February 5, 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION
*******PRIORITY REVIEW REQUESTED*******

Dear Sir/Madam,

The undersigned petitioner, submits this Suitability Petition, on behalf of a client pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FD&C Act") and in accordance with 21 C.F.R. § 10.20 and 21 C.F.R. §§ 10.30, requesting that the Commissioner of the Food and Drug Administration ("FDA") to declare that the drug product Magnesium Sulfate in Water for Injection, 3 g/100 mL (30 mg/mL) is suitable for submission in an Abbreviated New Drug Application ("ANDA").

I. ACTION REQUESTED

The petitioner requests that the FDA declare that Magnesium Sulfate in Water for Injection, 3 g/100 mL (30 mg/mL) is suitable for submission in an ANDA. As designated in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Reference Listed Drug ("RLD"), upon which this petition is based, is Magnesium Sulfate in Water for Injection, 2 g/50 mL (40 mg/mL), 4 g/50 mL (80 mg/mL), 4 g/100 mL (40 mg/mL), 20 g/500 mL (40 mg/mL) and 40 g/1000 mL (40 mg/mL), which are approved under New Drug Application ("NDA") N020309 currently held by Hospira Inc. The petitioner seeks to introduce a new 3 g/100 mL strength. Priority review of this petition is requested pursuant to Section III.B.6 of the GDUFA

Reauthorization Performance Goals and Program Enhancement Fiscal Years 2023-2027 (GDUFA III Commitment Letter) as the proposed product represents a new strength of a parenteral product that could aid in eliminating pharmaceutical waste.

II. STATEMENT OF GROUNDS

Sections 505(j)(2)(A)(iii) and 505(j)(2)(C) of the FD&C Act and 21 C.F.R. § 314.93 provide for the submission of an ANDA for a drug product that differs in ***strength*** from the RLD provided FDA has first approved a petition permitting the submission of such an application.

Magnesium Sulfate in Water for Injection, 2 g/50 mL (40 mg/mL), 4 g/50 mL (80 mg/mL), 4 g/100 mL (40 mg/mL), 20 g/500 mL (40 mg/mL) and 40 g/1000 mL (40 mg/mL) (NDA 020309) is an injectable solution dosage form. A copy of the Therapeutic Equivalence Evaluations (i.e., Orange Book) entry for RLD is provided in ***Attachment 1***.

Magnesium Sulfate in Water for Injection is indicated for the prevention and control of seizures in preeclampsia and eclampsia, respectively. 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. A copy of the current RLD prescribing information is provided in ***Attachment 2***.

As noted in the RLD's prescribing information (***Attachment 2)***; 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 intravenous 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. After the initial intravenous dose, some clinicians administer 1 to 2 g/hour by constant intravenous 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 recommended dosage of magnesium sulfate is 20 g per 48 hours.

Clinical literature and clinical practice references also describe magnesium sulfate dosing recommendations for preclampsia/eclampsia that include an intravenous loading dose of 4-6 grams followed by a maintenance dose of 1-2 grams.[1,2,3,4,5] Further 2-4 g doses have also been described in literature for patients with recurrent convulsions.[2,4] Clinical practice data also supports that 3 grams is a commonly prepared dose.

Currently available ready to administer magnesium sulfate products deliver doses of 1 g, 2 g, or 4 g, but the intermediate dose of 3 g is not available in a ready to administer format. A ready to administer product containing 3 g of magnesium sulfate allows for delivery of this intermediate dose as a part of the approved maintenance regimen to achieve the recommended serum magnesium level and total daily dose. It could result in use of fewer bags and less potential waste when 4 g doses are not needed and also provides a ready to administer magnesium sulfate product containing the frequently used 3 g dose that provides potential benefits associated with ready to administer products that do not require admixture prior to administration.

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[1] Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260. doi: 10.1097/AOG.0000000000003891. PMID: 32443079.

[2] Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet. 1995 Jun 10;345(8963):1455-63. Erratum in: Lancet 1995 Jul 22;346(8969):258. PMID: 7769899.

[3] Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D; Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002 Jun 1;359(9321):1877-90. doi: 10.1016/s0140-6736(02)08778-0. PMID: 12057549.

[4] Norwitz ER. Eclampsia. In: UpToDate, Lockwood CG, Schachter SC, and Barss VA (Eds), UpToDate, Waltham, MA. Accessed Nov 8, 2023.

[5] Lexicomp Online, Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed Nov 8, 2023.

The proposed drug product contains the same active ingredient, Magnesium Sulfate, as the RLD. Furthermore, the proposed drug product is also provided in the same injectable dosage form, route of administration, with the same formulation, but in 3 g/100 mL (30 mg/mL) strength in a bag presentation. The petition is thus seeking a change to total drug content only, while the uses, indications, warnings, and directions for use will remain unchanged.

The proposed drug product can nonetheless be expected to have the same therapeutic effect as the RLD when administered to patients for each condition of use in the RLD's prescribing information for which the applicant seeks approval. *See* 21 C.F.R. § 314.93(d)(2). This is because the proposed change in strength is consistent with the dosing recommendations in the RLD prescribing information and fall within the approved dosages and strengths of the RLD.

There are no proposed changes in labeling with the exception of the changes in total drug content per container (***Attachment 3***). The uses, indications, warnings, and directions for use will remain unchanged and the change in total drug content per container to 3 g should raise no questions of safety or efficacy.

III. INAPPLICABILITY OF THE PEDIATRIC RESEARCH EQUITY ACT (PREA)

The Pediatric Research Equity Act ("PREA"), enacted in December 2003, amended the FD&C Act by requiring certain applications for a drug submitted under FD&C Act §505 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. See FD&C Act § 505B(a)(I)(A)(i).

Specifically, PREA applies to all applications for a new active ingredient, dosage form, indication, route of administration, or dosing regimen. Petitioner asserts that PREA is not applicable to the proposed Magnesium Sulfate in Water for Injection, 3 g/100 mL (30 mg/mL) drug product because the proposed changes concern only new strength. As such, PREA should not serve as an impediment to the Agency granting this petition.

IV. ENVIRONMENTAL IMPACT

A claim of categorical exclusion of the requirements of an environmental assessment is made pursuant to 21 C.F.R. § 25.31.

V. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted when requested by the Commissioner following review of this petition.

VI. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Sincerely,

Martin Shimer

Digitally signed by Martin Shimer
Date: 2024.02.05 22:21:24 -05'00'

Martin H. Shimer
Executive Director
Lachman Consultant Services, Inc.

Please contact me at m.shimer@lachmanconsultants.com if you have any questions related to this petition.

VII. ATTACHMENTS

Attachment 1: FDA Orange Book page for RLD Magnesium Sulfate in Water for Injection.

Attachment 2: Prescribing Information for RLD Magnesium Sulfate in Water for Injection from DailyMed (updated October 23, 2023).

Attachment 3: Proposed Prescribing Information for Magnesium Sulfate in Water for Injection, 3 g/100 mL (30 mg/mL).

REFERENCES:

ACOG Practice Bulletin 2022

Lancet 1995

Altman D 2002

Norwitz ER 2023

Lexi-Drugs 2021