**Fresenius Kabi USA, LLC**

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January 9, 2019

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

**CITIZEN PETITION**

Dear Sir/Madam:

Fresenius Kabi USA, LLC (FK USA) submits this petition pursuant to 21 CFR 10.30 and in accordance with the regulations at 21 CFR 314.161 requesting the Commissioner of the Food and Drug Administration to provide a determination whether the drug product Sterile Water for Injection, USP, a 250 mL fill size is suitable for submission in an Abbreviated New Drug Application (ANDA).

## A. Action Requested

FK USA requests that the Commissioner of the Food and Drug Administration determine whether the drug product Sterile Water for Injection, USP, in a 250 mL fill size is suitable for submission in an ANDA. FK USA currently markets Sterile Water for Injection, USP in a 1000 mL fill size under ANDA 209689. The additional fill size would be submitted under ANDA 209689 as a Prior Approval Supplement (PAS). The listed drug upon which this petition is based is ICU Medical Inc. Sterile Water for Injection in a Plastic Container, 1000 mL bag. The listed drug is approved under NDA 018233. Petitioner seeks a change in fill size from a 1000 mL fill size to an additional 250 mL fill size.

## B. Statement of Grounds

FD&C Act § 505(j)(2)(A) permits the submission of an ANDA for a drug product that differs in strength from a listed drug after FDA has approved a petition submitted pursuant to FD&C Act § 505(j)(2)(C). The listed drug for the proposed drug product Sterile Water for Injection in a Plastic Container in a single-use 1000 mL bag. A copy of the current Orange Book entry for Sterile Water for Injection in a Plastic Container is included as **Attachment 1**. A copy of the current labeling for Sterile Water for Injection in a Plastic Container in included as **Attachment 2**. The petition proposes a new 250 mL fill size for Sterile Water for Injection.

A comparison of the previously approved drug product to the proposed drug product is provided in **Table 1**.

**Table 1 Comparison of the Reference Listed Drug and Proposed Drug Product**

| | **Reference Listed Drug** | **Proposed Drug Product** |
|---|---|---|
| Name | Sterile Water for Injection, USP | Sterile Water for Injection, USP |
| Conditions of Use (Indications) | Sterile Water for Injection is indicated for use only as a solvent or diluent vehicle for parenterally administered drugs or solutions, and as a source of water for parenteral fluid replenishment after suitable additives are introduced | Sterile Water for Injection is indicated for use only as a solvent or diluent vehicle for parenterally administered drugs or solutions, and as a source of water for parenteral fluid replenishment after suitable additives are introduced |
| Volume | 1000 mL | 250 mL and 1000 mL |
| Dosage Form | Injection | Injection |
| Active Ingredient | Water for Injection, USP | Water for Injection, USP |
| Route of Administration | Intravenous Injection | Intravenous Injection |

Historically, the Agency has required a firm to submit, and obtain approval of a Suitability Petition prior to permitting a change in the total drug content in a parenteral drug product (i.e. the amount or total volume, in a single container), even though the concentration of the drug product remains the same. The Agency has indicated that they consider this synonymous to a change in strength. The proposed drug product does not have a concentration as it is sterile water. The addition of the 250 mL fill size is synonymous to a change in strength. This petition is seeking a change in strength (total drug content) to include the 250 mL fill size.

Sterile Water for Injection is used as a diluent or solvent for parenterally administer drugs or solutions. The addition of the smaller fil size will help to minimize waste when a smaller volume is needed, since the containers are single use. The addition of the 250 mL fill volume will also alleviate the drug shortage of sterile water for Injection. For treatment in remote areas, the use of a smaller Intravenous bag would assist in the patient treatment logistics.

There will be no changes in the proposed labeling aside from the changes in how supplied sought in this petition. The uses, indications, warnings, and directions for use will remain the same as that of the previously approved drug product. Therefore, the petitioner's request for the Agency to find that a change in strength (total drug content from a 1000mL plastic container to a 250 mL plastic container) should raise no concerns of safety or efficacy and should be approved.

**C. Environmental Impact**

In Accordance with the requirements set forth in 21 CFR 25.31, the petitioner hereby requests a Categorical Exclusion from the requirements to prepare an Environmental Impact Assessment.

**D. Economic Impact**

Pursuant to 21 CFR 10.30(b) an economic impact analysis will be provided upon request.

**E. Certification**

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

Sincerely,

Jennifer Boysen

Digitally signed by Jennifer Boysen
DN: c=US, st=Illinois, l=Lake Zurich, ou=Fresenius, ou=IT, o=Fresenius Netcare, cn=Jennifer Boysen, email=jennifer.boysen@fresenius-kabi.com
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## Attachment 1 – Current Orange Book Listing of Sterile Water for Injection in Plastic Container

Display 50 records per page

Search for text in the table:

| Mkt. Status | Active Ingredient | Proprietary Name | Appl No | Dosage Form | Route | Strength | TE Code | RLD | RS | Applicant Holder |
|---|---|---|---|---|---|---|---|---|---|---|
| RX | STERILE WATER FOR INJECTION | STERILE WATER FOR INJECTION IN PLASTIC CONTAINER | N018233 | LIQUID | N/A | 100% | AP | RLD | RS | ICU MEDICAL INC |
| Mkt. Status | Active Ingredient | Proprietary Name | Appl No | Dosage Form | Route | Strength | TE Code | RLD | RS | Applicant Holder |

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

**STERILE WATER- water injection, solution**
**Hospira, Inc.**

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**Sterile Water for Injection, USP**

**FOR DRUG DILUENT USE ONLY**

**Flexible Plastic Container**

Rx only

## DESCRIPTION

Sterile Water for Injection, USP is a sterile, nonpyrogenic, solute-free preparation of distilled water for injection. It is for use only as a sterile solvent or diluent vehicle for drugs or solutions suitable for parenteral administration. The pH is 5.5 (5.0 to 7.0).

Sterile Water for Injection contains no bacteriostat, antimicrobial agent or added buffer and is intended only for single-dose injection after admixture with an appropriate solute or solution. When smaller amounts are required, the unused portion should be discarded.

Sterile Water for Injection is a pharmaceutic aid (vehicle) and parenteral fluid replenisher after addition of an appropriate solute.

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 inside the plastic container also can leach out certain chemical components of the plastic in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

## CLINICAL PHARMACOLOGY

When administered intravenously as a vehicle for drugs, sterile water for injection provides a source of water for parenteral fluid replenishment after sufficient solute is introduced to achieve an osmolarity of 112 mOsmol or more per liter.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirement ranges from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of electrolytes in the body compartments and sodium ($Na^+$) plays a major role in maintaining physiologic equilibrium.

## INDICATIONS AND USAGE

Sterile Water for Injection, USP is indicated for use only as a solvent or diluent vehicle for parenterally administered drugs or solutions and as a source of water for parenteral fluid replenishment after suitable additives are introduced.

For intravenous administration, an osmolar concentration not less than two-fifths (0.4) of the normal osmolarity of the extracellular fluid (280 mOsmol/liter) is essential to avoid intravascular hemolysis.

## CONTRAINDICATIONS

Do not administer without the addition of a solute.

## WARNINGS

FOR DRUG DILUENT USE ONLY.

Intravenous administration of Sterile Water for Injection, USP without additives may result in hemolysis.

The intravenous administration of sterile water for injection with additives can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of administered parenteral solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of such solutions.

**WARNING:** This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

## PRECAUTIONS

Do not use for intravenous injection unless the osmolar concentration of additives totals at least 112 mOsmol/liter (two-fifths of the normal osmolarity of the extracellular fluid — 280 mOsmol/liter).

Do not administer unless solution is clear and container is undamaged. Discard unused portion.

*Pregnancy Category C:* Animal reproduction studies have not been conducted with sterile water for injection. It is also not known whether sterile water containing additives can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sterile water for injection with additives should be given to a pregnant woman only if clearly needed.

*Pediatric Use:* The safety and effectiveness in the pediatric population are based on the similarity of the clinical conditions of the pediatric and adult populations. In neonates or very small infants the volume of fluid may affect fluid and electrolyte balance.

This product contains no more than 25 mcg/L of aluminum.

## ADVERSE REACTIONS

Reactions which may occur because of the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

## OVERDOSAGE

In the event of overhydration or solute overload, re-evaluate the patient and institute appropriate corrective measures. (See ***WARNINGS***.)

## DOSAGE AND ADMINISTRATION

Following suitable admixture of prescribed additive, the dose is usually dependent upon the age, weight and clinical condition of the patient.

### Drug Interactions

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic technique, mix thoroughly and do not store.

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

## HOW SUPPLIED

Sterile Water for Injection, USP is supplied in a single-dose 1000 mL flexible plastic container (NDC 0409-7990-09).

## INSTRUCTIONS FOR USE

### To Open

Tear outer wrap at notch and remove solution container. If supplemental medication is desired, follow directions below before preparing for administration. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

### To Add Medication

1. Prepare additive port.
2. Using aseptic technique and an additive delivery needle of appropriate length, puncture resealable additive port at target area, inner diaphragm and inject. Withdraw needle after injecting medication.
3. The additive port may be protected by covering with an additive cap.
4. Mix container contents thoroughly.

### Preparation for Administration

**(Use aseptic technique)**

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. **NOTE:** See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

**WARNING: DO NOT USE FLEXIBLE CONTAINER IN SERIES CONNECTIONS.**

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing.

Revised: June, 2010

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Hospira, Inc., Lake Forest, IL 60045 USA