



Attachment 2

Medical Rationale for the Proposed Product Included as Statement of Grounds

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Medical Rationale

Propofol Injectable Emulsion 1%, 100 mg/10 mL

PHARMACOLOGY:

Propofol Injectable Emulsion 1% is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. A therapeutic dose of propofol produces hypnosis rapidly, usually within 40 seconds from the start of an injection. The half-time for blood brain barrier equilibrium is approximately 1-3 minutes which accounts for the rapid induction of anesthesia.

Pharmacodynamic properties of propofol are dependent upon therapeutic blood concentrations. Steady state blood concentrations are generally proportional to infusion rates.

The pharmacokinetics of propofol are well described by a three compartment linear model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues.

INDICATIONS FOR USE:

Propofol Injectable Emulsion 1% is an intravenous sedative-hypnotic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adults and in children 3 years of age or older.

Propofol, when administered intravenously as directed, can be used to initiate and maintain MAC sedation during diagnostic procedures in adults.

Propofol may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures.

DOSAGE:

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors.

Hypothetical adult and pediatric dosages are presented in the following Tables 1, 2, and 3.

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Table 1
Dosing: Pediatric Induction

Weight (kg)	Weight (lbs.)	Dose 2.5 mg/kg	Dose 3.5 mg/kg
15 kg	33 lbs.	37.5 mg	52.5 mg
25 kg	55 lbs.	62.5 mg	87.5 mg
35 kg	77 lbs.	87.5 mg	122.5 mg
40 kg	88 lbs.	100 mg	140 mg

Table 2
Dosing: Adult Induction

Weight (kg)	Weight (lbs.)	Cardiac 0.5 mg/kg	Elderly Neurological 1 mg/kg	Elderly Cardiac 1.5 mg/kg	Neurological 2 mg/kg
50 kg	110 lbs.	25 mg	50 mg	75 mg	100 mg
60 kg	132 lbs.	30 mg	60 mg	90 mg	120 mg
70 kg	154 lbs.	35 mg	70 mg	105 mg	140 mg
80 kg	176 lbs.	40 mg	80 mg	120 mg	160 mg
90 kg	198 lbs.	45 mg	90 mg	135 mg	180 mg

Table 3
Dosing: MAC Sedation - Adult Induction & Maintenance
Short Procedures

Weight (kg)	Initiate	20 Minute Procedure		40 Minute Procedure	
		Maintenance		Maintenance	
	0.5 mg/kg	25 mcg/kg/min	75 mcg/kg/min	25 mcg/kg/min	75 mcg/kg/min
50 kg	25 mg	25 mg	75 mg	50 mg	150 mg
60 kg	30 mg	30 mg	90 mg	60 mg	180 mg
70 kg	35 mg	35 mg	105 mg	70 mg	210 mg
80 kg	40 mg	40 mg	120 mg	80 mg	240 mg
90 kg	45 mg	45 mg	135 mg	90 mg	270 mg

RATIONALE:

The currently marketed product, Diprivan[®] (propofol injectable emulsion 1%), is available in four sizes: 200 mg/20 mL single use ampoule, 500 mg/50 mL and

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100 mg/100 mL single use vials, and 50 mg/50 mL prefilled syringe. As indicated in the hypothetical case data set forth in Tables 1, 2 and 3, adult and pediatric dosages less than 200 mg per procedure are common place.

The proposed product size, 100 mg/10 mL in a 10 mL single use vial, does not pose a question of safety or effectiveness because the uses, doses, and route of administration of the proposed product are the same as those of the reference listed drug. The sole difference is the total amount of drug in the container. The 100 mg/10 mL drug product has the same concentration of the active and inactive ingredients as that of the reference listed drug product (10 mg/mL).

Market research indicates that the proposed 100 mg/10 mL product would be advantageous for practitioners as the 100 mg/10 mL size more closely approximates the dosing required for a typical patient.

Additionally, the 100 mg/10 mL strength would reduce the temptation and the opportunity for dosing multiple patients from a single drug container. This is critically important because, although the proposed product contains sodium metabisulfite (0.25 mg/mL) to retard microbial growth, Propofol Injectable Emulsion 1% can still support the growth of microorganisms and is not considered a preserved product under USP standards. Therefore, the availability of a 100 mg/10 mL strength would enhance patient safety.

The availability of Propofol Injectable Emulsion 1% in a single use vial with a strength of 100 mg/10 mL may result in a reduction in patient cost and waste disposal compared to Diprivan[®] because the smaller vial size contains propofol in an amount that is closer to dosages required for selected patients undergoing certain kinds of procedures.

SUMMARY:

In summary, the availability of Propofol Injectable Emulsion 1% in a 100 mg/10 mL single dose vial will offer safety, convenience, dosing flexibility and cost savings advantages over Diprivan[®] in a 200 mg ampoule, 500 mg vial, 1000 mg vial, or a 500 mg prefilled syringe. Specifically, since doses of approximately 100 mg are common when using an approved regimen, the proposed 100 mg size offers the advantage of flexibility and convenience to the practitioner (saves time and money), reduces the possibility of a dosing error (vial contents may be closer to the actual dosage required), and enhances patient safety (reduces the opportunity for product misuse that could introduce microbial and/or particulate contamination to the sterile product.)

The proposed drug product size is intended for use only as described in the **Indications and Usage** and **Dosage and Administration** sections of Gensia Sicor's draft package insert, provided in **Attachment 1**.

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Appended in **Attachment 3** is the package insert for Diprivan[®], AstraZeneca. The labeling for the proposed drug is essentially identical to that of AstraZeneca's Diprivan[®], but differs only with respect to the description of the product, product name, the how-supplied statement, and the specific manufacturer's information.

We believe that the information presented in this petition for Propofol Injectable Emulsion 1% with 0.025% Sodium Metabisulfite supports our claim that the product size is suitable for an abbreviated new drug application.

REFERENCES:

1. Package insert for Diprivan[®] for Injection, AstraZeneca. Revised August 1999.

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