CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020309Orig1s000

Trade Name:	**Magnesium Sulfate in Water for Injection, 40 and 80 mg/mL**
Generic Name:	
Sponsor:	**Abbott Laboratories**
Approval Date:	**June 24, 1994**
Indications:	**For the prevention and control of seizures (convulsions) in severe toxemia of pregnancy**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

APPROVAL LETTER

STOCKER 10 94

NDA 20-309

JUN 24 1994

Abbott Laboratories
Attention: Mr. Frederick A. Gustafson
Hospital Products Division
One Abbott Park Road (D-389 AP30)
Abbott Park, IL 60064-3500

Dear Mr. Gustafson:

Please refer to your October 15, 1992, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Magnesium Sulfate in Water for Injection, 40 mg/mL and 80 mg/mL.

We acknowledge receipt of your amendments dated December 10, 1992; February 11 and 22, 1993; May 25 and October 25, 1993; and February 17, 1994.

This new drug application provides for use as an intravenous anticonvulsant for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on October 25, 1993. Accordingly, the application is approved on this date.

However, we request that the following revision be made to the package insert at the next printing of the labeling or within 6 months from the date of this letter:

> In the package insert, the term **plasma** has been used interchangeably with the term **serum** even though the literature citations refer to **serum**. All references to the word **plasma** should be changed to **serum** to reflect current practice.

This change should be submitted as a "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c) and implemented at the next printing of the package insert or within 6 months, whichever occurs first. Please submit twelve copies (seven mounted on heavy weight paper) of the revised final printed labeling (FPL) when it is available and indicate when the change will be implemented.

In addition, please submit three copies of the introductory promotional material that you propose to use for the product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Dr. Lisa Stockbridge
Consumer Safety Officer
(301) 443-3520

Sincerely yours,

3/9/94

Solomon Sobel, M.D.
Director
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc:
Original NDA
HF-2 (with labeling)
HFC-130/JAllen
HFD-510
HFD-80 (with labeling)
HFD-510/PPrice/DGWu
HFD-240 (with labeling)
HFD-638 (with labeling)
HFD-735 (with labeling)
HFD-510/LStockbridge
Concurrences:EGalliers/3/7/PPrice/RBennett for PCorfman/AJordan/3/8/94/
DWu/YChiu/6/24./94/
Drafted by: SOlmstead/3/4/94/Edited: EGalliers/3/9/94/ft/lp/3/9/94/
N20309AP.001

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

OTHER ACTION LETTER(s)

ORIGINAL

NDA 20-309

MAY 18 1993

Abbott Laboratories
Attention: Mr. Frederick A. Gustafson
Director of Regulatory Affairs
Hospital Products Division
One Abbott Park Road (D-389 AP30)
Abbott Park, IL 60064-3500

Dear Mr. Gustafson:

Reference is made to your new drug application dated October 15, 1992, submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Magnesium Sulfate (b) (4)

We also refer to our correspondence dated February 11, 1993, and your amendments dated December 10, 1992, and February 22, 1993.

We have completed our review and find that the information presented is inadequate and that the application is not approvable under section 505(d)(1) of the Act and 21 CFR 314.125(b) in that the application does not contain bioavailability or bioequivalence data required under Part 320. The specific deficiencies are as follows:

Your application does not meet the criteria for a waiver under 21 CFR 320.22(b)(1)(ii), therefore, your firm must submit literature to support the serum levels referenced in the labeling to satisfy the bioavailability and bioequivalence requirements under 21 CFR 320.

In addition, we have the following manufacturing and quality control deficiencies that must be addressed before the application can be considered for approval:

1. Please provide information regarding source, assay, and storage for the reference standard of the drug substance.

2. Please submit information regarding container/closure system and stability data for the drug substance.

3. Data should be submitted to support your claim on the package insert that the amounts of water permeation and leaching chemical components are very small before the expiration period and do not affect the safety of the drug product.

4. The stability protocol for the drug product should also include tests for color, clarity, and pyrogenicity (to be conducted at the end of the stability testing). Volume loss should also be monitored unless data are provided to show that no significant volume loss occurs within 24 months.

VOL 4 1/1

5. A [redacted] (b) (4) expiration period cannot be granted based on the 3-month accelerated stability data. Moreover, a slight increase in potency has been observed for the samples stored at 40°C for 3 months. Please provide more stability data so that evaluation can be made on whether the product will remain within specification before reaching the [redacted] (b) (4) expiration dating.

6. The product name [redacted] (b) (4) on the carton and vial labels and in the package insert should be changed to "MAGNESIUM SULFATE INJECTION" with the same size lettering for each word.

7. The third and fourth sentence of the fourth paragraph in the DESCRIPTION section of the package insert should be revised to read, "Solutions in contact with the plastic container may leach out certain of its chemical components in very small amounts; however, biological testing was supportive of the safety of the plastic container materials."

In addition, your application did not include a Debarment Certification as required under the Generic Drug Enforcement Act of 1992. Your application must include a certification that you, the applicant, did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) (section 306(a) or (b)), in connection with such application.

Your application also did not include patent information nor did it include an integrated summary of safety and a safety update report required under 21 CFR 314.50(d)(5)(vi).

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other actions under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all deficiencies listed. A partial reply (one which does not address all outstanding deficiencies) will not be processed as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely yours,

/s/ 1/8/93

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-80
HFD-426/JHunt
HFD-500/LRipper
HFD-510/PPrice/PCorfman/DGWu/YYChiu/AJordan
HFD-511/SOlmstead/5/12/93/N20309NA.001
Concurrences: EGalliers/PPrice/PCorfman/DGWu/YYChiu/AJordan/5/17/93

5/18/93

NOT APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

LABELING

Labeling: AZ HFD-510
NDA No: 20309 Rec'd. 11-12-93
Reviewed by: _____

MAGNESIUM SULFATE IN WATER FOR INJECTION

Flexible Plastic Container
For Intravenous Use Only

DESCRIPTION

Magnesium Sulfate in Water for Injection is a sterile, nonpyrogenic solution of magnesium sulfate heptahydrate in water for injection. May contain sulfuric acid and/or sodium hydroxide for pH adjustment. The pH is 4.5 (3.5 to 6.5). It is available in 4% and 8% concentrations. See HOW SUPPLIED section for the content and characteristics of available dosage forms and sizes.

Magnesium Sulfate, USP heptahydrate is chemically designated $MgSO_4 \cdot 7H_2O$, colorless crystals or white powder freely soluble in water.

Water for Injection, USP is chemically designated H_2O.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period.

CLINICAL PHARMACOLOGY

Magnesium (Mg^{++}) is an important cofactor for enzymatic reactions and plays an important role in neurochemical transmission and muscular excitability.

Magnesium prevents or controls convulsions by blocking neuromuscular transmission and decreasing the amount of acetylcholine liberated at the end plate by the motor nerve impulse. Magnesium is said to have a depressant effect on the central nervous system, but it does not adversely affect the mother, fetus or neonate when used as directed in eclampsia or pre-eclampsia. Normal plasma magnesium levels range from 1.3 to 2.1 mEq/liter.

As plasma magnesium rises above 4 mEq/liter, the deep tendon reflexes are first decreased and then disappear as the plasma level approaches 10 mEq/liter. At this level respiratory paralysis may occur. Heart block also may occur at this or lower plasma levels of magnesium.

Magnesium acts peripherally to produce vasodilation. With low doses only flushing and sweating occur, but larger doses cause lowering of blood pressure. The central and peripheral effects of magnesium poisoning are antagonized to some extent by intravenous administration of calcium.

With intravenous administration the onset of anticonvulsant action is immediate and lasts about 30 minutes. Following intramuscular administration the onset of action occurs in about one hour and persists for three to four hours. Effective anticonvulsant serum levels range from 2.5 to 7.5 mEq/liter. Magnesium is excreted solely by the kidney at a rate proportional to the plasma concentration and glomerular filtration.

INDICATIONS AND USAGE

Magnesium Sulfate in Water for Injection is indicated for use as an intravenous anticonvulsant for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy. When used judiciously it effectively prevents and controls the convulsions of eclampsia without producing deleterious depression of the central nervous system of the mother or infant. However, other effective drugs are available for this purpose.

CONTRAINDICATIONS

Intravenous magnesium should not be given to mothers with toxemia of pregnancy during the two hours preceding delivery.

WARNINGS

Intravenous use in eclampsia should be reserved for immediate control of life-threatening convulsions.

Parenteral use in the presence of renal insufficiency may lead to magnesium intoxication.

PRECAUTIONS

Because magnesium is removed from the body solely by the kidneys, the drug should be used with caution in patients with renal impairment. Urine output should be maintained at a level of 100 mL every four hours. Monitoring serum magnesium levels and the patient's clinical status is essential to avoid the consequences of overdosage in toxemia. Clinical indications of a safe dosage regimen include the presence of the patellar reflex (knee jerk) and absence of respiratory depression (approximately 16 breaths or more/minute). Serum magnesium levels usually sufficient to control convulsions range from 3 to 6 mg/100 mL (2.5 to 5 mEq/liter). The strength of the deep tendon reflexes begins to diminish when serum magnesium levels exceed 4 mEq/liter. Reflexes may be absent at 10 mEq magnesium/liter, where respiratory paralysis is a potential hazard. An injectable calcium salt should be immediately available to counteract the potential hazards of magnesium intoxication in eclampsia.

Magnesium Sulfate in Water for Injection should be administered slowly to avoid producing hypermagnesemia.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with solutions from flexible plastic containers have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy Category A. Studies in pregnant women have not shown that magnesium sulfate injection increases the risk of fetal abnormalities if administered during all trimesters of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. However, because studies cannot rule out the possibility of harm, magnesium sulfate solution should be used during pregnancy only if clearly needed.

When administered by continuous intravenous infusion (especially for more than 24 hours preceding delivery) to control convulsions in toxemic mothers, the newborn may show signs of magnesium toxicity, including neuromuscular or respiratory depression. See OVERDOSAGE.

Nursing Mothers: Caution should be exercised when solutions from flexible plastic containers are administered to a nursing mother.

Pediatric Use: Safety and effectiveness of solutions from flexible plastic containers in children have not been well established.

ADVERSE REACTIONS

The adverse effects of parenterally administered magnesium usually are the result of magnesium intoxication. These include flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and central nervous system depression proceeding to respiratory paralysis.

Hypocalcemia with signs of tetany secondary to magnesium sulfate therapy for eclampsia has been reported.

OVERDOSAGE

Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. Disappearance of the patellar reflex is a useful clinical sign to detect the onset of magnesium intoxication. In the event of overdosage artificial ventilation must be provided until a calcium salt can be injected intravenously to antagonize the effects of magnesium.

In adults intravenous administration of 5 to 10 mEq of 10% calcium gluconate will usually reverse respiratory depression or heart block due to magnesium intoxication. In extreme cases, peritoneal or hemodialysis may be required.

Hypermagnesemia in the newborn may require resuscitation and assisted ventilation via endotracheal intubation or intermittent positive pressure ventilation as well as intravenous calcium.

DOSAGE AND ADMINISTRATION

Magnesium Sulfate in Water for Injection is intended for intravenous use only. For the management of pre-eclampsia or eclampsia, intravenous infusions of dilute solutions of magnesium (1% to 8%) are often given in combination with intramuscular injections of 50% Magnesium Sulfate Injection, USP. Therefore, in the clinical conditions cited below, both forms of therapy are noted, as appropriate.

In Eclampsia

In severe pre-eclampsia or eclampsia, the total initial dose is 10 to 14 g of magnesium sulfate. To initiate therapy, 4 g of *Magnesium Sulfate in Water for Injection* may be administered intravenously. The rate of I.V. infusion should generally not exceed 150 mg/minute, or 3.75 mL of a 4% concentration (or its equivalent) per minute, except in severe eclampsia with seizures. Simultaneously, 4 to 5 g (32.5 to 40.6 mEq) of magnesium sulfate may be administered intramuscularly into each buttock using undiluted 50% Magnesium Sulfate Injection, USP. After the initial I.V. dose, some clinicians administer 1-2 g/hour by constant I.V. infusion.

Subsequent intramuscular doses of 4 to 5 g of magnesium sulfate may be injected into alternate buttocks every four hours, depending on the continuing presence of the patellar reflex, adequate respiratory function, and absence of signs of magnesium toxicity. Therapy should continue until paroxysms cease.

A serum magnesium level of 6 mg/100 mL is considered optimal for control of seizures. A total daily (24 hr) dose of 30 to 40 g magnesium sulfate should not be exceeded. In the presence of severe renal insufficiency, frequent serum magnesium concentrations must be obtained and the maximum dosage of magnesium sulfate is 20 g per 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not administer unless solution is clear. Discard unused portion.

HOW SUPPLIED

Magnesium Sulfate in Water for Injection is supplied in single-dose flexible plastic containers as follows:

		Total/Container			
List No.	**Size Container**	**Magnesium Sulfate****	**Magnesium Ion**	**Magnesium Sulfate** Concentration**	**Osmolarity mOsmol/Liter (calc.)**
6729	100 mL	4 g	32.5 mEq	4% (40 mg/mL)	325
6730	50 mL*	4 g	32.5 mEq	8% (80 mg/mL)	649

*Partial fill container 50 mL volume in 100 mL container.

** As the heptahydrate.

WARNING: DO NOT USE FLEXIBLE CONTAINER IN SERIES CONNECTIONS.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C/77°F); however, brief exposure up to 40°C does not adversely affect the product.

Caution: Federal (USA) law prohibits dispensing without prescription.

RAO4779-R2-Rev. June, 1993

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Labeling: AZ HFD-80
NDA No: 20209 Rec'd. 11/12/93
Reviewed by: _____

50 mL NDC 0074-6730-13

MAGNESIUM SULFATE

IN WATER FOR INJECTION

80 mg/mL **4g** TOTAL

EACH 50 mL CONTAINS MAGNESIUM SULFATE HEPTAHYDRATE 4 g (EQUIVALENT TO 32.5 mEq MAGNESIUM) IN WATER FOR INJECTION. MAY CONTAIN SULFURIC ACID AND/OR SODIUM HYDROXIDE FOR pH ADJUSTMENT. pH 4.5 (3.5 TO 6.5). 649 mOsmol/LITER (CALC.). SINGLE-DOSE CONTAINER. DISCARD UNUSED PORTION. FOR I.V. USE. USUAL DOSAGE: SEE INSERT. STERILE, NONPYROGENIC. USE ONLY IF SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED. MUST NOT BE USED IN SERIES CONNECTIONS. RECOMMENDED STORAGE: ROOM TEMPERATURE (25°C). AVOID EXCESSIVE HEAT. PROTECT FROM FREEZING. CAUTION: FEDERAL (USA) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

 RA04800-R3-8/93 PRINTED IN USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

One Unit

TO OPEN – TEAR AT NOTCH

Drug additives should not be made to the solution. The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when pouch is opened. Recommended storage: Room temperature (25° C). Avoid excessive heat. Protect from freezing. See insert. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

Caution: Federal (USA) law prohibits dispensing without prescription.

50-3532-R5-7/91

ABBOTT LABORATORIES, NORTH CHICAGO, IL60064, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

MEDICAL REVIEW(S)

O/m STEAD

FEB 10 199?

Medical Officer's Original Summary of NDA 20-309

NDA 20-309

Applicant: Abbott Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

Submission Date: November 11, 1993

1 General Information:

a. Name of Drug:

(1) Generic: Magnesium Sulfate Heptahydrate Solution

(2) Trade: Magnesium Sulfate in Water for Injection

b. Pharmacologic Category: Intracellular cation

c. Proposed Clinical Use: Treatment of Preeclampsia/Eclampsia

d. Dosage form and route of administration: Magnesium sulfate heptahydrate 4 g (equivalent to 32.5 mEq Magnesium) in water for injection

e. Related drugs: Other CNS depressants/electrolyte replenishers

2 Manufacturing Control Data: See Chemist review

3 Pharmacology Review: See Pharmacologist review

4 Biopharmaceutics Review: See Biopharmaceutic review

5 Clinical Background:

This NDA was originally filed on October 15, 1992. The purpose of submitting an NDA was that the firm was changing from a glass container to a PVC flexible container. During a December 3, 1992 meeting it was concluded the application was acceptable to file. However, the application not did meet criteria for a waiver of the biopharm regulations because the magnesium sulfate currently on the market was not the subject of an approved NDA; it was marketed prior to 1938. In a letter dated February 11, 1993, Abbott was informed that a literature search would be required to support serum levels referenced in the labeling.

In a letter dated May 18, 1993, Abbott was again informed that their application did not meet criteria for a waiver under 21 CFR 320.22 (b) (ii), and that they must submit literature to support the serum levels referenced in the labeling to satisfy the bioavailability and bioequivalence requirements under 21 CFR 320. Additionally, chemistry deficiencies were also listed.

On October 25, 1993, Abbott responded to the our May 18, 1993 letter and submitted data to support the serum data referenced in the labeling. Dr. Hae-

Young Ahn of our Biopharm division, reviewed serum data submitted to support the firm package insert. She found this data to be acceptable, but stated the package insert should delete references to plasma levels.

In addition, a literature search was provided of studies in the U.S. from 1983 to 1993. Multiple literature reviews showed, as expected, that this product is safe and effective for the labeled indication. This reviewer agrees that magnesium sulfate is the reference product for the treatment of preeclampsia/eclampsia in pregnancy not only in the U.S. but for most of the world.

6 Labeling:

The clinical pharmacology section is now upgraded and adequate references are provided to document serum levels of magnesium sulfate. The **Indications and Usage** section, the **Contraindications** section, and the **Warning** section are satisfactory. The **Precautions** section has been upgraded and references provided for therapeutic levels of magnesium sulfate. The section, **Overdosage**, under **Adverse Reactions**, is very good and provides excellent information in the treatment of hypermagnesemia.

7 Conclusion:

Referenced articles provided are now sufficient to support approval of this NDA.

8 Recommendation:

This NDA is approvable from the clinical viewpoint.

Phill H. Price, M.D.
2/9/94

2.9.94

cc. IND/NDA
HFD-340
HFD-510 (NDA/IND)
HFD-510/PPrice/PCorfman/WpFiles:20309mor.nda

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

CHEMISTRY REVIEW(S)

Olmstead

FEB 23 1994

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-309 **Review #:** 2 **Date Reviewed:** 2/23/94

Submission Type	Document Date	CDER Date	Assigned Date
Original	10/21/92		
Amendment	10/25/93		

Name & Address Of Applicant: Abbott Laboratories
One Abbott Park Road
Illinois 60064

ORIGINAL

Drug Product Name
Proprietary:
Established: Magnesium Sulfate in Water for Injection
Code Name/#:
Chem. Type/Ther. Class: SVP

ANDA Suitability Petition/DESI/Patent Status: N/A
Pharmacol. Category/Indication: Anticonvulsant
Dosage Form: Injection
Strengths: 40 mg/mL and 80 mg/mL
Route Of Administration: Intravenous
Dispensed: X Rx ____ OTC
Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

$MgSO_4.7H_2O$, Mol. Wt. 120.38

Remarks:

The amendment of 10/25/93 provides for response to chemistry deficiencies outlined in Chem. Rev. #1 and communicated to the applicant in an FDA letter dated 2/11/93.

Conclusions & Recommendations:
All the chemistry deficiencies and information requests have been addressed. From chemistry standpoint, this NDA is now approvable, pending an acceptable FUR. Method validation for assay is not required because the procedure is a USP method.

Org. NDA 20-309
HFD-510
HFD-510/D.G.Wu/
HFD-510/S. Olmstead
HFD-510/Y.Chiu
HFD-102/C.Kumkumian
R/D Init by : Y Chiu 2/28/94

Duu-Gong Wu, Ph.D.
Review Chemist
Filename: 20309.ND2

SUPPORTING DOCUMENTS:
DMF 931(Abbott Laboratories, Type III, (b) (4)), DMF 1218(Abbott Laboratories, Type I)

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

5 Pages have been Withheld in Full Immediately Following this Page as B4 (CCI/TS)

[redacted]

MAR 1 2 1993

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510 Olmstead
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-309 Date Reviewed: 3/11/93
Review #: 1 Reviewer: Duu-Gong Wu

Submission Type	Document Date	CDER Date	Assigned Date
Original	10/21/92	10/21/92	11/6/92
Amendment	2/22/93	3/4/93	

Name & Address Of Applicant: Abbott Laboratories
One Abbott Park Road
Illinois 60064

Drug Product Name
Proprietary:
Established: Magnesium Sulfate (b) (4)
Code Name/#:
Chem. Type/Ther. Class: SVP
ANDA Suitability Petition/DESI/Patent Status: N/A
Pharmacol. Category/Indication: Anticonvulsant
Dosage Form: Injection
Strengths: 40 mg/mL and 80 mg/mL
Route Of Administration: Intravenous
Dispensed: X Rx ____ OTC
Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

$MgSO_4.7H_2O$, Mol. Wt. 120.38
Remarks:

The subject drug is currently marketed by Abbott Laboratories in glass containers in the same concentrations and volumes as proposed in this application. Abbott Laboratories is filing this NDA to package the product in PVC plastic containers according to 21 CFR 310.509, which requires an NDA for any parenteral drug packaged in a plastic container. The finished product will be either a 50 mL fill or 100 mL fill and packaged in flexible 100 mL PVC containers in a 1:1 overwrap configuration. Magnesium sulfate has been used as an intravenous anticonvulsant for the prevention and control of seizures in severe toxemia of pregnancy. The firm stated that PVC container is currently approved in more than sixty NDAs in HFD-160, HFD-530, and HFD-630. The safety and efficacy of the PVC material from which the finished container is fabricated have been well established in preclinical and clinical studies. Abbott has authorized FDA to reference **NDA 16-366** and **NDA 16-367** in HFD-160 for data and Abbott's **DMF 931** for full information on the container formulations, and manufacturing procedure. In a telephone inquiry on 2/19, Abbott referred to a recently approved NDA 20-161 (Potassium Chloride) for most updated information regarding chemistry and microbiology for the PVC container with identical size and configuration. The cross-reference letter dated 2/22/93 has been received on 3/4/93.

Conclusions & Recommendations:
The NDA will become approvable when a number of minor chemistry deficiencies are responded or corrected. Refer to draft letter for detailed comments.

Org. NDA 20-309
HFD-510
HFD-510/D.G.Wu/
HFD-510/E. Galliers
HFD-510/Y. Chiu
HFD-102/C.Kumkumian

Duu-Gong Wu, Ph.D.
Review Chemist Filename: 20309.ND1

R/D Init by: YChiu 3/12/93

SUPPORTING DOCUMENTS:
NDA 16-366, NDA 16-367, DMF 931(Abbott Laboratories, Type III, (b) (4)
(b) (4)), DMF 1218(Abbott Laboratories, Type I)

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

15 Pages have been Withheld in Full Immediately Following this Page as B4 (CCI/TS)

cc:
HFD-324 ICEB R/F
HFD-324 EER File
HFD-510 Duu-Gong Wu
3/8/94:vsp
VERA'S DISK
15214.FUR:March 7,1994

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

03-FEB-94
Dictated

NDA 20-309
Magnesium Sulfate (b) (4)
40 and 80 mg/mL in Flexible Containers

SUBMISSION DATE: October 25, 1993

Abbott Laboratories
Abbott Park, IL

REVIEWER: Hae-Young Ahn, Ph.D.

TYPE OF SUBMISSION: Amendment

Code: 5S

SYNOPSIS: The sponsor submitted an original NDA for changing from a glass container to a PVC flexible container on 10/15/1992. The application did not meet the criteria for a waiver of in vivo bioavailability under 21 CFR 320.22(b) (1) (ii), because the magnesium sulfate product that is currently on the market was not the subject of an approved NDA. It was marketed prior to 1938. Literature to support the serum levels referenced in the labeling was requested in order to meet the biopharm regulations. A nonapprovable letter was sent to the sponsor by the Division of Metabolism and Endocrine Drug Product on May 18, 1993. The sponsor has now submitted an amendment with the literature information to support the serum levels referenced in the labeling.

RECOMMENDATION:
The Division of Biopharmaceutics has reviewed the Amendment to NDA 20-309 which was submitted on October 25, 1993 and finds it acceptable to support the NDA's approval by providing information to document the package insert's drug levels. However, Comment #1 should be communicated to the sponsor.

Please convey the Recommendation and Comment #1 to the sponsor.

COMMENTS:
1. In the package insert in some sentences the term plasma has been used for the term serum even though the literature citations indicate serum. Since for magnesium sulfate levels, serum is used in current practice, the package insert should be corrected to reflect the serum levels.

Haeyoung Ahn 1/31/94

Hae-Young Ahn, Ph.D.
Reviewer, Division of Biopharmaceutics

RD initiated by J. Hunt 1/28/94
Biopharm Day 1/31/94 (Ludden, Malinowski, Fleischer, Hepp, Miller, and Hunt)
FT initiated by J. Hunt J. Hunt 2/1/94

cc: NDA 20-309, HFD-510, HFD-340 (Vish), HFD-426 (Ahn, Fleischer), Chron, Drug, Review, FOI (HFD-19)

SEP 21 1993

NDA 20-309
Magnesium Sulfate (b) (4)
40 and 80 mg/mL in Flexible Containers

SUBMISSION DATE: October 15, 1992

Abbott Laboratories
Abbott Park, IL

REVIEWER: Hae-Young Ahn, Ph.D.

TYPE OF SUBMISSION: Original NDA

SYNOPSIS: Magnesium sulfate is an intravenous anticonvulsant indicated for the prevention and control of seizures in severe toxemia of pregnancy. The sponsor has submitted an original NDA for changing container from glass container to the PVC flexible container. The application did not meet the criteria for a waiver of in vivo bioavailability under 21 CFR 320(b) (1) (ii), because the magnesium sulfate currently on the market was not the subject of an approved NDA, since it was marketed prior to 1938. Literature to support the serum levels referenced in the labeling was requested to meet biopharm regulation. A nonapprovable letter was sent to the sponsor by the Division of Endocrine and Metabolism (stamp dated on May 18, 1993). Therefore, further review is not necessary.

Hae-Young Ahn 9/20/93

Hae-Young Ahn, Ph.D.
Reviewer, Division of Biopharmaceutics

RD initiated by J. Hunt for MDA 9/20/93

FT initiated by J. Hunt for MDA 9/20/93

cc: NDA 20-309, HFD-510, HFD-340 (Vish), HFD-426 (Ahn, Fleischer), Chron, Drug, Review, FOI (HFD-19)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

PHARMACOLOGY REVIEW(S)

Olmstead

MAR 10 1993

NDA 20-309

March 10, 1993

Abbott Labs Inc.
Abbott Park, Ill.

Submitted: Oct. 21, 1992

Pharmacology Review of NDA

Drug: Magnesium sulfate

Indication: anticonvulsant for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy.

This drug is currently approved for this indication; The reason for the new NDA is for the change from glass to PVC flexible containers. The PVC containers are approved in over 60 NDA's in HFD-160, -530, and -630. The same plastic was approved in NDA 20-161.

Conclusion: Pharmacology recommends approval of NDA 20-309.

A Jordan

Alex Jordan, PhD

Orig. NDA 20-309
HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020309Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION

1. Active Ingredient(s): Magnesium Sulfate

2. Strength(s): 40 mg/mL and 80 mg/mL

3. Trade Name: Magnesium Sulfate in Water for Injection

4. Dosage Form: Liquid in Flexible Plastic Container

5. Route of Administration: Intravenous

6. Applicant Firm Name: Abbott Laboratories

7. NDA Number: 20-309

8. Approval Date: To be determined.

9. Exclusivity - Date first ANDA could be approved and length of exclusivity period:

   Not applicable

10. Applicable patent numbers and expiration date of each: Not applicable.

Frederick A. Gustafson 10/25/93

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division
Abbott Laboratories

Date

EXCLUSIVITY SUMMARY FOR NDA # 20-309 SUPPL #_____

Trade Name (none) Generic Name Magnesium Sulfate in Water for Injection

Applicant Name Abbott HFD # 510

Approval Date If Known 6-24-94

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /✓/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 7-90

cc: Original NDA Division File HFD-85 Mary Ann Ward HFD 510/Gail Stockbridge/Stockbridge

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-316 _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_✓_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ 3/4/94
Signature Date
Title: CSO

_____ 3/9/94
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-85 Mary Ann Ward

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-309 Trade (generic) names magnesium sulfate (b) (4)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Sharon Olmstead — 5/13/93

Signature of Preparer — Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Exhibit XII

Debarment Certification

We include a signed certification statement as required under the Generic Drug Enforcement Act of 1992, Section 306(k) (1) of the act (21 USC 335a(k) (1)). We also include a response to the request for a list of relevant convictions.

CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS

FOR APPROVAL OF A DRUG PRODUCT

Under the new law, any application for approval of a drug product submitted on or after June 1, 1992, must include:

> "a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application."

Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

Frederick A. Gustafson — 10/25/93 (Date)
Director, Regulatory Affairs
Hospital Products Division
Abbott Laboratories
North Chicago, Illinois

LIST OF RELEVANT CONVICTIONS FOR PERSONS DEBARRED OR NOT DEBARRED

Per letter from the Office of Generic Drugs dated January 15, 1993, abbreviated applications must contain a list of relevant convictions, as described in section 306(a) and (b) of the GDEA*, of the applicant and affiliated persons (i.e. contractors, et. al.) responsible for the development or submission of the application, which have occurred within five years before the date of the application. Firms with no convictions to list should submit a statement to that effect.

Abbott Laboratories states that it has no such convictions to list.

- Generic Drug Enforcement Act of 1992
  Section 306(k) (1) of the act (21 USC 335a(k) (1)).

Frederick A. Gustafson — 10/25/93
Frederick A. Gustafson — Date
Director, Regulatory Affairs
Hospital Products Division
Abbott Laboratories
North Chicago, Illinois

ABBOTT

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

May 13, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

GENERAL CORRESPONDENCE

RE: NDA 20-309 Magnesium Sulfate (b) (4) 40 mg/mL and 80 mg/mL in Flexible Containers

Preapproval inspection for the above referenced products is currently underway at our North Chicago, Illinois, manufacturing facility. Abbott hereby submits additional information as requested by FDA field inspector Susan Bruederle. Ms. Bruederle noted that our raw material specification for Magnesium Sulfate, USP (Heptahydrate), Drug Code 43748, lists (b) (4) . However, production stability batches manufactured in support of this submission used *only* Magnesium Sulfate, USP (Heptahydrate) sourced from (b) (4) Ms. Bruederle indicated that she would approve the use of (b) (4) only for these products. She further requested that we provide documentation to insure that this would be done.

Accordingly, we have established a *new drug code*, Code 42267, for Magnesium Sulfate, USP (Heptahydrate). Code 42267 is *identical* to Code 43748 except that (b) (4) is listed as the sole supplier. A copy of our specifications for Code 42267 is appended in Exhibit I. The qualitative composition for the subject products has been revised to indicate Code 42267, and is appended in Exhibit II.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division
Phone: (708) 937-3213
Fax: (708) 938-7867
5-94fda.jxn

11 Pages have been Withheld in Full Immediately Following this Page as B4 (CCI/TS)

ABBOTT

Hospital Products Division

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

BC

ORIG AMENDMENT

February 17, 1994

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

GENERAL CORRESPONDENCE

RE: NDA 20-309 Magnesium Sulfate (b) (4) 40 mg/mL and 80 mg/mL in Flexible Containers

Abbott hereby submits additional information as requested in a telephone conversation held on February 15, 1994, between Dr. Duu-Gong Wu of the Administration and Jill Nicholson of Abbott Laboratories.

First, we were asked to provide additional data supporting the long term shelf life of the subject drugs. Appended in Exhibit I are updated stability data for two production lots of the subject drugs. Data are now available through (b) (4) and fully support an (b) (4) shelf life for the products. Appended in Exhibit II are stability data for currently marketed sodium chloride and dextrose diluent products which *use the same packaging as the subject drugs*. These data have already been supplied to the Administration via Annual Progress Reports, and serve to further support an (b) (4) shelf life for the subject drugs.

Second, we were asked to provide additional information regarding the lack of a reference standard for the determination of magnesium potency. The response from our Analytical Chemist is as follows:

> "Magnesium Sulfate Injection, List Nos. 6729 and 6730, are solutions of magnesium sulfate in water. The potency is determined by titration (b) (4). The (b) (4) is a USP volumetric solution and is standardized by the normal USP procedure which uses (b) (4) as the reference standard. The identity of both the magnesium and sulfate are determined by the normal USP identity tests for these two ions. These identity tests, when combined with the potency test, insure the quality and identity of the product, and a magnesium sulfate reference standard is not required."

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES
Frederick A. Gustafson
Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division
Phone: (708) 937-3213
Fax: (708) 938-7867

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

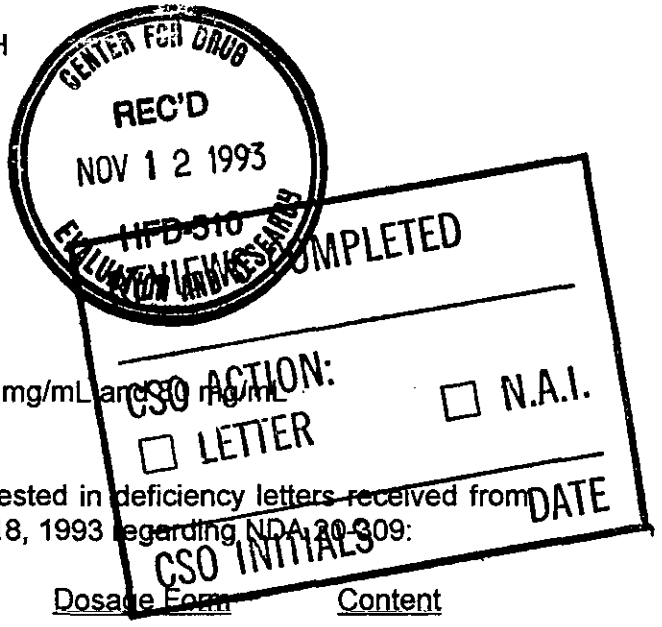
AZ

ABBOTT

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

ORIGINAL

October 25, 1993



CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

RE: NDA 20-309 Magnesium Sulfate (b) (4) 40 mg/mL and 80 mg/mL in Flexible Containers

Abbott hereby submits additional information as requested in deficiency letters received from the Administration dated February 11, 1993 and May 18, 1993 regarding NDA 20-309:

List Number	Product	Dosage Form	Content
6729	Magnesium Sulfate (b) (4)	100 mL Flexible Container	40 mg/mL
6730	Magnesium Sulfate (b) (4)	50 mL in 100 mL Flexible Container	80 mg/mL

The letter dated February 11, 1993 requested that we submit literature to support the serum levels referenced in the labeling, in order to meet the bioavailability and bioequivalence requirements under 21 CFR 320.

The letter also stated "although the magnesium sulfate currently marketed in plastic containers was the subject of a full NDA, it is not the same concentration as your product. Therefore your pending application does not meet the criteria for a waiver under 21 CFR 320.22(b)(1)(ii)."

These issues were reiterated in the letter dated May 18, 1993, which stated "your application does not meet the criteria for a waiver under 21 CFR 320.22(b)(1)(ii), therefore, your firm must submit literature to support the serum levels referenced in the labeling to satisfy the bioavailability and bioequivalence requirements under 21 CFR 320."

We assume the full NDA to which you are referring is that for Lyphomed's (b) (4)®, NDA 19-316. (b) (4) is a concentrated small volume parenteral product, which is indicated for both eclampsia and hypomagnesemia. A variety of dosages for both intramuscular and intravenous administrations are listed in its enclosure, which is supplied in Exhibit I. However, the Abbott products which are the subject of this submission, are indicated *only* for intravenous use in eclampsia. It would therefore be appropriate to restrict our comparison to the dosage described in the (b) (4) insert for intravenous administration in eclampsia.

We acknowledge the fact that the concentrations of our premixed magnesium sulfate solutions (40 mg/mL and 80 mg/mL) are not the same as Lyphomed's (b) (4) (500 mg/mL). However, Lyphomed's enclosure recommends that their small volume parenteral product be diluted prior to administration. The Abbott products, as premixes, require no dilution. *Both* (b) (4) and Abbott products recommend an initial loading dose of 4 grams. *Both* (b) (4) *and Abbott products recommend the same maximum infusion rate, i.e. 150 mg/minute.* Hence, the actual amount of drug being delivered to the patient over time, as well as the total amount delivered, is identical for the indication requested. This relationship is depicted in the chart provided in Exhibit II.

Furthermore, data show that *regardless* of the initial admixed concentration of magnesium sulfate, after intravenous infusion, final blood levels are essentially equivalent. Exhibit III provides a general discussion on the definition and determination of fluid spaces within the human body and the apparent distribution space determined for magnesium sulfate. A comparison of final blood levels of magnesium after distribution may thus be made for the diluted (b) (4) and Abbott premixed products; *these blood levels are essentially identical.*

Lastly, we provide literature references, as requested, to support each of the serum levels mentioned in our package insert. A copy of our newly revised insert is provided in Exhibit IV, with the literature references provided alongside. Magnesium sulfate has been used for the *treatment of eclampsia for many years; the serum levels referenced in our insert are listed as* standard values in textbooks.

We trust that the foregoing discussion and information provided in Exhibits I - IV clearly demonstrate that these simple, aqueous solutions may be considered bioequivalent for the *indication requested.*

The deficiency letter dated May 18, 1993, also contained the following requests:

Request 1: Please provide information regarding source, assay and storage for the reference standard of the drug substance.

Response 1: There is no reference standard for the potency assay for magnesium sulfate. The assay is a simple titration (b) (4) (b) (4) As such, there is no information regarding source, assay and storage of a reference standard for the drug substance.

Request 2: Please submit information regarding container/closure system and stability data for the drug substance.

Response 2: Magnesium sulfate heptahydrate is the hydrated form of magnesium sulfate, an inorganic salt. The sulfate is the fully oxidized form of this salt, and is not expected to degrade significantly. Storage specifications have been established for this drug substance. The material is to be stored in a well-closed container. Stability data for representative lots of this substance have been gathered by the bulk drug vendor and are presented in Exhibit V. The data show no potency changes or changes in loss on ignition testing for this product after long term storage.

Request 3: Data should be submitted to support your claim on the package insert that the amounts of water permeation and leaching chemical components are very small before the expiration period and do not affect the safety of the drug product.

Response 3: The amount of water loss experienced by the subject products is very small due to the utilization of (b) (4) foil overwraps. (b) (4) The label copy on the overwrap reminds the customer to store the product in the overwrap until ready for use. A copy of this overwrap labeling is presented in Exhibit VI.

(b) (4)

Abbott Laboratories hereby authorizes the Administration to refer to Drug Master File 931 on behalf of this submission.

Request 4: The stability protocol for the drug product should also include tests for color, clarity, and pyrogenicity (to be conducted at the end of the stability testing). Volume loss should also be monitored unless data are provided to show that no *significant volume loss occurs* (b) (4).

Response 4: Our long term experience with magnesium sulfate injectable solutions formulated at up to 50% (500 mg/mL) concentration is that such solutions remain colorless throughout their shelf life. (b) (4). Although not a compendial requirement, solution color was monitored for informational purposes on production lots 64-777-JE and 64-778-JE manufactured and placed on accelerated stability studies. Color was checked at *every* room temperature (25°C) and elevated temperature (40°C) test interval; all test results indicated (b) (4) We therefore feel that routine testing of this product for color is unwarranted.

Response 4: (continued) The marketed product stability protocols for the drug products, as supplied in the original submission (p. 1-342) already included a test for clarity, noted as "Physical Appearance." The protocols have, however, been updated to include tests for pyrogen and fill volume. The updated protocols, along with copies of the test methods for physical appearance, pyrogen and fill volume, are appended in Exhibit VII.

Request 5: A (b) (4) expiration period cannot be granted based on the 3-month accelerated stability data. Moreover, a slight increase in potency has been observed for the samples stored at 40°C for 3 months. Please provide more stability data so that evaluation can be made on whether the product will remain within specification before reaching the (b) (4) expiration dating.

Response 5: Magnesium sulfate solutions remain very stable over their shelf life. Potency may increase slightly over time since the subject products are packaged in flexible plastic containers which allow for a small amount of water loss. As discussed in response (3) above, the amount of water loss experienced by the subject products under normal storage conditions is very small due to the utilization of (b) (4) foil overwraps. (b) (4) However, this increase in potency may be more noticeable after prolonged storage at elevated temperatures (40°C).

Additional stability data on the two production lots are provided in Exhibit VIII for review. These data continue to support a (b) (4) expiration dating period for these products.

Request 6: The product name (b) (4)" on the carton and vial labels and in the package insert should be changed to "MAGNESIUM SULFATE INJECTION" with the same size lettering for each word.

Response 6: This request will be addressed in two parts.

Regarding the product name:
The product name requested by the Administration, "MAGNESIUM SULFATE INJECTION," is the official USP monograph title for injectable magnesium sulfate solutions. The General Notices section of USP XXII, <p. 2>, states:

> "The designation USP in conjunction with the official title on the label of an article is a reminder that the article purports to comply with USP standard...The standards apply equally to articles bearing the official titles or names...whether or not the added designation 'USP' is used."

Thus, if we were to adopt the title "MAGNESIUM SULFATE INJECTION," for the subject drug products, with or without the added designation "USP," we would be required to meet all of the specification limits listed in the USP for Magnesium Sulfate Injection, USP.

Response 6: (continued) The subject drug products, however, *do not* meet all of the specifications listed in the corresponding USP monograph. Our product pH range (3.5 to 6.5) is different from that listed in the USP monograph (5.5 to 7.0). This specific issue was discussed between reviewing chemist Dr. Duu-Gong Wu of the Administration and Ms. Jill Nicholson of Abbott Laboratories on March 11, 1993 [redacted (b) (4)] l. The subject drug remains well within its established pH range of 3.5 to 6.5. This pH range is similar to many commonly infused large volume intravenous solutions, such as dextrose (pH 3.2 to 6.5), and bears no medical significance.

However, due to this difference in pH specification limits, we feel that it is not appropriate to name the subject product "MAGNESIUM SULFATE INJECTION."

The General Notices section of the USP further states:

> "Where an article fails to comply in identity with the identity prescribed in the USP...such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the Pharmacopeia."

Our original product name, [redacted (b) (4)] was chosen to differentiate from the USP title as allowed above.

Ms. Sharon Olmstead of the Administration and Ms. Jill Nicholson of Abbott Laboratories held several telephone conversations about this deficiency letter request, during which the above information was conveyed. On July 27, 1993, Ms. Olmstead stated that a product title other than "MAGNESIUM SULFATE INJECTION," may be proposed, adding that the term "Injection" was preferable [redacted (b) (4)]

We therefore propose the title "MAGNESIUM SULFATE IN WATER FOR INJECTION." This format is similar to our other specialty premixed products which, for various reasons, cannot use a USP title:

NDA 20-201	Dobutamine in 5% Dextrose Injection
ANDA 62-414	Gentamicin Sulfate in 0.9% Sodium Chloride Injection
NDA 19-805	Heparin Sodium in 5% Dextrose Injection
ANDA 71-438	Ritodrine Hydrochloride 150mg in 5% Dextrose Injection
ANDA 63-081	Tobramycin Sulfate in 0.9% Sodium Chloride Injection

Copies of final printed labeling bearing the newly proposed title are appended in Exhibit IX.

Response 6: (continued)

Regarding the same size lettering for the title:

Abbott Laboratories' Hospital Products Division has begun a concentrated effort to improve the clarity and readability of their product labeling via an internal program entitled "HPD Labeling Enhancement Initiative." The program's basic definition and Mission Statement are appended in Exhibit X. In brief, product labeling is modified graphically to enhance key information about the particular drug. Usually, the product name is modified so that the drug identity is emphasized over other elements of the product name. Other enhancements are applied on a case-by-case basis. The enhanced labeling is generally applied to the primary container and secondary carton or overwrap (if present).

To date, this program has been enthusiastically received by both health care practitioners and various divisions of the FDA. Examples of recently approved products which utilize enhanced labeling are as follows:

NDA 20-161	10 mEq and 20 mEq Potassium Chloride Injection (Division of Medical Imaging, Surgical and Dental Drug Products)
NDA 20-201	Dobutamine in 5% Dextrose Injection (Division of Cardio-Renal Drug Products)
NDA 19-978	Bupivicaine HCl Injection, USP (ADD-Vantage Kit) (Division of Pilot Drugs)
ANDA 73-510	Morphine Sulfate Injection, USP (Office of Generic Drugs)

Representative examples of the FDA approved labeling for these products are appended in Exhibit XI.

We have provided final printed labeling samples of *enhanced* primary container and overwrap labeling for the subject drug in Exhibit IX. Twelve copies of final printed labeling are provided.

Request 7: The third and fourth sentence of the fourth paragraph in the DESCRIPTION section of the package insert should be revised to read, "Solutions in contact with the plastic container may leach out certain of its chemical components in very small amounts; however, biological testing was supportive of the safety of the plastic container materials."

Response 7: The requested revision has been made. A revised package insert is appended in Exhibit IX. Twelve copies of final printed labeling are provided.

Request 8: In addition, your application did not include a Debarment Certification as required under the Generic Drug Enforcement Act of 1992. Your application must include a certification that you, the applicant, did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) (section 306(a) or (b)), in connection with such application.

Response 8: The requested certification is provided in Exhibit XII.

Request 9: Your application also did not include patent information nor did it include an integrated summary of safety and a safety update report required under 21 CFR 314.50(d)(5)(vi).

Response 9: Patent and exclusivity information is supplied in Exhibit XIII. A summary of safety is supplied in Exhibit XIV.

We trust that this information is complete and that the application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division
Phone: (708) 937-3213
Fax: (708) 938-5964

G:\jxn\10-93fda.jxn

ABBOTT

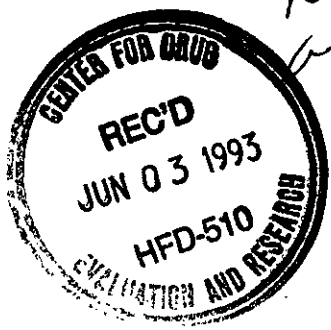
ORIGINAL

Hospital Products Division

ORIG NEW CORRES

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

May 25, 1993



CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

RE: NDA 20-309 Magnesium Sulfate (b) (4), 40 mg/mL and 80 mg/mL in Flexible Containers

Abbott Laboratories hereby amends the above referenced supplemental new drug application to notify the FDA of our intent to file an amendment in response to the Administration's letters of February 11, 1993 and May 18, 1993.

The filing of this amendment is anticipated on or before July 31, 1993.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213
5-93fda.jxn

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I.

CSO INITIALS 80 DATE 6/28/93

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

NDA ORIG AMENDMENT

BC

February 22, 1993

ATTENTION: CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

RE: NDA 20-309 Magnesium Sulfate (b) (4) 40 mg/mL and 80 mg/mL in Flexible Containers

4/16/93 Noted per Dr. Wu the letter has been included in chron. rev. #1.

GENERAL CORRESPONDENCE

Abbott Laboratories hereby submits additional information as requested in a telephone conversation held today between Dr. Duu-Gong Wu of the Administration and Jill Nicholson of Abbott Laboratories regarding NDA 20-309:

List Number	Product	Dosage Form	Content
6729	Magnesium Sulfate (b) (4)	100 mL Flexible Container	40 mg/mL
6730	Magnesium Sulfate (b) (4)	50 mL in 100 mL Flexible Container	80 mg/mL

Dr. Wu requested reference to a *previously approved* New Drug Application wherein sterilization data for package configurations identical to those called out in the above *pending* NDA had been reviewed.

Sterilization data may be found in NDA 20-161, for 0.745% and 1.49% Potassium Chloride Injection, USP in PVC flexible containers, which has been recently reviewed and approved by the Division of Medical Imaging, Surgical and Dental Drug Products. The specific sections may be located as follows:

Engineering Validation Attachment IV Vol. II Page 2-179

Microbiological Validation Solution Microbial Challenges	Attachment I	Vol. II	Page 2-354 and Page 2-356
Master Solution Calculations	Attachment II	Vol. II	Page 2-387 and Page 2-392
Maintenance of Sterility	Attachment III	Vol. II	Page 2-411

A copy of the FDA approval letter for NDA 20-161 is appended.

Please contact us if we can be of additional assistance.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

2-93fda.jxn

Olmstead

FEB 11 1993

NDA 20-309

Abbott Laboratories
Attention: Mr. Frederick A. Gustafson
Hospital Products Division
One Abbott Park Road (D-389 AP30)
Abbott Park, IL 60064-3500

Dear Mr. Gustafson:

Reference is made to your new drug application (NDA) dated October 15, 1992, submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Magnesium Sulfate (b) (4)

On the basis of our initial review of your new drug application referred to above, received on October 15, 1992, and acknowledged on November 5, 1992, we have determined that the application is acceptable to file. However, we request that your firm submit literature to support the serum levels referenced in the labeling. This information is necessary to meet the bioavailability and bioequivalence requirements under 21 CFR 320.

We also refer to your correspondence dated December 10, 1992, requesting a reevaluation of the Agency's position regarding the information requested above.

As discussed in the May 26, 1992, meeting between our Division and your firm, further internal discussion was warranted to determine if a new drug application would meet the requirements for a waiver or whether bioavailability data would be required. Although the magnesium sulfate currently marketed in plastic containers was the subject of an approved full new drug application, it is not the same concentration as your product. Therefore, your pending application does not meet the criteria for a waiver under 21 CFR 320.22(b)(1)(ii).

We look forward to receipt of the above requested information which is necessary to complete our review.

If you have any questions regarding this NDA, please contact Ms. Sharon Olmstead at (301) 443-3510.

Sincerely yours,

2/11/93

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-510/PPrice
HFD-511/SOlmstead/1/23/93/C:\UTERINE/NDA\N20309IR.001/ft/nls/2/9/93

2/10/93

Concurrences: PPrice/PCorfman/1/25/JHunt/EGalliers/1/26/93
Revised per EGalliers' comments 2/9/93
Concurrences: EGalliers/2/9/93

INFORMATION REQUEST

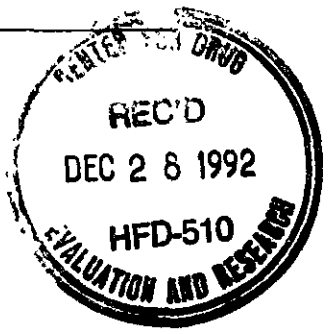
ABBOTT

ORIGINAL

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

BB

NDA ORIG AMENDMENT



December 10, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

RE: NDA 20-309 Magnesium Sulfate (b) (4) (40 mg/mL and 80 mg/mL)

Dr. J. Hunt and Dr. H. Young, FDA Division Of Metabolism And Endocrine Drug Products, HFD #510, telephoned Dr. T. Willer, Abbott Laboratories, on December 3, 1992, concerning the above-referenced NDA. The specific purpose of the call concerned Abbott's request for a waiver of bioavailability requirements.

Dr. Sobel discussed this issue with his staff on December 3, 1992. Dr. Hunt reported that the Agency feels that no waiver will be granted. Abbott must obtain supportive documentation via literature or clinical studies. The Agency requires blood level information for the "new" indication at the "new" dose levels as a function of administration and time, as part of a safety/efficacy study.

Reference was made to a meeting between the Agency and Abbott Laboratories on May 26, 1992, in which this information was discussed in general. The above information is the Agency's resolution of issues resulting from that meeting.

Abbott Laboratories would like to state that it is seeking neither a new indication nor a new dose. Abbott currently markets the proposed drug product in glass containers at 40 mg/mL and 80 mg/mL. This application seeks to put this product in the same size containers except that the proposed container is a flexible PVC container. The subject application proposes no "new" indication for the subject drug. The requested indication is for use as an intravenous anticonvulsant for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy. Based on this information, we request a reevaluation of the Agency's stated position.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division
(708) 937-3213

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Olmstead

NDA 20-309
Magnesium Sulfate (b) (4)
Abbott Laboratories

December 3, 1992

Memorandum of Internal Meeting

FDA Staff:

Dr. Sobel	Dr. Wu
Dr. Troendle	Mr. Hunt (HFD-426)
Dr. Price	Dr. Ahn (HFD-426)
Dr. Chiu	Ms. Olmstead, CSO

Purpose: 45-day meeting.

Discussion and Conclusions:

Medical Acceptable to file. Indication for acute treatment of toxemia/hypomagnesemia. Aluminum testing is not necessary because the renal toxicity is not an issue of concern.

Chemistry Acceptable to file. Microbiology review is not necessary because the methods have already been validated.

Pharmacology Acceptable to file.

Microbiology Acceptable to file.

Biopharm Acceptable to file. Literature to support the serum levels referenced in the labeling should be requested to meet biopharm regulations 21 CFR 320. The application does not meet the criteria for a waiver of the biopharm regs because the magnesium sulfate currently on the market was not the subject of an approved NDA, it was marketed prior to 1938.

A letter will be issued requesting literature to support the serum levels referenced in the labeling.

Sharon Olmstead
Sharon N. Olmstead, CSO

NDA 20-309

NOV 5 1992

Abbott Laboratories
Attention: Mr. Frederick Gustafson
Hospital Products Division
One Abbott Road
Abbott Park, Illinois 60064

Dear Mr. Gustafson:

We have received your new drug application submitted pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Date of Application:	October 15, 1992
Date of Receipt:	October 21, 1992
Name of Drug Product:	Magnesium Sulfate (b) (4) (40 mg/mL and 80 mg/mL)
Our Reference Number:	NDA 20-309

Unless we find the application not acceptable for filing, the filing date will be December 21, 1992.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions regarding this NDA, please contact Ms. Enid Galliers at 301-443-3510.

Sincerely yours,

11-4-92

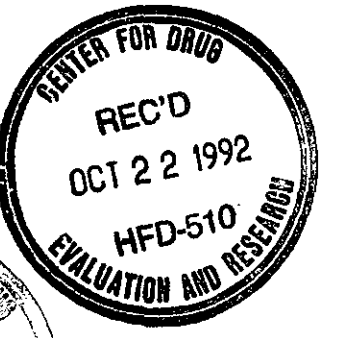
Enid Galliers
Acting Supervisory Consumer Safety Officer
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

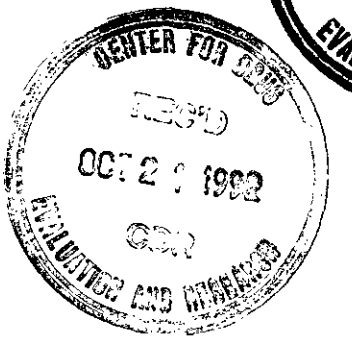
cc: Arch. NDA
HFD-80
HFD-510
HFD-510/YChiu/PCorfman/AJordan
HFD-510/EGalliers/11.4.92/ ft/11/4/92/ \20309ack.nda

ACKNOWLEDGE (ACK)

ABBOTT

Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500





October 15, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

RE: Magnesium Sulfate (b) (4) 40 mg/mL and 80 mg/mL in Flexible Containers

ORIGINAL NEW DRUG APPLICATION

Abbott Laboratories hereby submits an original New Drug Application for the above-referenced product in accordance with 21 CFR 314.50. This drug will be supplied as a sterile, nonpyrogenic solution in a flexible polyvinylchloride container in the following dosage forms:

List Number	Product	Dosage Form	Content
6729	Magnesium Sulfate (b) (4)	100 mL Flexible Container	40 mg/mL
6730	Magnesium Sulfate (b) (4)	50 mL in 100 mL Flexible Container	80 mg/mL

The subject drug is indicated for use as an intravenous anticonvulsant for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy.

The subject drug is currently marketed by Abbott Laboratories in glass containers in the same concentrations and volumes as proposed in this application for the PVC flexible container. Magnesium sulfate has been indicated for use as an intravenous anticonvulsant for the prevention and control of seizures in severe toxemia of pregnancy prior to 1938, i.e., it is a grandfathered drug for this indication. The reason Abbott Laboratories is filing the subject NDA is because we wish to package the product in PVC plastic containers. Reference is made to 21 CFR 310.509, which requires an NDA for any parenteral drug packaged in a plastic container.

The PVC container we intend to use is currently approved in more than sixty NDAs in HFD-160, HFD-530, and HFD-630. The safety and efficacy of the PVC material from which the finished container is fabricated have been well established in preclinical and clinical studies included in NDA 16-366 and NDA 16-367 in HFD-160. Authorization is hereby given to allow the Agency to reference the aforementioned NDAs for these data, as well as to reference Abbott Laboratories' DMF 931 for full information on the container formulations, manufacturing procedure, etc.

Abbott Laboratories will manufacture the finished dosage forms at its currently approved Hospital Products Division, North Chicago, Illinois facility (Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064). Please refer to Abbott Laboratories Drug Master File 1218 for a full description of this facility.

Please see the accompanying Table of Contents for a list of data supporting this submission. We request [redacted] (b) (4) *expiration dating* based on the accelerated stability data enclosed herein.

At the request of the Agency we will provide samples of the drug substance and finished dosage form.

We trust that the application is complete in all respects and would appreciate an expeditious review and approval.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson

Frederick A. Gustafson
Director,
Regulatory Affairs
Hospital Products Division
(708) 937-3213

Magsul.tfw/2-3

Magnesium sulfate
(Packaged in plastic/large volume parenteral)

May 26, 1992
Abbott Labs

MEMORANDUM OF MEETING

D/V

Participants:

FDA :
P. Corfman
P. Price
J. Hunt, HFD-426
E. Galliers

Abbott Labs:
Robert Wilkins, M.D., Associate Medical Dir.
Fred Gustafson, Director, Regulatory Affairs
Stacy Carbone, Clinical Research Associate

Purpose: The firm requested this pre-NDA meeting to determine the acceptability of a literature-supported NDA for magnesium sulfate for [redacted] (b) (4)

Discussion and Conclusions: FDA stated that the literature submitted was inadequate to support an NDA for magnesium sulfate [redacted] (b) (4) and that randomized, controlled, safety and efficacy studies would be required for an NDA. Since two studies are required to demonstrate safety and efficacy, the firm will pursue the possibility of gaining access to raw data and right of reference to one or two of the best studies in the literature.

A problem noted in the literature which would require resolution prior to initiation of new studies is to establish appropriate dosages and the specific method of administration.

Although FDA requested a placebo-controlled study, the firm argued that investigators would be very unlikely to comply with the randomization schedule unless an active control (e.g., ritodrine) is used. Despite a preference for a placebo control, FDA would accept an active control. (b) (4)

Discussions of sample size for a new clinical trial ended with the agreement to include that issue when considering any protocol.

Although long-term follow-up of neonates is preferred, the Agency would accept follow-up for 5 months after birth with the usual neuromuscular endpoints.

In the meantime, the firm will prepare an NDA to meet the requirement at 21 CFR 310.509 because they plan to market a plastic-packaged, "pre-fill" magnesium sulfate (large volume parenteral) product. Magnesium sulfate - packaged in glass - has been marketed since before 1938 and thus did not require an approved NDA. It was stated that the indications in the current labeling are [redacted] (b) (4) eclampsia, and preeclampsia, and they will be the only indications listed in the NDA. Mr. Hunt, HFD-426, will inform the firm after internal discussion whether that NDA would require bioavailability data or whether it would be suitable for any of several types of waivers.

E M Galliers

Enid Galliers, CSO

cc: HFA-224
HFD-510/Uterine acting agents
All FDA Participants
HFD-510/SSobel/JShort/YChiu/
HFD-510/EGalliers/5.26.92/ft/nls/7/7/92 \magsulpn.mom
Concurrences: PPrice, PCorfman, 5.28.92/JHunt, HFD-426, 7.6.92

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Frederick A. Gustafson, Director
Abbott Laboratories
Hospital Products Division
D-389, AP30-1
Abbott Park, IL 60064

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Frederick A. Gustafson, Director
Hospital Products Division Div. 23681 (D-389)
One Abbott Park Road
Abbott Park, IL 60064

3. TELEPHONE NUMBER *(Include Area Code)*
(708) 937-3213

4. PRODUCT NAME Magnesium Sulfate (b) (4) 40mg/mL & 80mg/mL in Flexible Containers

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER.

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES *(See reverse if answered YES)* ☐ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES *(See reverse if answered YES)* ☐ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Frederick A. Gustafson, GS	Director, Regulatory Affairs	5/13/94

DRM FDA 3397 (12/93)

2a

3/94

ODE VII ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 20-309 Drug Magnesium Sulfate in Water for Injection

Applicant Abbott CSO Olmstead phone X3510

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures	AP ✓ AE____ NA____
2. ACTION PACKAGE TRACKING FORM	
3. Completed copy of this CHECKLIST in package	Chem/Ther Types 5S
4. LABELING (package insert and labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx PI and HFD-210 review of OTC insert.)	Draft____ Final ✓ Revised Draft____
5. SUMMARY BASIS OF APPROVAL. (Copy of previous version with ODE's comment as well as disk, FPL and sign-off sheet must accompany revised or final version. If no SBA, include memo stating what reviews will be used as SBA equivalent.)	SBA____ Revised SBA____ SBA Equivalent ✓
6. PATENT INFORMATION ✓	EXCLUSIVITY CHECKLIST ✓
7. Debarment Certification (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992)	✓ (no clinical data)
8. DIVISION DIRECTOR'S MEMO (If more than 1 review)	____
GROUP LEADER'S MEMO (for any 1 discipline,	____
PEDIATRIC PAGE (separate reviews with	✓
MEDICAL REVIEW (a sheet of colored paper.	N/A (no clinical data)
SAFETY UPDATE REVIEW (Any conflicts between	N/A
STATISTICAL REVIEW (reviews must have	✓
BIOPHARMACEUTICS REVIEW (resolution documented.	N/A
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	N/A
Statistical Review of Carcinogenicity Study(ies)	✓
CHEMISTRY REVIEW	OK ✓ No____
Date EER completed 1/14/93 (attach signed form or CIRTS printout); FUR needed ____ requested ✓	Yes (attach)____ No ✓ (not required)
Have the methods been validated? Rec'd 6/24/94	✓
Environmental Assessment Review, "AC" Dated 6/20/94	N/A
MICROBIOLOGY REVIEW	Yes____ No____
Has the monograph been approved?	
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES (If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.)	N/A (no clinical data)
10. CORRESPONDENCE and MEMOS OF TELECONS	✓
11. MINUTES OF MEETINGS	✓
Date of End-of-Phase II Meeting ____	
Date of pre-NDA Meeting 5/26/92	
12. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript	Minutes____ Info Alert____ Transcript____ No mtg ✓
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	N/A
14. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes____ No ✓ Yes, documentation attached____ No, included in AP ltr ✓
15. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes ✓ No____
16. Integrated Summary of Safety	✓
17. NDA (especially Medical/Statistical) Summary	✓

9/9/92

ODE I/II ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 20-309 Drug Magnesium Sulfate (b) (4)

Applicant Abbott CSO Olmstead

LVP

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures	AP____ AE____ NA X
2. ACTION PACKAGE TRACKING FORM	
3. Completed copy of this CHECKLIST in package	Chem/Ther Types 55
4. LABELING (package insert and labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx PI and HFD-210 review of OTC insert.)	Draft X Final____ Revised Draft____
5. SUMMARY BASIS OF APPROVAL. (Copy of previous version with ODE's comment as well as disk, FPL and sign-off sheet must accompany revised or final version. If no SBA, include memo stating what reviews will be used as SBA equivalent.)	SBA N/A Revised SBA____ SBA Equivalent____
6. PATENT INFORMATION AND EXCLUSIVITY CHECKLIST	✓
7. DIVISION DIRECTOR'S MEMO (If more than 1 review for any 1 discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented.)	
GROUP LEADER'S MEMO	
PEDIATRIC PAGE	✓
MEDICAL REVIEW	
SAFETY UPDATE REVIEW	safety update was not submitted
STATISTICAL REVIEW	not required
BIOPHARMACEUTICS REVIEW	
PHARMACOLOGY REVIEW (Include IND reviews if no NDA review	✓
Statistical Review of Carcinogenicity Study (ies)	
CHEMISTRY REVIEW	✓
Has establishment inspection been satisfactorily completed?	Yes (attach) ✓ No____
Have the methods been validated?	Yes____ No____
MICROBIOLOGY REVIEW	not required
Has the monograph been approved?	Yes____ No____
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.	N/A
9. CORRESPONDENCE and MEMOS OF TELECONS	✓
10. MINUTES OF MEETINGS	✓
Date of End-of-Phase II Meeting____	
Date of pre-NDA Meeting 5/26/92	
11. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript	Minutes____ Info Alert____ Transcript____ No mtg ✓
12. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	N/A
13. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes____ No ✓ Yes, documentation attached__ No, included in AP ltr____
14. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes____ No ✓ Medical and Biopharm (see memo)
15. Integrated Summary of Safety	info. was not submitted
16. NDA (especially Medical/Statistical) Summary	✓

5/28/92

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUGS AND BIOLOGICS

ACTION PACKAGE TRACKING

(For New Drug Applications And Subsequent Submissions)

INSTRUCTIONS

1. Guidance for completion of this form is shown on the reverse of Part 4.
2. Tear off a page as each shaded area is completed.

SECTION A

NDA NUMBER	CSO NAME	TYPE OF DECISION	
20-309	Olmstead	☐ APPROVED ☐ APPROVABLE ☒ NOT APPROVABLE	
DOCUMENT TYPE: N	SEEQUENCE NUMBER: 000	DATE ACTION LETTER DRAFTED: 5/12/93	SBA REQUIRED: ☐ YES ☒ NO

SECTION B

DIVISION LEVEL CONCURRENCE CYCLES

NAME	DISCIPLINE	RECEIPT DATE	ACTION DATE
Enid Galliers [signature]	Supervisory CSO	5/14	5/16/93
Phill Price MD [initials]	Medical Officer		[illegible]
Phil Corfman MD [initials]	Group Leader	[illegible]	5/[illegible]
Duu Gong Wu PhD [initials]	Chemist	[illegible]	[illegible]
Yuan-Yuan Chiu, PhD [initials]	Supervisor / Chemist	5/17	5/17/93
Alex Jordan, Ph.D. [initials]	Supervisor / Pharmacologist	[illegible]	[illegible]

DATE TO DIVISION DIRECTOR

SECTION C

LETTER CLEARANCE CYCLE

(Complete the following for letters returned for revisions)

RETURNED FOR REVISIONS	DATE RETURNED TO DIVISON DIRECTOR

DIVISION DIRECTOR ACTION DATE [signature] 5/18/93

☐ SENT TO OFFICE DIRECTOR ☐ FINAL LETTER SIGNED

SECTION D

DATE RETURNED TO DIVISON	DATE RETURNED TO OFFICE DIRECTOR

FINAL LETTER STAMP DATE

SECTION E

TYPING CYCLE

(Complete anytime during the review process)

DOCUMENT FORMAT	DATE TO TYPIST	DATE TYPED	TYPIST'S INITIALS

FORM FDA 3329 (6/87) PART 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; March 31, 1990.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT
Abbott Laboratories

DATE OF SUBMISSION
May 13, 1994

TELEPHONE NO *(Include Area Code)*
(708) 937-3213

ADDRESS *(Number, Street, City, State and Zip Code)*
One Abbott Park Road
Abbott Park, Illinois 60064

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-309

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Magnesium Sulfate

PROPRIETARY NAME *(If any)*

CODE NAME *(If any)*

CHEMICAL NAME
$MgSO_4$ $7H_2O$

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
PVC Flexible Container	I.V.	40 & 80 mg/ml

PROPOSED INDICATIONS FOR USE

I.V. anticonvulsant for the prevention and control of seizures (convulsions) in severe toxemia of pregnancy.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
X
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*