August 27, 2013

Attention: DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector: Potential under-dosing or failure to activate

Dear Wholesaler, Healthcare Professional and Emergency Personnel:

Meridian Medical Technologies, a Pfizer Inc. company, would like to inform you that based on a review of product lots at its manufacturing site, Meridian personnel determined that a small number of DuoDote® Auto-Injectors are out of specification. This could potentially prevent some of the units from activating or cause the patient to receive less of the drug than is intended. Delivery of clinically inadequate drug doses is infrequent and occurs in approximately 7 units out of a thousand DuoDote® Auto-Injectors.

DuoDote® Auto-Injector is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.

Organophosphorus poisoning can result in cardiac arrest, respiratory distress and/or arrest, and seizures. Pralidoxime has its most critical effect in relieving the respiratory muscle paralysis. Inadequate dosing with pralidoxime will delay this effect and if treatment is delayed too long, the reversal of muscle paralysis may no longer occur. Atropine reduces secretions in the mouth and respiratory passages, relieves airway constriction, and may reduce centrally-mediated respiratory paralysis caused by organophosphorous chemicals. Inadequate dosing with atropine will delay resolution of these problems.

In cooperation with the U.S. Food and Drug Administration (FDA) and other government agencies, Meridian currently is investigating the issue, implementing corrective action and developing a product replacement plan.

Recommendations to Health Care Providers
We advise customers to retain the product they currently have and to use it per the enclosed product instructions until additional information about replacement product becomes available. Emergency medical professionals and other trained health care providers should carefully follow the product label. As directed in the label, three units of auto-injectors should be available for use with each patient.
Health care providers are directed to verify the visible presence of the needle following administration and to follow these instructions:

1. After the DuoDote® Auto-Injector triggers, hold it firmly against the injection site for approximately 10 seconds. Remove the DuoDote® Auto-Injector from the thigh and look at the green tip.
   a. If the needle is visible, the drug chamber contents will have been administered but in some instances the DuoDote® may not have contained the full intended dose
   b. If the needle is not visible, check to be sure the gray safety release has been removed, and then repeat the administration instructions.
   c. If the needle is still not visible, deploy another unit and repeat the injection.

2. Wait 10 to 15 minutes after the first injection. If the patient does not develop severe symptoms, no further injection is required but definitive medical care should be sought immediately.

3. If at any time after the first injection the patient experiences severe symptoms, two additional injections should be administered in rapid succession and definitive medical care should be sought immediately.

As mentioned above, the company is working with the FDA and other government agencies to resolve the situation. Meridian and government agencies are working together to ensure that customers receive replacement product as quickly as possible, and based on priority of need. FDA is actively reviewing data related to DuoDote® performance beyond its labeled expiration date, and will provide additional information and guidance regarding expired product or product nearing its expiration date. Product beyond expiry should be held for the time being until further guidance can be provided by FDA.

Recommendations to wholesalers
It is not recommended that you return the product you currently have. However, it is important that this information be provided to all appropriate dispensing staff. If you further distributed this product to any other accounts, please communicate this information to those accounts immediately.
Reporting
As of the date of this letter there have been no field-related reports of any adverse effects related to this issue.

As with all medical products, healthcare professionals and consumers are strongly encouraged to report any adverse events that are associated with the use of DuoDote® to either Pfizer Safety (1-800-438-1985) or the FDA’s MedWatch Adverse Event Reporting Program either online, by regular mail, or fax:

- Online: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
- Regular mail: use postage-paid, pre-addressed Form FDA 3500 available at: [www.fda.gov/MedWatch/getforms.htm](http://www.fda.gov/MedWatch/getforms.htm)
  Mail to address on the pre-addressed form
- Fax: 1-800-FDA-0178

Indication
DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector is indicated for the treatment of poisoning by organophosphorous nerve agents as well as organophosphorous insecticides.

Important Safety Information
The DuoDote® Auto-Injector should be administered by emergency medical services personnel who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication. It is intended as an initial treatment of the symptoms of organophosphorous nerve agent or insecticide poisoning; definitive medical care should be sought immediately.

Individuals should not rely solely upon agents such as atropine and pralidoxime to provide complete protection from organophosphorous nerve agents and insecticide poisoning. Primary protection against exposure to organophosphorous nerve agents and insecticides is the wearing of protective garments including masks designed specifically for this use. Evacuation and decontamination procedures should be undertaken as soon as possible. Medical personnel assisting evacuated victims of organophosphorous nerve agent or insecticide poisoning should avoid contaminating themselves by exposure to the victim's clothing.

In the presence of life-threatening poisoning by organophosphorous nerve agents or insecticides there are no absolute contraindications to the use of DuoDote®. When symptoms of poisoning are not severe, DuoDote® should be used with extreme caution in people with heart disease, arrhythmias, recent myocardial infarction, severe narrow angle glaucoma, pyloric stenosis, prostatic hypertrophy, significant renal insufficiency, chronic pulmonary disease, or hypersensitivity to any compound of the product.
No more than three doses should be administered unless definitive medical care (eg, hospitalization, respiratory support) is available. Elderly people and children may be more susceptible to the effects of atropine. DuoDote® is pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Safety and effectiveness in children have not been established.

Muscle tightness and sometimes pain may occur at the injection site. The most common adverse effects of atropine can be attributed to its antimuscarinic action and include dryness of mouth, blurred vision, dry eyes, photophobia, confusion, headache, and dizziness among others. Pralidoxime chloride's adverse effects include changes in vision, dizziness, headache, drowsiness, nausea, tachycardia, increased blood pressure, muscular weakness, dry mouth, emesis, rash, dry skin, hyperventilation, decreased renal function, excitement, manic behavior, and transient elevation of liver enzymes and creatine phosphokinase. When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone.

Please see enclosed full Prescribing Information.

If you require further information about this product, please call 1-866-478-6277.

I thank you for your time and consideration in this matter.

Best Regards,

[Signature]

Tom Handel
SVP-Commercial Pharmaceuticals
Duodol® (atropine and pralidoxime chloride) Injection
Rx Only
Aspirge 2.5 mg/0.5 mL, Paezolidoxime Chloride 600 mg/0.5 mL
Sterile solutions for intramuscular use only

FOR USE IN NERVE AGENT AND INSECTICIDE POISONING ONLY

THE UNDERTIE AUTO-INJECTOR LIES WITHIN DUODELO® AND IS DESIGNED TO DELIVER COMPREHENSIVE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDES

PROPER AUTO-INJECTION DEVICE IS DESIGNED TO CARRY CHEMICAL NERVE AGENTS AND INSECTICIDES. THE DEVICE IS THE PACKAGING AND INSECTICIDE POISONING SPECIFICALLY FOR THIS USE. EXAMINATION AND ADMINISTRATION PROCEDURES SHOULD BE REVIEWED AS SOON AS POSSIBLE. CHEMICAL POISONING ASSESSMENT AND TREATMENT FOR CHEMICAL NERVE AGENTS SHOULD INCLUDE A HERITAGE REPORTED BY THE PACKAGING AND INSECTICIDE POISONING DEVICE TO THE PATIENT'S HEALTH CARE PROVIDER.

DESCRIPTION
Each prefilled Duodol® Auto-Injector contains a small premeasured dose of atropine and pralidoxime chloride in a self contained unit, specifically designed for administration by oral or subcutaneous injection.

The Duodol® Auto-Injector delivers the following:
- 2.5 mg atropine sulfate (as atropine base), in 0.5 mL, purpure, cyanogen, crystals, 37.4 mg pure atropine sulfate, and 0.2 mL, colorless, clear, aqueous solution.
- 600 mg pralidoxime chloride, in 0.5 mL, purpure, pralidoxime chloride, 60.0 mg pralidoxime chloride, and 0.3 mL, clear, colorless solution.

The Phosphate solution is sterile and isopropyl alcohol contains 0.9% and 0.4 mL, sterile, colorless, clear, aqueous solution.

The atropine sulfate is a white, crystalline, odorless substance.

The pralidoxime chloride is a white, crystalline, odorless substance.

The atropine pralidoxime combination is used for the treatment of poisoning due to organophosphorus compounds in all types of nerve agents, including nerve gas.

Chemically, atropine sulfate is an alkaloid, in which the basic structure is that of a tropine, and its formula is C₂₅H₄₉NO₄S. The empirical formula of pralidoxime chloride is C₃₃H₃₅NO₅S.

CAUTION
Atropine can cause an increase in heart rate and blood pressure. It can cause a drop in blood pressure if given in large doses.

Other medications that cause an increase in heart rate and blood pressure should be avoided.

The atropine pralidoxime combination is used for the treatment of poisoning due to organophosphorus compounds in all types of nerve agents, including nerve gas.

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General
The dose used is of atropine and pralidoxime chloride, each in 2.5 mg/0.5 mL, and 600 mg/0.5 mL.

DOSAGE AND ADMINISTRATION
Dose: 2.5 mg atropine sulfate (as atropine base) and 600 mg pralidoxime chloride is indicated for the treatment of poisoning due to organophosphorus compounds in all types of nerve agents, including nerve gas.

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PROCAVAMOL is an orally administered prodrugs of meclofenamate sodium and naproxen sodium. When ProCAVAMOL is administered orally, it is metabolized in the body to release meclofenamate sodium and naproxen sodium, which are responsible for its therapeutic effects.

PROCAVAMOL is available in a strengths of 75 mg, 150 mg, and 225 mg. Each tablet contains meclofenamate sodium and naproxen sodium in a ratio of 4:3. The inactive ingredients in each tablet are lactose, magnesium stearate, and corn starch.

SIDE EFFECTS:

ProCAVAMOL may cause side effects similar to those of meclofenamate sodium and naproxen sodium, including:

- Nausea
- Vomiting
- Abdominal pain
- Headache
- Dizziness
- Dry mouth
- Constipation
- Diarrhea
- Drowsiness
- Rash
- Allergic reactions

ProCAVAMOL should be used cautiously in patients with a history of hepatic or renal disease, or those taking other medications that may affect liver function.

PROCAVAMOL should be taken with food to reduce the risk of gastrointestinal irritation.

PROCAVAMOL may interact with other medications, so it is important to inform your healthcare provider of all medications you are taking before starting ProCAVAMOL.

PROCAVAMOL should not be used by patients with a history of aspirin or nonsteroidal anti-inflammatory drug (NSAID) allergy.

PROCAVAMOL should be used with caution in pregnant or breastfeeding women, as there is no information available about its safety in these populations.

PROCAVAMOL should be used with caution in children or adolescents, as there is no information available about its safety in these populations.

PROCAVAMOL should be stored at room temperature, between 15°C and 30°C (59°F and 86°F), and protected from moisture.


INSTRUCTIONS FOR THE USE OF THE DUODOPETE AUTO-INJECTOR

1. Unpack the DUODOPETE Auto-Injector from the package.
2. Stand the DUODOPETE Auto-Injector up and press the red button to release the dose.
3. Attach the DUODOPETE Auto-Injector to the skin at the site of injection.
4. Press the red button to release the dose. The DUODOPETE Auto-Injector will hold the dose until it is fully engaged.
5. If the DUODOPETE Auto-Injector does not hold the dose until it is fully engaged, then the dose may not have been administered properly.
6. If the DUODOPETE Auto-Injector is used in a patient who is known to be allergic to the medication, then the injection should be administered with caution.
7. If the DUODOPETE Auto-Injector is used in a patient who is known to have a history of allergy, then the injection should be administered with caution.

DUODOPETE Auto-Injector is available in strengths of 50 mg and 100 mg of meclofenamate sodium and naproxen sodium. Each DUODOPETE Auto-Injector contains a syringe that provides a precise amount of medication.

Manufactured by:
Medibloc Medical Technologies, Inc.
Columbia, SC 29218
A subsidiary of Kings Pharmaceuticals, Inc.
1-800-757-2017

© 2011 by Medibloc Medical Technologies, Inc.
September 11, 2013

Attention: DuoDote® (atropine and pralidoxime chloride injection) Auto Injector

Dear Wholesaler, Healthcare Professional and Emergency Personnel:

Further to Meridian’s letter dated August 27, 2013, please see the attached memorandum from the U.S. Food and Drug Administration regarding extending the expiration date of certain lots of DuoDote® (atropine and pralidoxime chloride injection) Auto-Injectors.

If you require further information about the attached memo, please contact Brad Leissa at brad.leissa@fda.hhs.gov or Brooke Courtney at brooke.courtney@fda.hhs.gov.

If you require further information regarding the August 27 letter, please call Meridian’s customer service office at 866-478-6277.

Best Regards,

[Signature]

Tom Handel
SVP-Commercial Pharmaceuticals
Memorandum

Date: September 5, 2013

To: Pfizer/Meridian Medical Technologies

From: Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, and Luciana Borio, MD, Assistant Commissioner for Counterterrorism Policy and Director, Office of Counterterrorism and Emerging Threats

Subject: DuoDote® (atropine and pralidoxime chloride injection) Auto-Injector Expiry Dating

On August 27, 2013, you issued a Dear Healthcare Provider Letter regarding DuoDote auto-injector potential under-dosing or failure to activate. In the letter, you explained that “based on a review of product lots at its manufacturing site, Meridian personnel determined that a small number of DuoDote® Auto-Injectors are out of specification” and that “FDA is actively reviewing data related to DuoDote® performance beyond its labeled expiration date, and will provide additional information and guidance regarding expired product or product nearing its expiration date. Product beyond expiry should be held for the time being until further guidance can be provided by FDA.”

In follow up to the letter, FDA requests that this memorandum regarding expired product or product nearing its expiration date be communicated to the wholesalers, healthcare professionals, and emergency personnel who received the August 27 letter. FDA is aware that the following lots of DuoDote are approaching expiration or have already passed their original expiry date (see table below). Based on FDA’s review of scientific data, FDA has concluded that, provided the products have been stored under labeled storage conditions, it is scientifically supportable for lots of DuoDote listed in the following table to be used for an additional year (1 year) beyond the manufacturer’s original labeled expiry date.

DuoDote product is used for organophosphorous nerve agent or insecticide poisoning. FDA authorizes, pursuant to Section 564A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the following lots of DuoDote to be stored or used for nerve agent poisoning up to one (1) year beyond the manufacturer’s original labeled expiry date, provided that the products have been stored under the labeled storage conditions.1 While Section 564A does not apply to product held

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1 Section 564A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) authorizes FDA to extend the shelf life of certain stockpiled medical countermeasures intended to support the nation’s ability to protect the public health or military preparedness and effectiveness. Under Section 564A(b) of the FD&C Act, products with extended expiry will not be deemed unapproved, adulterated, or misbranded. An expiry date extension must be supported by an appropriate scientific evaluation that is conducted or accepted by FDA. This authority is limited to eligible products.
or used for insecticide poisoning, FDA will not take enforcement action with regard to the storage or use for insecticide poisoning of the following lots of DuoDote up to one (1) year beyond the manufacturer's original labeled expiry date, provided that the products have been stored under the labeled storage conditions.

FDA is not requiring or recommending that the identified lots be relabeled with the new use date.

**DuoDote Auto-Injector Lots**

<table>
<thead>
<tr>
<th>Lot Number</th>
<th>Manufacturer's Original Expiry Date</th>
<th>New Use Date (up to 1 year beyond manufacturer's original expiry date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9AE307</td>
<td>March 31, 2013</td>
<td>March 31, 2014</td>
</tr>
<tr>
<td>9AE356</td>
<td>March 31, 2013</td>
<td>March 31, 2014</td>
</tr>
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<td>9AE545</td>
<td>March 31, 2013</td>
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<tr>
<td>9AE645</td>
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<td>June 30, 2014</td>
</tr>
<tr>
<td>9AE835</td>
<td>September 30, 2013</td>
<td>September 30, 2014</td>
</tr>
</tbody>
</table>

For questions related to this memorandum, please contact Brad Leissa at brad.leissa@fda.hhs.gov or Brooke Courtney at brooke.courtney@fda.hhs.gov.