AstraZeneca

DEC 17 2001

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Re: **Docket Number 01P-0430/CP1**
Comments to ANDA Suitability Petition for 200 mL Size Propofol Injectable Emulsion Containing 0.025% Sodium Metabisulfite

Dear Sir:

Reference is made to the Suitability Petition ("Petition") dated September 17, 2001 in which GensiaSicor Pharmaceuticals, Inc. ("Petitioner") requests permission to submit an abbreviated new drug application ("ANDA") for Propofol Injectable Emulsion 1% with 0.025% sodium metabisulfite in a 200 mL vial container.

AstraZeneca Pharmaceuticals LP ("AstraZeneca") requests that the Food and Drug Administration ("FDA"), in its review of the Petition, consider several issues:

- Whether there is sufficient rationale for a 200 mL vial of propofol for adult anesthesia uses in view of the prior public health concerns relating to multi-dosing;
- Whether the use of 200 mL vials in ICU sedation will result in administration times exceeding those in the approved label (12 hours);
- Whether the oxidation of propofol and peroxidation of lipid components in SCP present new safety risks to a class of already compromised at-risk patients. There is new scientific research pertaining to potential adverse product-specific changes in the composition of sulfite-containing propofol ("SCP") that occur over time as the product is exposed to air. These problems may be exacerbated by the use of larger 200 mL vials which increase exposure of SCP to air and cause potential chemical stability problems in this formulation.

We request that the above factors and information be incorporated into FDA's risk-benefit analysis of whether approval for the change requested in the Petition should be granted.

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01P-0430

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I. Because only a very limited population of adult surgery patients require 200 mL propofol for anesthesia, approval of a 200 mL vial may encourage multi-dosing of the product.

In the Petition, the Petitioner states that a 200 mL vial will increase clinician dosing flexibility for adult surgical patients who require higher doses of propofol for anesthesia, or for adult surgical patients undergoing longer surgical procedures. To support this statement, the Petitioner provides dosing charts for 50 to 90 kg patients for 3- and 5-hour procedures.[1/] Contrary to the Petitioner's data, however, available data suggests that a 200 mL propofol vial would be used with only a small percentage of the surgical patient population. This is based on the fact that the majority (69%) of surgical patients undergo procedures in ambulatory surgery settings.[2/] Procedures done in ambulatory surgery settings tend to be shorter than those done in inpatient settings, thus requiring far less propofol than indicated in the Petitioner's charts. Additionally, data from Hospital Research Associates indicate that while 70% of inductions include use of propofol, less than 10% of maintenance anesthetics include use of propofol.[3/] Only a very small group of patients actually would use a single-use 200 mL vial of propofol during typical surgery. Therefore, the need for the 200 mL vial is minimal in the surgical setting.

In the absence of a clinical need for a single use 200 mL vial, based on historical clinical practice and prior public health (FDA and Centers for Disease Control) concerns regarding use of a single-use propofol vial for multiple patients (commonly referred to as multi-dosing) and misuse,[4/] it can be expected that, in order to make the use of 200 mL vials economical, clinicians and health care professionals may engage in multi-patient use. The approval of a 200 mL single use propofol vial which can replenish a 20 mL syringe up to 10 times, the dose commonly used for propofol induction of anesthesia, could make multi-dosing much more tempting and, hence, more likely.

The availability of a 200 mL vial also may encourage health care providers to extend infusion during ICU sedation beyond the labeled 12 hour period and, thus, increase the opportunity for microbial growth. As evidenced by the data in the Petition, many patients sedated in ICU will

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1/ See GensiaSicor Pharmaceuticals, Inc., Suitability Petition for 200 mL Size Propofol Injectable Emulsion Containing 0.025% Sodium Metabisulfite (Medical Rationale) at pp. 000022-000023, Appendix 1.

2/ See "Outpatient Surgery Increases as New Centers Taper Off," HealthCare Purchasing News, February 1998 p. 21, Appendix 2.

3/ See Hospital Research Associates, Projected Operating Room and Surgicenter cases, Anesthetic Audit, 1996, 1997, 1998, 1999 and 2000, Appendix 3.

4/ See Appendix 4, for a brief chronology of CDC/FDA concerns with propofol administration.

not utilize all of the 2000 mg of propofol within the required time frame. Information provided in Table 3 of the Petition, titled Adult ICU Patients Dosing During 12 hour Infusion, for example, demonstrates that a 70 kg patient receiving propofol for the maximum approved 12 hour period of infusion generally would not require 2000 mg of propofol.

In some cases – particularly in overburdened intensive care units-, health care providers may extend the infusion time beyond 12 hours to ensure complete consumption of the 200 mL vial, increasing the opportunity for microbial growth. Moreover, these safety risks may be compounded in adult patients of 70 kg or less receiving propofol at lower infusion rates.

II. Approval of a 200 mL sulfite-containing propofol product will increase the potential for the formation of free radicals and lipid peroxides over-extended administration periods.

The Petitioner asserts in its medical rationale for the change that the 200 mL vial also provides additional dosing flexibility for clinicians with ICU sedation patients. However, new data suggests that the use of a 200 mL vial of SCP during typical ICU sedation will increase sulfite oxidation, which may result in the production of increased levels of lipid peroxide products such as malondialdehyde ("MDA") and 4-hydroxynonenal.[5/] The literature suggests that increased amounts of free radicals and lipid peroxidation products such as MDA which could result from the infusion of SCP into ICU patients already experiencing oxidative stress may further compromise their health.[6/] More specifically, the oxidative conditions created by sulfite present four problems specific to SCP that appear to progress over time of exposure under conditions of simulated infusion that could adversely affect patient safety. These processes are:

5/ See Baker, MT, Ph.D. Laboratory Report: Studies of Sulfite Reactivity in Metabisulfite Containing Propofol Emulsions, Figure 1, December 1, 2001 (hereinafter "Baker Lab Report"). See Appendix 5.

6/ See e.g., Bulger EM, Maier RV. Antioxidants in Critical Illness. Arch. of Surgery 2001, 136 (1): 1201-7; Bella P, Bahl R, Sane AS. Oxidative Stress Status: Possible Guidelines for Clinical Management of Critically Ill Patients. Panminerva Medica 2001, 43(1): 27-31; Das UN. Free Radicals, Cytokines and Nitric Oxide in Cardiac Failure and Myocardial Infarction. Molec. & Cell. Biochem. 2000, 215 (1-2): 145-52 (stating that free radicals play a major role in atherosclerosis and myocardial infarctions); Raha S, Robinson BH. Mitochondria, Oxygen Free Radicals, Disease and Aging. Trends in Biochemical Sciences, 2000, 25 (10): 502-8 (discussing the importance of hydroxyl radical in diseases where respiratory chain function is abnormal). Bertrand Y. Oxygen-Free Radicals and Lipid Peroxidation in Adult Respiratory Distress Syndrome. Intensive Care Medicine, 1985, 11(2): 56-60. Sahin U., Unlu M., Ozguner F. Lipid Peroxidation and Glutathione Peroxidase Activity in Chronic Obstructive Pulmonary Disease Exacerbation: Prognostic Value of Malondialdehyde. Journal of Basic & Clinical Physiology & Pharmacology, 2001, 12(a): 59-68. See Appendix 6.

1. **The oxidation of the metabisulfite into free radicals**:

When SCP is exposed to oxygen in air, the sulfite, which is liberated from sodium metabisulfite in the aqueous phase, oxidizes forming highly reactive sulfite free radicals.[7/] The signal from electron spin resonance demonstrates that sulfite free radicals are initially present in SCP, increase over the course of a 6 hour simulated infusion, and then decrease to about the initial level at 12 hours.[8/]

2. **The peroxidation of lipid components of the emulsion vehicle**:

Lipid peroxidation is a chain reaction that once started, becomes self-propagating and leads to the oxidation of polyunsaturated fatty acids. In biological systems, this chain reaction disrupts the structure of biological membranes, and produces toxic metabolites such as MDA.[9/] These toxic metabolites present a potentially significant risk to already compromised ICU patients.[10/] MDA is detectable in freshly opened SCP, demonstrating that peroxidation of the lipid vehicle is occurring. Furthermore, MDA increases during a simulated 12-hour infusion.[11/]

MDA is generated from linolenic acid, one of the minor lipids within propofol formulations.[12/] In the reaction, sulfite-free radicals attack unsaturated double bonds throughout the emulsion, generating substances that present known health risks to patients. This reaction is only one example of similar chemical reactions that may occur within the emulsion that could generate significantly higher quantities of lipid peroxides. Additional reactions likely include the formation of high levels of 4-hydroxynonenal from linoleic acid.[13/]

7/ See Baker Lab Report, supra n. 5, Appendix 5.

8/ See Baker Lab Report, supra n. 5, at Figure 10, Appendix 5.

9/ See Slatter, DA, Bolton CH, Bailey, AJ. The Importance of Lipid-Derived Maldondialdehyde in Diabetes. Diabetologia 2000, 43(5): 550-7. See Appendix 6.

10/ See supra n. 6.

11/ See Baker, MT, Dehring DJ, Gregerson MS. Sulfite Catalyzed Lipid Peroxidation in Propofol Emulsions (manuscript), Appendix 7; see also Figure 8, Baker Lab Report, Appendix 5.

12/ See Baker, MT, "Chemical Processes in Metabisulfite Containing Propofol Emulsion," Emulsion Chemistry Seminar, presented to FDA August 24, 2000 (Chart of major lipid constituents in each milliliter of Diprivan), Appendix 8a at p.3.

13/ See e.g., Schneider, C., Tallman, KA, Porter NA, Brash AR. Two Distinct Pathways of Formation of 4-Hydroxynonenal – Mechanisms of Nonenzymatic Transformation of the 9- and 13 Hydroperoxides of Linoleic Acid to 4-Hydroxyalkenals. Journal of Biological Chemistry, June 2001, 276 (24); 20831-20838; Koh YH, Yoon SJ, Park JW. Lipid

The potential clinical implications of this are demonstrated in a recent animal study which shows that the well-known antioxidant effect of propofol is attenuated by the inclusion of the additive metabisulfite contained in the Petitioner's product, as measured by increased levels of products of oxidative stress, ethane (a product of lipid peroxidation) and CO (a product of heme-oxygenase) in sheep treated with sulfite-containing propofol compared with DIPRIVAN.[14/]

3. **The oxidation of propofol**:

On exposure to air, the sulfite-containing propofol emulsion generates a yellow color, which is not observed in DIPRIVAN when similarly exposed. This degradant has been demonstrated to be an oxidation product of propofol, specifically, propofol dimer quinone. Yellowing, propofol dimer and propofol dimer quinone formation, were noted at approximately 6 hours of simulated intravenous infusion.[15/]

All of the above-mentioned SCP-specific phenomena could be exacerbated by the approval of a larger SCP vial because, in comparison to 50 or 100 mL presentations of the product, a large volume SCP formulation likely will be exposed to a greater volume of air for longer periods.

III. Conclusion.

AstraZeneca asks that FDA carefully consider the enclosed information which suggests that due to the limited population of patients who would use a 200 mL of propofol, there is little need for this presentation. This limited need must be balanced against the risk that a 200 mL vial likely will encourage multi-dosing and misuse during anesthesia induction and maintenance and

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Peroxidation Product-Mediated DNA Damage and Mutagenicity, Journal of Biochemistry and Molecular Biology, May 1997, 30 (3): 188-193; Poli, G, Schaur RJ, 4-Hydroxynonenal un the Pathomechanisms of Oxidative Stress. Iubmb Life, Oct-Nov. 2000, 50 (4-5): 315-321. See Appendix 6.

14/ In the animal model, an increase in extravasation of albumin tagged methylene blue in the lungs of the sheep treated with the metabisulfite formulation was seen, demonstrating an increased permeability of this vascular bed in these animals compared to those treated with DIPRIVAN. See Brown RH, Wagner, EM, Cope KA. Propofol & EDTA Decreases Oxidative Stress In Vivo: Effects of Preservative (submitted to Anesthesiology, Nov. 26, 2001). See Appendix 9.

15/ See Baker, MT, "Chemical Processes in Metabisulfite Containing Propofol Emulsion," Emulsion Chemistry Seminar, presented to FDA August 24, 2000, Appendix 8b, pp. 1-6 and 8c, pp. 1-2; see also Baker Lab Report, supra n. 5, Figures 3-7, and 9, Appendix 5.

extended hang times during ICU sedation that may allow microbial growth following extrinsic contamination. Moreover, a 200 mL vial of SCP could result in the generation of potentially high levels of free radicals and other lipid peroxidation products resulting from sulfite oxidation during ICU sedation. As discussed above, lipid peroxidation products and free radicals may present potential health risks from additional oxidative stress to already compromised at-risk ICU patients. We therefore request that the above factors and information be incorporated into FDA's risk benefit analysis of whether approval for the change requested in the Petition should be granted.

If you require any clarification or further information, please do not hesitate to contact me.

Respectfully submitted,

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Koh YH, Yoon SJ, Park JW. Lipid Peroxidation Product-Mediated DNA Damage and Mutagenicity, Journal of Biochemistry and Molecular Biology, May 1997, 30 (3): 188-193.

Poli, G, Schaur RJ, 4-Hydroxynonenal in the Pathomechanisms of Oxidative Stress, Iubmb Life, Oct-Nov. 2000, 50 (4-5): 315-321.

Appendix 7 — Baker, MT, Dehring DJ, Gregerson MS. Sulfite Catalyzed Lipid Peroxidation in Propofol Emulsions (manuscript).

Appendix 8 — Baker, MT, "Chemical Processes in Metabisulfite Containing Propofol Emulsion," Emulsion Chemistry Seminar, presented to FDA August 24, 2000.

Appendix 9 — Brown RH,. Wagner, EM,. Cope KA, Propofol + EDTA Decreases Oxidative Stress In Vivo: Effects of Preservative (submitted to Anesthesiology, Nov. 26, 2001).