

/S/  
Thomas F. Oliver, Ph.D., Chemist

Filename: N20-789.N(BZ).02

MAY 17 1999

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

NDA 20-789

CHEM. REVIEW #4

REVIEW DATE 12-MAY-99

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

ORIGINAL  
AMENDMENT .N(BZ)  
AMENDMENT .N(BL)  
AMENDMENT .N(BC)

19-MAR-97  
19-AUG-98  
28-DEC-98  
21-APR-99

19-MAR-97  
20-AUG-98  
29-DEC-98  
23-APR-99

26-OCT-98  
04-JAN-99  
23-APR-99

NAME AND ADDRESS OF APPLICANT

Dainippon Pharmaceutical U.S.A. Corporation  
c/o Elan Pharmaceuticals  
800 Gateway Blvd  
South San Francisco, CA 94080

DRUG PRODUCT NAME

Proprietary: Zonegran™  
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Code Name/Number: AD-810, CI-912  
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PHARMACOLOGICAL CATEGORY/INDICATION

Anti-Convulsants

DOSAGE FORM

Capsules

STRENGTHS

100 mg

ROUTE OF ADMINISTRATION

Oral

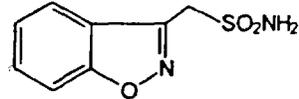
DISPENSED

XXX RX \_\_\_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

1,2-Benzisoxazole-3-methanesulfonamide

C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S; Mol. Wt. 212.23; CAS Registry #: 68291-97-4



SUPPORTING DOCUMENTS

DMF

RELATED DOCUMENTS: None

CONSULTS: Dr. Kooros Mahjoob (FDA) performed a statistical consult on stability data (assay); found acceptable.

Dr. Iftekhar Mahmood (FDA) performed a biopharm consult on dissolution comparability (F<sub>2</sub>); found acceptable.  
EER requested (4/15/99); pending

REMARKS/COMMENTS: The corporate name has changed to "Elan Pharmaceuticals, Inc." in 1999 from Athena Neurosciences, Inc. The sponsor requests a 36-month expiration date (previously requested 24 months). Stability data for three primary batches [redacted] was provided to support the extension. Dr. Mahjoob's analysis of the stability data support the 36-month expiration date. Modifications in the manufacturing have been found acceptable based on the submitted information and an acceptable review by Dr. Mahmood (biopharm). The sponsor has added a new container-closure system (professional sample [redacted] blister) [redacted] for three packaging DMF #'s [redacted] were provided in the submission.

CONCLUSIONS & RECOMMENDATIONS: Recommend that NDA 20-789 is approved contingent upon a satisfactory recommendation from the Office of Compliance [redacted]

[redacted] The proposed 36-month expiration date is acceptable for: 100 cc [redacted] bottles, 950 cc [redacted] bottles, and [redacted] blisters, based upon the supporting stability data. The new container-closure system [redacted] blister professional sample) is acceptable and a 12-month expiration date is recommended. The proposed changes to the label are acceptable for the [redacted] bottles; label will read [redacted]

[redacted] The proposed changes to the label are not acceptable for the [redacted] and professional sample [redacted] blister packages; label should read [redacted]

The recommended dissolution specification [redacted]

cc: Orig. NDA 20-789  
HFD-120  
HFD-120/T Oliver  
HFD-120/JWare  
HFD-120/MGuzewska  
R/D Init by: ME [redacted]

[redacted] 5.17.99

[redacted] TSO/ Thomas F. Oliver, Ph.D., Chemist

Filename: N20-789.N(BZ)