A Company of the Fresenius Kabi Group

URGENT: PROPOFOL UPDATE

March 9, 2010

Dear Healthcare Professional,

Due to the ongoing critical shortage of Propofol Injection in the United States market, APP continues to coordinate with the FDA to increase the availability of propofol products.

In late 2009, APP, in conjunction with the FDA, initiated importation of an international propofol 1% product, **Fresenius Propoven 1%** (propofol 1%) to help alleviate propofol shortages. This temporary importation ended as of February 1, 2010 when all initial **Fresenius Propoven 1%** (propofol 1%) inventories were depleted.

The FDA recognizes that there continues to be a propofol shortage; therefore, APP in agreement with the FDA, has been authorized to *reintroduce* **Fresenius Propoven 1%** (propofol 1%) to the US market. **Fresenius Propoven 1%** (propofol 1%) is manufactured in FDA inspected facilities by APP's parent company, Fresenius Kabi AG. All of these facilities are in compliance with FDA manufacturing standards.

At this time, no other entity except APP is authorized by FDA to import or distribute **Fresenius Propoven 1%** (propofol 1%). Any sales of **Fresenius Propoven 1%** (propofol 1%) vials from any entity other than APP will be considered a violation of the Food, Drug and Cosmetic Act and will be subject to enforcement by FDA.

Effective immediately, APP will offer three propofol 1% versions:

	DIPRIVAN®	**APP Propofol 1%** (generic DIPRIVAN®)	**Fresenius Propoven 1%** (propofol 1%)
20mL SD Vial	NDC # 63323-260-20	NDC # 63323-270-20	Product # 831453
50Ml SD Vial	NDC # 63323-260-50	NDC # 63323-270-50	Product # 3170051
100mL SD Vial	NDC # 63323-260-65	NDC # 63323-270-65	Product # 3170031

APP's Propofol Injectable Emulsion, USP formulation is identical to DIPRIVAN®

Fresenius Propoven 1% (propofol 1%) contains the same active ingredient, propofol, in the same concentration as DIPRIVAN® (propofol 1%) and is a clinically acceptable substitute to other currently marketed generic propofol products in the United States. **It is important to note that there are some key differences in the formulation and labeling between the US marketed propofol products and the international Fresenius Propoven 1% (propofol 1%), that you need to be aware of:**

- **Fresenius Propoven 1%** (propofol 1%) contains a combination of long-chain triglycerides (LCT), similar to those found in DIPRIVAN®; however, **Fresenius Propoven 1%** (propofol 1%) also contains medium-chain triglycerides (MCT) that are not present in the DIPRIVAN® formulation. As with DIPRIVAN® and other propofol products, special care should be applied in patients with disorders of fat metabolism, patients receiving Total Parenteral Nutrition (TPN), and in patients with other conditions where lipid emulsions must be used with caution.
- **Fresenius Propoven 1%** (propofol 1%) does **NOT** contain an anti-microbial retardant such as ethylenediaminetetraacetic acid (EDTA), sodium meta-bisulfate, or benzyl alcohol/sodium benzoate.
    - **STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING.** Each vial of **Fresenius Propoven 1%** (propofol 1%) is intended only for single administration for an individual patient. **Vials are not intended for multidose use.**
    - Unused **Fresenius Propoven 1%** (propofol 1%) should be discarded within 6 hours after the vial has been opened.
    - As with any propofol 1% used for IV infusion, discard all product and infusion therapy systems after 12 hours.
- **Fresenius Propoven 1%** (propofol 1%) is contraindicated in patients who are allergic to soy or peanut.
- The barcode used on **Fresenius Propoven 1%** (propofol 1%) product is an international pharmaceutical manufacturing code and may not be appropriately recognized by scanning systems used in the United States.

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Institution should confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being prepared and administered to individual patients.

- **Fresenius Propoven 1%** (propofol 1%) product information sheet contains a *patient information leaflet* as part of the international requirement for propofol 1%. For questions regarding **Fresenius Propoven 1%** (propofol 1%) in the United States, please contact APP Medical Information at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com.

The product comparison table below also highlights the differences between DIPRIVAN® and **Fresenius Propoven 1%** (propofol 1%).

Please click here for package inserts: APP DIPRIVAN® & Fresenius Propoven 1%

To further supplement supply, APP maintains its commitment to expedite the manufacturing of DIPRIVAN® and APP propofol to maintain continuous releases on all product presentations. We believe the combination of continuous DIPRIVAN® and APP propofol releases in addition to availability of **Fresenius Propoven 1%** (propofol 1%) will help alleviate this market shortage.

Please evaluate the use of **Fresenius Propoven** (propofol 1%) in your institution and begin placing orders immediately. If your institution is not willing to use **Fresenius Propoven** (propofol 1%), you may continue to order DIPRIVAN® and/or APP propofol; APP will continue to fill those order through the allocation process. APP will reserve some DIPRIVAN® and/or APP propofol for those patients where **Fresenius Propoven** (propofol 1%) is contraindicated. Customers have the following options when ordering DIPRIVAN®, APP propofol, or **Fresenius Propoven** (propofol 1%):

- Wholesalers can place drop ship orders on a customer's behalf directly with APP.
- Customers can order directly from APP by contacting Customer Service at 1-888-386-1300 between 7 a.m. – 6 p.m. Central Standard Time.
- **Fresenius Propoven** (propofol 1%) is not returnable and not for resale.

Until further notice, all propofol products, including DIPRIVAN®, APP propofol, and **Fresenius Propoven** (propofol 1%), will remain on an allocation process. APP will make reasonable attempts to fill your orders. APP will be closely monitoring the distribution of DIPRIVAN®, APP propofol, and **Fresenius Propoven 1%** (propofol 1%) to help manage continued imbalances in supply.

If you have additional questions, please contact Customer Service at 1-888-386-1300, Monday – Friday, between the hours of 7:00 a.m. and 6:00 p.m. (CST) or APP Medical Information at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com. This communication and updated product information is available on the APP web site www.APPpharma.com as well as on the FDA Drug Shortage web site http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.

To report adverse events among patients administered **Fresenius Propoven 1%** (propofol 1%), please call 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST). Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using FDA Form 3500 at http://www.fda.gov/medwatch/index.html.

We urge you to contact our Medical Information department at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com if you have any questions about the information contained in this letter or the safe and effective use of **Fresenius Propoven 1%** (propofol 1%).

Sincerely,

Arthur Pelletier
Vice President, Quality Assurance/Quality Control

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Comparison Table:

APP Label DIPRIVAN® (propofol 1%)	Fresenius Label Propoven 1% (propofol 1%)
N36323-269-203 • Contains EDTA, which inhibits microbial growth up to 12 hours • Use strict aseptic technique • Contamination can cause fever, infection/sepsis, and/or other life-threatening illness • Begin use promptly after opening; Discard within specified time limit (See package insert) • Do not use if contamination is suspected Dosage: See accompanying Professional Information Brochure. Store between 4-22°C (40-72°F). Do not freeze. US Pat 5,714,520 5,731,355 5,731,356 5,908,869 LOT EXP 35387-00 402342A NDC 63323-269-20 260920 DIPRIVAN® 1% INJECTABLE EMULSION, USP propofol 10 mg/mL propofol FOR I.V. ADMINISTRATION 20 mL single-patient infusion vial Sterile, nonpyrogenic Rx only SHAKE WELL BEFORE USING Mfd. for: APP Pharmaceuticals, LLC Schaumburg, IL 60173 Made in Italy	Fresenius Propoven 1% Emulsion for Injection or Infusion Propofol 20 ml Each 1 ml contains 10 mg Propofol. Each 20 ml vial contains 200 mg Propofol. Also contains soybean oil refined, triglycerides medium-chain, purified egg phosphatide, glycerol, oleic acid, sodium hydroxide and water for injections. For single injection or infusion in an individual patient. Not a multiple dose container. Keep out of the reach and sight of children. Do not store above 25°C. Do not freeze. Use only if the emulsion is homogeneous and the container is undamaged. Containers should be shaken before use. If two layers can be seen after shaking, the emulsion should not be used. Use as directed by a medical practitioner. Any portion of the contents remaining after first use should be discarded. Batch no.:/Expiry date: MA Holder: Fresenius Kabi Ltd, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, U.K. PL 08828/0167 PA 566/36/2 POM 333 231
30363232269501 Manufactured for: APP Pharmaceuticals, LLC Schaumburg, IL 60173 Made in Italy 35373-00 402347A US Pat 5,714,520 5,731,355 5,731,356 5,908,869 LOT EXP • Contains EDTA, which inhibits microbial growth up to 12 hours • Use strict aseptic technique • Contamination can cause fever, infection/sepsis, and/or other life-threatening illness • Begin use promptly after opening; Discard within specified time limit (See package insert) • Do not use if contamination is suspected Sterile, nonpyrogenic SHAKE WELL BEFORE USING Dosage: See accompanying Professional Information Brochure. In addition to the active component, propofol, the formulation contains: soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL) and disodium edetate (0.005%); with sodium hydroxide to adjust pH. Store between 4-22°C (40-72°F). Do not freeze. Rx only NDC 63323-269-50 260950 DIPRIVAN® 1% INJECTABLE EMULSION, USP propofol 10 mg/mL propofol FOR I.V. ADMINISTRATION 50 mL single-patient infusion vial	Fresenius Propoven 1% Emulsion for Injection or Infusion Propofol 50 ml Each 1 ml contains 10 mg Propofol. Each 50 ml vial contains 500 mg Propofol. Also contains soybean oil refined, triglycerides medium-chain, purified egg phosphatide, glycerol, oleic acid, sodium hydroxide and water for injections. For single injection or infusion in an individual patient. Not a multiple dose container. Keep out of the reach and sight of children. Use only under aseptic conditions. Do not store above 25°C. Do not freeze. The sterile emulsion contains no preservative. Use only if the emulsion is homogeneous and the container is undamaged. Containers should be shaken before use. If two layers can be seen after shaking, the emulsion should not be used. Use as directed by a medical practitioner. Any portion of the contents remaining after first use should be discarded. MA Holder: Fresenius Kabi Ltd, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA 7 1 NT, U.K. POM PL 08828/0167 PA 556/36/2 Batch no.: Expiry date: M093557/01 GB
N 3 63323-269-65 4 EPQ • Contains EDTA, which inhibits microbial growth up to 12 hours • Use strict aseptic technique • Contamination can cause fever, infection/sepsis, and/or other life-threatening illness • Begin use promptly after opening; Discard within specified time limit (See package insert) • Do not use if contamination is suspected Dosage: See accompanying Professional Information Brochure. In addition to the active component, propofol, the formulation contains: soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL) and disodium edetate (0.005%); with sodium hydroxide to adjust pH. Shake vial before use. Store between 4-22°C (40-72°F). Do not freeze. Manufactured for: APP Pharmaceuticals, LLC Schaumburg, IL 60173 Made in Italy US Pat 5,714,520 5,731,355 5,731,356 5,908,869 LOT EXP 35380-00 402348A NDC 63323-269-65 260965 DIPRIVAN® 1% INJECTABLE EMULSION, USP propofol 10 mg/mL propofol FOR I.V. ADMINISTRATION Sterile, nonpyrogenic Rx only 100 mL single-patient infusion vial SHAKE WELL BEFORE USING	Fresenius Propoven 1% Emulsion for Injection or Infusion Propofol 100 ml Each 1 ml contains 10 mg Propofol. Each 100 ml vial contains 1000 mg Propofol. Also contains soybean oil refined, triglycerides medium-chain, purified egg phosphatide, glycerol, oleic acid, sodium hydroxide and water for injections. For single injection or infusion in an individual patient. Not a multiple dose container. Keep out of the reach and sight of children. Use only under aseptic conditions. Do not store above 25°C. Do not freeze. The sterile emulsion contains no preservative. Use only if the emulsion is homogeneous and the container is undamaged. Containers should be shaken before use. If two layers can be seen after shaking, the emulsion should not be used. Use as directed by a medical practitioner. Any portion of the contents remaining after first use should be discarded. POM PL 08828/0167 PA 566/36/2 Batch No.: Expiry date: Fresenius Kabi MA Holder: Fresenius Kabi Ltd, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, U.K. M091557/01 GB

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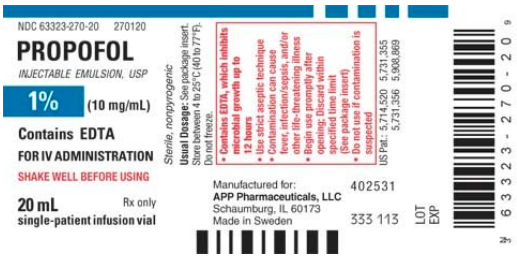
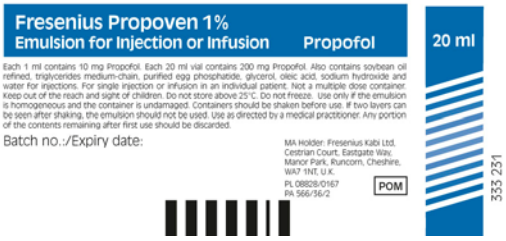
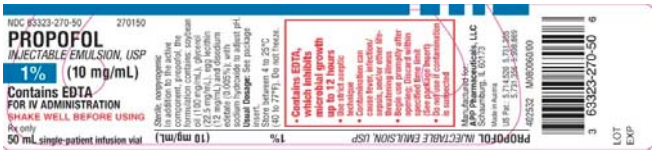
APP Label Propofol 1%	Fresenius Label Propoven 1% (propofol 1%)
	
	

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DIPRIVAN® and APP Propofol (propofol 1%)	Fresenius Propoven 1% (propofol 1%)	What does this mean to you, as a Healthcare Professional?
Contains ethylenediaminetetraacetic acid (EDTA)	**Does not contain a preservative** such as ethylenediaminetetraacetic acid (EDTA), benzyl alcohol/sodium benzoate, or sodium meta-bisulfate	**Fresenius Propoven 1%** (propofol 1%) **IS** a single dose vial for administration to a single patient. **Strict aseptic technique must always be maintained during handling**
Indications and contraindications: see package insert	Indications and contraindications: see package insert **Please note: see package insert on 4.2 method of administration, 4.3 contraindications, and 4.4 special warning and precautions for use**	**Fresenius Propoven 1%** (propofol 1%) may be used for induction of anesthesia in patients above the age of 3 years or for maintenance of anesthesia in patients above the age of 2 months
Contains long-chain triglycerides (LCT)	Contains a combination of medium-chain triglycerides (MCT) plus long-chain triglycerides (LCT)	The presence of MCTs should be taken into consideration when treating patients with disorders of fat metabolism or who are receiving TPN.
Unit of use barcode on individual vials	No unit of use barcode	The barcode used on **Fresenius Propoven 1%** (propofol 1%) may not register accurately on US scanning systems. Other means of confirming the correct drug is being prepared and administered to the correct patient should be utilized.
N/A	Contains a *patient information leaflet*.	For questions **regarding Fresenius Propoven 1%** (propofol 1%) in the United States, please contact APP Medical Information at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com.

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