

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-983

PROPRIETARY NAME REVIEW(S)



Memorandum

Date: July 28, 2006

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CC: **Diane C. Smith, PharmD**
Project Manager
Division of Medication Errors and Technical Support

Subject: **Proprietary Name Rebuttal Response**
NDA 21-983,
Meridian Medical Technologies

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3 Page(s) Withheld

 ✓ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Michelle Safarik
7/28/2006 04:38:46 PM
DDMAC REVIEWER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: 07/07/2006
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OSE REVIEW #:
05-0297-2

TO: Russell Katz, M.D.
Director, Division of Neurology Products
HFD-120

THROUGH: Alina R. Mahmud, R.Ph., M.S., Team Leader
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Division of Medication Errors and Technical Support, HFD-420

FROM: Jinhee L. Jahng, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

Duodote
(Atropine and Pralidoxime Chloride) Injection,
2.1 mg/0.7 mL and 600 mg/2 mL

NDA #: 21-983

SPONSOR: Meridian Medical Technologies

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Duodote. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before the NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.
2. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Duodote acceptable from a promotional perspective.
4. The CDER Labeling and Nomenclature Committee recommends the established name be 'atropine **and** pralidoxime chloride injection', with a statement of concentration for each solution. DMETS therefore suggests revising all labels and labeling to reflect this recommendation (i.e. replace "plus" with "and").

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND PACKAGING REVIEW

DATE OF REVIEW: August 4, 2006

NDA: 21-983

NAME OF DRUG: **Duodote**
(Atropine and Pralidoxime Chloride) Injection
2.1 mg/0.7 mL and 600 mg/2 mL

NDA HOLDER: Meredian Medical Technologies

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neurology Products (HFD-120), for assessment of the proprietary name, "Duodote", regarding potential name confusion with other proprietary or established drug names. In a previous review (ODS Consult # 05-0297 and OSE Review # 05-0297-1), both DDMAC and the Division thought the names [redacted] and [redacted] to be overly fanciful and overstating the efficacy of the product. Therefore, DMETS did not conduct a safety review of the proposed names, [redacted] and [redacted]. However, in ODS Consult # 05-0297 DMETS expressed concerns about how the established name should be presented since the active ingredients are not packaged as a premixed solution containing both ingredients. We deferred this issue to Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee for the proper designation of the established name. Subsequently, the chemist, Dr. Martha Heimann, in collaboration with Dr. Poochikian, recommended that the established name be 'atropine and pralidoxime chloride injection', with a statement of concentration for each solution.

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Subsequent to the initial review, the sponsor submitted a rebuttal to DDMAC's objection to [redacted]. DDMAC and the Division maintained their objection to [redacted] and the sponsor submitted two alternate names, [redacted] and Duodote. DDMAC objected to the name [redacted] because they found it to be misleading. As per e-mail correspondence with the Division of Neurology Products, the Division concurs with DDMAC's comments. Therefore, DMETS did not proceed with the safety review of the proposed proprietary name, [redacted], since the Division supports DDMAC's objection to the name based on promotional concerns. Carton labels, container and insert labeling were provided for review and comment.

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PRODUCT INFORMATION

There is an Atropine/Pralidoxime Chloride formulation (NDA 21-175) held by the US Army, but this application currently appears in the "Discontinued" portion of the FDA Orange Book. Meridian Medical Technologies states that they are planning to make Duodote available by [redacted]. Duodote is expected to replace the Mark I™ Kit and to be maintained by Federal, state and local government

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agencies, public health, EMS personnel, _____
_____ The injectors are intended for self-treatment, caregiver treatment and
available: _____

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Duodote is a prefilled auto-injector providing a single intramuscular dose of atropine and pralidoxime chloride for the treatment of nerve agent and insecticide poisoning. Each Duodote auto-injector delivers two antidotes: 2.1 mg atropine and 600 mg of pralidoxime chloride. Duodote should be used only if symptoms of nerve agent or insecticide poisoning are occurring in a situation where nerve agent or insecticide exposure is known or suspected.

In an environment where nerve agent (or nerve gas) or insecticide exposure is known or suspected, the following are mild and severe symptoms of nerve agent intoxication. Individuals may not have all of the symptoms:

MILD SYMPTOMS

- Blurred vision and sore eyes
- Tearful eyes
- Runny nose
- Increased salivation such as sudden drooling
- Chest tightness or difficulty breathing
- Tremors throughout the body or muscular twitching
- Nausea and vomiting
- Involuntary secretions (phlegm from lungs/airway)

SEVERE SYMPTOMS

- Strange or confused behavior
- Severe difficulty breathing or severe secretions from lungs/airway
- Severe muscular twitching and general weakness
- Involuntary urination and defecation (feces)
- Convulsions
- Unconsciousness

Give one Duodote if the victim experiences two or more MILD symptoms of nerve gas or insecticide exposure. Two additional Duodote injections given in rapid succession are recommended 10 minutes after administering the first Duodote injection if the victim develops any of the SEVERE symptoms listed above.

If a victim is either unconscious or has any of the SEVERE symptoms listed above, immediately administer three Duodote injections in the victim's mid-lateral thigh in rapid succession.

Each Duodote auto-injector contains a sterile solution of atropine injection and a sterile solution of pralidoxime chloride injection in two separate internal chambers. When activated, Duodote sequentially administers both drugs intramuscularly through a single needle in one injection. Duodote will be available in a single unit carton, containing a sterile solution of Atropine Injection (atropine, 2.1 mg/0.7 mL) and a sterile solution of Pralidoxime Chloride Injection (pralidoxime chloride, 600 mg/2 mL) in two separate internal chambers. When activated, Duodote sequentially administers both drugs intramuscularly through a single needle in one injection.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Duodote to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Duodote. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Duodote acceptable from a promotional perspective.
2. The Expert Panel identified nine proprietary names that were thought to have the potential for confusion with Duodote. These products are listed in Table 1 (see pages 5 and 6), along with the dosage forms available and usual dosage.

APPEARS THIS WAY ON ORIGINAL

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual dose*	Other**
Duodote	Atropine and Pralidoxime Chloride Injection 2.1 mg/0.7 mL and 600 mg/2 mL	<i>Treatment of Mild Symptoms:</i> Give one dose if the victim experiences two or more mild symptoms of nerve gas or insecticide exposure. If the victim develops any of the severe symptoms, give two additional injections in rapid succession 10 minutes after administering the first. <i>Treatment of Severe Symptoms:</i> If a victim is either unconscious or has any of the severe symptoms listed above, immediately administer 3 injections into the victim's mid-lateral thigh in rapid succession.	
Decadron	Dexamethasone Tablets 0.5 mg, 0.75 mg	Dosage requirements are variable and must be individualized based on disease and response of patient.	LA
Depakote Depakote ER	Divalproex Sodium Delayed-Release Tablets 125 mg, 250 mg, 500 mg Divalproex Sodium Sprinkle Capsules 125 mg Divalproex Sodium Extended-Release Tablets 250 mg, 500 mg	Delayed-release: <i>Mania:</i> 750 mg daily in divided doses. Titrate to a clinical response with a trough plasma concentration between 50 and 125 mcg/mL. The maximum recommended dosage is 60 mg/kg/day. <i>Migraine:</i> 250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day. Sprinkle capsules, delayed-release tablets and extended-release tablets: <i>Epilepsy:</i> For monotherapy, conversion to monotherapy, and adjunctive therapy, initiate therapy at 10 to 15 mg/kg/day, increasing dosage by 5 to 10 mg/kg/week to achieve optimal clinical response. Usual therapeutic range (50 to 100 mcg/mL). For Simple and Complex Absence Seizures, the initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.	LA
Duodopa (Orphan Drug and Foreign drug)	Levodopa and carbidopa	Information not available.	SA/LA
DuoDerm (OTC) DuoDerm CGF (OTC) DuoDerm Extra Thin (OTC)	Sterile dressings Sterile paste Sterile granules Sterile Control Gel Formula Dressing Sterile Extra Thin Control Gel Formula Dressing	Dressings: For the local management of dermal ulcers, pressure ulcers, leg ulcers, superficial wounds, protective dressings, and postoperative wounds. Paste: For use in association with DuoDerm dressings for local management of exudating dermal ulcers.	LA
Duocet	Hydrocodone Bitartrate and Acetaminophen Tablets 5 mg and 500 mg	1 to 2 tablets every 4 to 6 hours as needed.	LA

Product Name	Dosage form(s), Established name	Usual dose*	Other**
Duodote	Atropine and Pralidoxime Chloride Injection 2.1 mg/0.7 mL and 600 mg/2 mL	<i>Treatment of Mild Symptoms:</i> Give one dose if the victim experiences two or more mild symptoms of nerve gas or insecticide exposure. If the victim develops any of the severe symptoms, give two additional injections in rapid succession 10 minutes after administering the first. <i>Treatment of Severe Symptoms:</i> If a victim is either unconscious or has any of the severe symptoms listed above, immediately administer 3 injections into the victim's mid-lateral thigh in rapid succession.	
DuoNeb	Ipratropium Bromide and Albuterol Sulfate Inhalation Solution 0.5 mg/3 mg in 3 mL unit-dose vials	One 3 mL vial administered 4 times daily via nebulization with up to 2 additional 3 mL doses allowed per day, if needed.	LA
Duocaine	Lidocaine Hydrochloride and Bupivacaine Hydrochloride Injection 10 mg/mL and 3.75 mg/mL	<i>Peribulbar nerve block:</i> 6 to 12 mL <i>Retrobulbar and facial nerve block:</i> 2 to 5 mL For healthy adults, when used without epinephrine the maximum total dose should not exceed 12 mL (120 mg lidocaine and 45 mg bupivacaine). When used with epinephrine, the maximum total dose should not exceed 20 mL (200 mg lidocaine and 75 mg bupivacaine).	LA
Duotan PD Suspension	Pseudoephedrine Tannate and Dexchlorpheniramine Tannate 75 mg and 2.5 mg	10 to 20 mL (2 to 4 teaspoonfuls) not to exceed 8 teaspoonfuls in 24 hours).	LA
Duonate-12	Phenylephrine Tannate and Pyrilamine Tannate 5 mg and 30 mg	> 6 years – 5 to 10 mL every 12 hours 2 to 6 years – 2.5 to 5 mL every 12 hours < 2 years – titrate dose individually	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Duodote with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Duodote (see page 7). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p><i>Duodote</i> <i>#1</i> <i>WAD</i></p>	<p>Duodote #1 Use as directed.</p>
<p>Inpatient RX:</p> <p><i>Duodote i.d.</i></p>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Duodote, the primary concerns relating to look-alike and sound-alike confusion with Duodote are Decadron, Depakote/Depakote ER, Duodopa, DuoDerm, Duocet, DuoNeb, Duocaine, Duotan PD Suspension, and Duonate 12.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Duodote.

1. Decadron and Duodote were found to have look-alike similarities. Decadron (dexamethasone) is a glucocorticoid. The dosage requirements are variable and must be individualized based on disease and response of the patient. Decadron is available as a 0.5 mg and 0.75 mg tablet.

Decadron and Duodote both begin with a "D" and the upstroke letter, "d" is placed in similar positions which gives the name its similar appearance. Additionally, the letters "-eca-" and "-uo-" may resemble each other if not precisely scripted (see writing sample below).

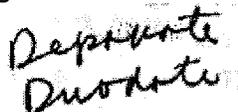
Duodote
Decadron

However, Decadron and Duodote differ with respect to dosage form (tablet vs. injection), route of administration (oral vs. intramuscular), frequency of administration (once daily vs. one time use), and strength (0.5 mg and 0.75 mg vs. 2.1 mg/0.7 mL and 600 mg/2 mL). Since two tablet strengths exist for

Decadron, the possibility that Duodote and Decadron would be confused is minimized since the Decadron strength must be specified. DMETS therefore believes the potential for confusion to be minimal given the differences in product characteristics.

2. Depakote/Depakote ER are names identified to look similar to Duodote when scripted. Depakote/Depakote ER are anticonvulsants containing divalproex sodium. Depakote/Depakote ER are indicated for epilepsy. Additionally, the delayed-release divalproex sodium is also indicated for mania and migraines. The usual daily dose of Depakote/Depakote ER varies depending on the indication and the individual clinical response. Typically, the usual therapeutic range is 50 to 125 mcg/mL. Depakote/Depakote ER is available as a 125 mg, 250 mg, and 500 mg delayed-release tablet, a 250 mg and 500 mg extended release tablet, and a 125 mg sprinkle capsule.

Depakote/Depakote ER and Duodote begin with the letter "D" and end with the letters, "-ote". The "k" and "d" in Depakote/Depakote ER and Duodote, respectively, are both upstroke characters which are placed in similar positions, increasing their propensity to look-alike (see writing sample below). However, the extra letter wedged between the "D" and "a" in Depakote/Depakote ER, help to differentiate it from Duodote, which has one letter less than Depakote/Depakote ER (eight letters vs. seven).

A handwritten sample comparing the words 'Depakote' and 'Duodote'. The word 'Depakote' is written above 'Duodote'. The 'k' in 'Depakote' and the 'd' in 'Duodote' are both upstroke characters, and the 'a' in 'Depakote' is wedged between the 'D' and the 'o', which helps differentiate it from 'Duodote'.

Despite some orthographic similarities, Depakote/Depakote ER and Duodote have many differences in their product characteristics. They differ with respect to dosage form (tablet or capsule vs. injection), route of administration (oral vs. intramuscular), frequency of administration (multiple times daily vs. one time use), and dosage strength (125 mg, 250 mg, 500 mg vs. 2.1 mg/0.7 mL and 600 mg/2 mL). Since multiple strengths exist for Depakote/Depakote ER, the possibility that Duodote and Depakote/Depakote ER would be confused is minimized since the Depakote/Depakote ER strength must be specified. Given the differences in product characteristics, DMETS believes the potential for error is minimized.

3. Duodopa was identified as a name that resembles Duodote in sound and appearance when pronounced and scripted. Duodopa is an experimental Orphan Drug containing the active ingredients, levodopa and carbidopa, indicated for Parkinson's disease. This drug is also available overseas in Sweden, containing the same active ingredients. No other information is available regarding its product characteristics.

The beginning five letters, "Duodo-" in Duodopa and Duodote are identical and each name has seven letters (see sample on page 9), contributing to their look-alike and sound-alike characteristics. The "p" and the "t" have the propensity to sound similar, especially if the prefixes of each name are emphasized, however, their distinctive upstroke and downstroke qualities help to differentiate them in appearance. Since Duodopa is investigational, coupled with the information that it is marketed in Sweden, DMETS believes the actual possibility for confusion with this product name to be minimal due to the area of marketing.

duodopa
duodote

4. DuoDerm was found to have look-alike similarities to Duodote when scripted. DuoDerm is a family trade name used for the over-the-counter (OTC) products, DuoDerm, DuoDerm CGF, and DuoDerm Extra Thin. These products are available as a paste (to be used in association with the DuoDerm dressing), granules, and flexible hydroactive dressing.

Duodote and DuoDerm share the first four letters, "Duod-". However, the "t" in Duodote looks distinct from the "r" in DuoDerm and helps to differentiate the two names from one another.

Duodote
DuoDerm

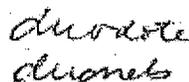
DuoDerm and Duodote differ with respect to dosage form (dressing or paste vs. injection), route of administration (topical vs. intramuscular), frequency of administration (as needed for dermal ulcers vs. one time use), dosage strength (none specified vs. 2.1 mg/0.7 mL and 600 mg/2 mL), and prescription status (OTC vs. Rx). Despite some overlapping orthographic similarities, DMETS believes the potential for a medication error is minimized given the differences in their product characteristics.

5. Duocet and Duodote were found to have look-alike similarities. Duocet is an opioid analgesic combination containing 5 mg of Hydrocodone and 500 mg of Acetaminophen per tablet. Duocet is indicated for the management of mild to moderate pain and is typically given as 1 to 2 tablets every 4 to 6 hours as needed. Duocet and Duodote share the same prefix, "Duo-", and also have the letter "t" in the sixth position (see writing sample below). However, the upstroke character "d" in Duodote, helps to differentiate the two names from each other. Additionally, Duocet and Duodote have different dosage forms (tablet vs. injection), route of administration (oral vs. intramuscular), frequency of administration (every 4 to 6 hours as needed vs. one time use), and dosage strength (5 mg/500 mg vs. 2.1 mg/0.7 mL and 600 mg/2 mL). Also, although both products are available in only one strength, the quantity specified for Duodote will most likely be less than that ordered for Duocet (i.e. 1 or 2 vs. 10 to 30). For the aforementioned reasons, DMETS believes the likelihood for a medication error to occur is minimal.

Duocet
Duodote

6. DuoNeb was identified as a name with similar appearance to Duodote. DuoNeb is a combination of the β_2 -adrenergic bronchodilator, albuterol sulfate, and the anticholinergic bronchodilator, ipratropium bromide. DuoNeb is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator. The recommended dose of DuoNeb is one 3 mL vial administered 4 times per day via nebulization with up to 2 additional 3 mL doses allowed per day. DuoNeb is available as 0.5 mg ipratropium/3 mg albuterol sulfate inhalation solution in 3 mL unit dose vials.

The look-alike characteristics of DuoNeb and Duodote stem from use of same prefix, 'Duo' and the second 'd' in Duodote, if not prominently scripted with an upstroke, may resemble an 'n' (see writing sample below). However, the remaining letters, '-ote', help to differentiate the two names from one another.



Additionally, DuoNeb and Duodote have different dosage forms (inhalation solution vs. injection), route of administration (oral vs. intramuscular), frequency of administration (4 times daily vs. one time use), and dosage strength (0.5 mg/3 mg vs. 2.1 mg/0.7 mL and 600 mg/2 mL). DMETS believes the potential for confusion is minimal given their varying product characteristics and orthographic differences.

7. Duocaine and Duodote were found to look-alike when handwritten. Duocaine is a combination local anesthetic containing 10 mg/mL of lidocaine hydrochloride and 3.75 mg/mL bupivacaine hydrochloride. Duodote is indicated for the production of local or regional anesthesia for ophthalmologic surgery by peripheral nerve block techniques such as paravulbar, retrobulbar, and facial blocks. The usual dose for peribulbar nerve block is 6 mL to 12 mL and for retrobulbar and facial nerve block it is 2 mL to 5 mL. The maximum dosage limit in each case should be individualized after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site.

Duocaine and Duodate have identical prefixes, 'Duo-', but the remaining letters are distinct and help to differentiate the two names from one another (see below).



Additionally, Duocaine will most likely be used in an inpatient or clinic setting, whereas Duodote may be used on an outpatient basis. Duocaine and Duodote vary with respect to route of administration (peribulbar or retrobulbar vs. intramuscular) and dosage strength (10 mg/mL and 3.75 mg/mL vs. 2.1 mg/0.7 mL and 600 mg/2 mL). For the aforementioned differences in product characteristics, DMETS believes the potential for error is minimal.

8. Duotan PD Suspension was found to have look like Duodote, if the modifier, 'PD Suspension', is omitted. The omission of modifiers is a common source of error.⁷ Research supporting the omission of modifiers was published in the *Journal of Internal Medicine* by Timothy S. Lesar. Thus, we must evaluate potential look-alike similarity without the modifier. Duotan PD Suspension is a combination decongestant and antihistamine containing 75 mg of pseudoephedrine tannate and 2.5 mg of dexchlorpheniramine tannate per 5 mL. Duotan PD Suspension is indicated for the temporary relief of nasal congestion and pressure, runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to the common cold, sinusitis, hay fever, or other upper respiratory allergies (allergic rhinitis). The recommended dose is 10 mL to

⁷ Lesar, Timothy S. Prescribing Errors Involving Medication Dosage Forms. *Journal of General Internal Medicine* 2002;17:579-87.

20 mL (2 to 4 teaspoonfuls) every 12 hours not to exceed 8 teaspoonfuls in 24 hours. Duotan PD suspension is available in 16 fluid ounce and 4 fluid ounce bottles.

Duotan and Duodote owe their look-alike similarity to their identical prefixes, 'Duo-', and the placement of upstroke letters, 't' and 'd', in the fourth position of Duotan and Duodote, respectively. Additionally, the 'a' in Duotan resembles the second 'o' in Duodote when scripted (see writing sample below). However, the upstroke letter, 't' in Duodote helps to differentiate Duodote for Duotan. Because Duotan and Duodote are available in only one strength (75 mg/2.5 mg per 5 mL vs. 2.1 mg/0.7 mL and 600 mg/2 mL), the prescriber would not necessarily have to specify the strength when prescribing the medication. However, other varying characteristics such as dosage form (suspension vs. injection), route of administration (oral vs. intramuscular), unit designation ('mL' or 'tsp' vs. 'mg'), and frequency of administration (every 12 hours vs. one time use) help to differentiate the two products from each other. Despite some overlapping look-alike characteristics, DMETS believes the potential for confusion is minimized because of their product differences.

9. Duonate-12 and Duodote were found to have look-alike similarities, if the modifier, '12', is omitted. The omission of modifiers is a common source of error.⁸ Research supporting the omission of modifiers was published in the *Journal of Internal Medicine* by Timothy S. Lesar. Thus, we must evaluate potential look-alike similarity without the modifier. Duonate-12 is a pediatric decongestant and antihistamine containing 5 mg of phenylephrine tannate and 30 mg of pyrilamine tannate per 5 mL. Duonate-12 is used to relieve congestion, sneezing, and water eyes due to colds, flu, or hay fever. The usual dose is: < 2 years – titrate dose individually, 2 to 6 years – 2.5 mL to 5 mL every 12 hours, > 6 years – 5 mL to 10 mL every 12 hours. Duonate-12 is available in a 118 mL unit-of-use bottle with an oral syringe.

Duonate-12 and Duodote share the same prefix, 'Duo-', and similar looking endings, '-ate' vs. '-ote' (see writing sample below).

Additionally, if the second 'd' in Duodote is not prominently scripted with an upstroke, it may resemble an 'n'.

However, Duonate-12 and Duodote have different dosage forms (suspension vs. injection), route of administration (oral vs. intramuscular), frequency of administration (every 12 hours vs. one time use), and dosage strength (5 mg/30 mg vs. 2.1 mg/0.7 mL and 600 mg/2 mL). Duonate-12 is product used exclusively for pediatric patients. Despite some orthographic similarities, DMETS

⁸ Lesar, Timothy S. Prescribing Errors Involving Medication Dosage Forms. *Journal of General Internal Medicine* 2002;17:579-87.

believes the potential for confusion to be minimal given the varying product characteristics.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Duodote, DMETS focused on safety issues relating to possible medication errors. DMETS identified the following areas of improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. In a previous review (ODS Consult #05-0297), DMETS made recommendations to consult with Dr. Guirag Poochikian, the CDER Labeling and Nomenclature Committee Chair regarding the proper designation of the established name 'atropine and pralidoxime chloride injection'. Subsequently, the chemist, Dr. Martha Heimann, in collaboration with Dr. Poochikian, recommended that the established name be 'atropine **and** pralidoxime chloride injection', with a statement of concentration for each solution. DMETS therefore suggests revising all labels and labeling to reflect this recommendation (i.e. replace "plus" with "and").
2. In a letter dated June 21, 2006, the sponsor states in "bullet d" that "The injectors are intended for _____, caregiver treatment and _____
_____. However, DMETS notes that the container label and carton label graphics appear to convey that the dose is only to be _____ the phrasing in the DOSAGE AND ADMINISTRATION section of the insert labeling conveys that Duodote is to be administered by someone else. Thus, DMETS suggests that the sponsor rephrase or include some sort of statement that makes it evident that Duodote may be _____ given by a caregiver.

b(4)

b(4)

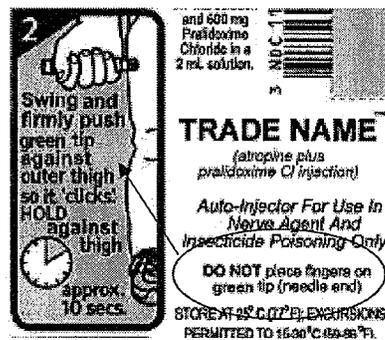
3. _____

b(4)

B. CONTAINER LABEL - Drug Device

1. See comment A1 and A2.
2. The proprietary and established names are not the most prominent information on the label. These names are embedded in the text and are not clearly visible. We recommend relocating the proprietary and established names (ex. Top right) so that it appears at the top of the label.
3. The established name is not at least 1/2 the size of the proprietary name. Thus, increase the size of the established name per 21 CFR 201.10(g)(2).
4. The strength does not appear prominently on the label. Revise labels so that the strength is present immediately below and commensurate in size to the established name.

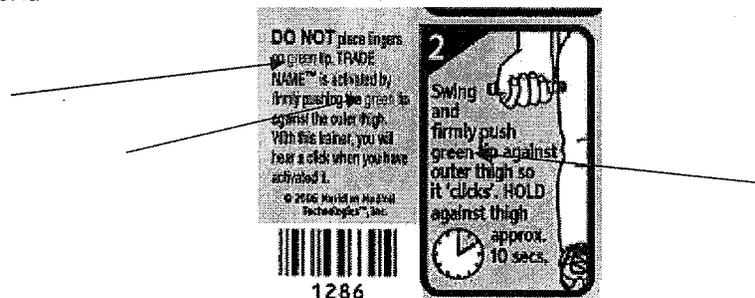
5. The route of administration (for Intramuscular use only) is embedded within the text on the label and is not very visible. Increase the prominence of this statement so that it is more visible and is a stand alone statement outside of the text.
6. Include a "one time use" statement so that the user is clear there is only one dose per injection.
7. The readability of the green color font contrasted with the grey background is poor. Revise the labeling to improve the readability of the text.
8. Post-marketing errors demonstrate that users handling auto-injector devices have accidentally misfired the auto-injector into a person's thumb instead of their thigh. This is likely due to the location of the safety cap and the location of the injector needle. A typical syringe will have a safety cap at the end where the needle is located to protect the user. For some, the placement is counterintuitive and results in misuse of the auto-injector. Therefore, DMETS recommends also including the statement "DO NOT place fingers on green tip" in the graphic instruction section (see red circle and arrow).



9. DMETS notes that the Sponsor uses a clock to signal how long the device should be held against the outer thigh. However, the clock without numbers could lead the user to think it should be held in place for 10 minutes and not 10 seconds.

C. CONTAINER LABEL - Training Device

1. See comment B-8.
2. The green font color contrasted with the blue background color is difficult to read (see picture below). Revise the background color to improve readability of the text.



3. Remove or decrease the prominence of the "Trade Name" on the trainer device to prevent potential for confusion with the auto-injector containing active drug product.

D. CARTON LABELING

1. See comments A1, A2, B3, B5, B6, and B8.
2. The proprietary and established names and the strength are not the most prominent information on the label. The company name appears more prominent than the proprietary/established names and strength. DMETS is concerned that the company name may be confused with the proprietary name. Decrease the prominence of the company name and increase the prominence of the proprietary/established names and the strength.
3. Since Duodote is an injectable, the inactive ingredients should be listed quantitatively and qualitatively. Revise the labeling to include the inactive ingredients per 21 CFR 201.100(b)(5).
4. The graphic instructions are numbered but do not correlate to the numbers in the "Important Duodote Auto-Injector Information" section. The location and proximity of these two items leads one to believe that they correspond to one another. Revise the labeling to include a different system of numbering in the latter mentioned section.

E. INSERT LABELING

1. See comments A1 and A2.
2. The container labels and labeling include graphic pictures to assist in guiding the user on the correct administration of Duodote. These images are absent in the DOSAGE AND ADMINISTRATION section INSTRUCTIONS FOR THE USE OF THE DUODOTE AUTO-INJECTOR. Revise the labeling so that these images are also included in the insert labeling.

APPEARS THIS WAY ON ORIGINAL

Appendix A – DMETS Prescription Study Results

<u>Voice</u>	<u>Inpatient</u>	<u>Outpatient</u>
Duodote	Duodote	Duodote
duodote	Duodote	Duodote
Duadote	Duodote	Duodate
Duadote	Duodote	Duodate
Duodote	DUODOTE	Duodate
Duodote	Duodote	Duodote
Do-a-dote	Duodote	Duodate
Duadote	Duodote	Duodote
Duadote	Duodote	Duodote
Duodote	Duodote	Diodate
Duodote	Duodote	Duodote
	Duodote	Duodate
	Duodote	Duodate
	Duodote	
	Duodote	
	Duodate	
	Duodote	

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/s/

Denise Toyer
9/13/2006 07:47:16 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/13/2006 10:34:41 AM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

MEMO

To: Russell Katz, MD
Director, Division of Neurology Products, HFD-120

From: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, WO22, Mailstop 4447

Through: Kristina Arnwine, PharmD, Acting Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support (DMETS), WO22, Mailstop 4447

Date: November 29, 2005

Re: ODS Consult 05-0297, _____ (Atropine and Pralidoxime), 2.1 mg/0.7 mL plus 600 mg/2 mL
NDA 21-983

b(4)

This memorandum is in response to an October 18, 2005 request from your Division for a review of the proprietary name, _____ (NDA 21-983). Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommend the use of the proposed proprietary name _____ because it is overly fanciful and overstates the efficacy of the product.

b(4)

DDMAC objects to the proposed trade name _____ because it is overly fanciful, suggesting some unique effectiveness or composition. Atropine and pralidoxime are two chemical entities that are currently available. Furthermore, when considering the indication is for treatment after exposure to a nerve agent poisoning, the proposed trade name overstates the effectiveness. When breaking this name down it contains to parts, _____ most likely referring to _____ and _____. The suffix _____ literally means _____. Therefore, the proposed trade name misleadingly suggests that _____ can and _____ mitigating any potential for complications. Without substantial evidence to support that _____ will treat all patients exposed to any _____ the proposed trade name overstates the effectiveness of the drug product.

b(4)

Please note that 21 CFR 201.10(c)(3) states that a proprietary name that implies that the drug or ingredient has some unique effectiveness or composition would be misleading, if the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name. In addition, the statute also provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or

otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

As per e-mail correspondence with the Division of Neurology Products project manager, Jacqueline Ware, on November 29, 2005, the Division concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, _____, since the Division supports DDMAC's objection to the name based on promotional concerns.

b(4)

Although DMETS is not reviewing the proprietary name, we have concerns with the established name of the product since the product is supplied as a dual-chamber syringe that contains two different active ingredients that are currently available on the market. The current presentation of the established name is "atropine plus pralidoxime chloride injection". However, _____ contains two chambers separated by a plunger. The front chamber contains atropine injection 2.1 mg/0.7 mL and the rear chamber contains pralidoxime chloride injection 600 mg/2 mL. When the injector safety release is removed and the green activation tip is pressed against the mid-outer thigh, the injector activates and rapidly sequentially injects atropine, 2.1 mg, and then, pralidoxime, 600 mg, intramuscularly through one needle. Since the active ingredients are not packaged as a premixed solution containing both ingredients, the product is not considered to be a combination drug product until activated. As such, DMETS is concerned about how the established name should be presented. We recommend consulting Guirag Poochikian, Chair, CDER Labeling and Nomenclature Committee for the proper designation of the established name.

b(4)

If you have any questions for DDMAC, please contact the Senior Regulatory Review Officer, Catherine Gray. If you have any other questions or need clarification, please contact the medication errors project manager, Diane Smith at 301-796-0538.

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/s/

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12/14/2005 08:46:26 AM
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