DEAR "HEALTHCARE PROVIDER" LETTERS

The following are two of the most recent "Dear Healthcare Provider" letters that address new information about safety concerns. These letters are forwarded by FDA's office for MedWatch to the MedWatch partners and posted on the internet at www.fda.gov/medwatch/safety. The regulations covering mailing of important information are also enclosed.

This is the retyped text of a letter from GlaxoWellcome, Inc. Contact the company for a copy of any referenced enclosures.

May 2000

Important Drug Warning

Re: Potential safety concerns with the large amount of propylene glycol in AGENERASE® (amprenavir) Oral Solution.

Dear Health Care Professional:

Glaxo Wellcome Inc., is writing to inform you of important changes to the labeling for AGENERASE (amprenavir) Oral Solution, a protease inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 4 years of age and older. These changes highlight the potential risks associated with the large amount of the excipient propylene glycol in AGENERASE Oral Solution.

Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. This enzyme pathway does not attain full adult activity until 12 to 30 months of age. Some patients (infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole) are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Additionally, other patient subgroups as described below may also be at risk. Although, we have received no reports of death or serious injury that have been attributed to propylene gylcol in AGENERASE Oral Solution, there are potential safety concerns regarding AGENERASE Oral Solution due to its high propylene glycol content.

To communicate this important information to health care professionals, the prescribing information for AGENERASE Oral Solution has been revised. The revised boxed warning and the additions to the sections DESCRIPTION, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION are as follows.

The following paragraphs show the complete text of the change to labeling for each section of the package insert for AGENERASE Oral Solution:

- BOXED WARNING (new statements in the box are underlined):

290

AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

- **DESCRIPTION:**

Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE Oral Solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

- **INDICATIONS AND USAGE:**

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

- **CONTRAINDICATIONS:**

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see WARNINGS and PRECAUTIONS).

- **WARNINGS:**

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

If patients require treatment with AGENERASE Oral Solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from AGENERASE Oral Solution to AGENERASE

Capsules as soon as they are able to take the capsule formulation.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

- **PRECAUTIONS:**

Information for Patients:

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole AGENERASE Oral Solution should be used only when AGENERASE Capsule or other protease inhibitor formulations are not therapeutic options.

Patients treated with AGENERASE Capsules should be cautioned against switching to AGENERASE Oral Solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount propylene glycol in AGENERASE Oral Solution.

Patients should be advised that drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution.

Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient propylene glycol (see CONTRAINDICATIONS and WARNINGS). Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

- **OVERDOSAGE:**

AGENERASE Oral Solution contains large amounts of propylene glycol. In the event of overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene glycol can be removed by hemodialysis.

- **DOSAGE AND ADMINISTRATION:**

Consideration should be given to switching patients from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation (see WARNINGS).

In addition to the above changes in the prescribing information, the Patient Information leaflet has been amended to address the information provided in this letter. A copy of this Patient Information is printed at the end of the enclosed package insert. This Patient Information is supplied to pharmacies with each bottle of the product for dispensing to the patient.

Glaxo Wellcome is committed to providing you with the most current product information for the management of your patients being treated with AGENERASE. You can assist us in monitoring the safety of AGENERASE by reporting adverse reactions to the Glaxo Wellcome Product Surveillance Department at 1-888-825-5249 or to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.fda.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Please refer to the enclosed revised prescribing information for AGENERASE Oral Solution. If you have questions about the new information or want additional medical information about

AGENERASE Oral Solution, please contact the Glaxo Wellcome Customer Response Center at 1-888-TALK2GW (1-888-825-5249).

Sincerely,

Marc Rubin, M.D.
Vice President, Therapeutic Development and Product Strategy
HIV, Infectious Disease and Hepatitis

Glaxo Wellcome, Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, North Carolina 27709-3398
Telephone: 919 483-2100

Return to Summary

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

This is the retyped text of a letter from Wyeth-Ayerst Laboratories. Contact the company for a copy of any referenced enclosures.

March 2000

Dear Healthcare Professional:

This letter is to inform you about changes to the prescribing information for Fluothane (halothane, U.S.P.). Many of these changes are intended to highlight and expand upon information already present in the labeling for Fluothane. Much of this information is well-known to persons familiar with the administration of halothane. However, important new information has been included to reflect current scientific opinion, accepted standards of care, and safety information in an effort to ensure the anesthesia care provider remains informed in making treatment decisions regarding the administration of Fluothane.

Arrhythmias in Children Undergoing Halothane Anesthesia for Out-patient Dental Surgery

In a prospective randomized trial conducted in the United Kingdom, the efficacy and safety of halothane and sevoflurane were compared in children undergoing dental surgery in an out-patient setting. It should be noted that in this study general inhalational anesthesia was administered by "nasal masks", and patients were not intubated. Patient end-tidal CO2, if measured in this study, was not reported. The trial demonstrated a strong association between halothane and ventricular arrhythmias, especially ventricular tachycardia.[1]

Q-T Interval Prolongation and Arrythmias

Halothane has been reported to cause prolongation of the Q-T interval. Q-T interval prolongation constitutes a risk of ventricular tachycardia, including torsade de points. This should be taken into consideration when contemplating the use of halothane in patients with existing Q-T prolongation or in patients receiving other drugs known to prolong the Q-T interval.

These reports confirm the pro-arrhythmic potential of halothane.

Revisions to Prescribing Information for Fluothane

The prescribing information for Fluothane has been revised to include information on circumstances under which Fluothane may be administered. This information is found in the beginning of the **Warnings** section of the revised Fluothane prescribing information.

> Fluothane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen

enrichment, and circulatory resuscitation must be immediately available. Unless recognized standards for anesthesia care are adhered to and qualified personnel present and equipment and drugs are on hand to manage emergencies, halothane should not be administered.

The decision to administer halothane should include an assessment of the individual patient and the safety profile of halothane (e.g., pro-arrhythmic properties, hepatotoxicity, malignant hyperthermia).

Halothane administration is commonly associated with arrhythmias, some of which may be fatal. The risk of arrhythmias during halothane anesthesia may be increased in certain procedures (e.g., dental surgery), clinical states (metabolic abnormalities, hypoxia and/or hypercapnia, pre-existing Q-T prolongation or history of arrhythmias), and populations (e.g., children).

The new prescribing information for Fluothane contains several other revisions in the **Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosing and Administration** sections. Many of these revisions have been made to reflect current scientific opinion and accepted standards of care. The major revisions include the following:

- The **Contraindications** section has been modified and expanded to include patients with known sensitivity to halothane or other halogenated anesthetics; patients with known or suspected susceptibility to malignant hyperthermia; obstetrical anesthesia except when uterine relaxation is required; and patients who have developed jaundice or acute hepatic damage from previous exposure to halothane unless other causes of liver damage were demonstrated.

- The **Warnings** section has been modified and expanded to include information moved from the previous **Precautions** section on hepatotoxicity and malignant hyperthermia. Cases of halothane-associated liver toxicity ("halothane hepatitis"), in some instances leading to liver failure and death, have been described in the literature and in spontaneous reports. Repeat exposure to halothane within a short period of time is not recommended. This expanded information on hepatotoxicity and malignant hyperthermia reflects current recommendations on diagnosis, monitoring, and treatment.

- The **Precautions** section has been modified and expanded to include new information on PEDIATRIC USE, additional information on DRUG INTERACTIONS and new subsections on GERIATRIC USE and LABORATORY TESTS.

If you are aware of any serious adverse events associated with the administration of Fluothane, we encourage you to report such information to Wyeth-Ayerst Laboratories at 1-800-934-5556 or to the Food and Drug Administration MedWatch Program by telephone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, by internet at www.FDA.gov/medwatch, or by mail to the following address: MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

A copy of the revised Fluothane prescribing information is included with this letter. If you have any questions regarding the information discussed in this letter, please call 1-800-934-5556 or write to: Wyeth-Ayerst Laboratories, Global Product Information and Labeling Division, 150-B1 Building, P.O. Box 8299, Philadelphia, PA 19101-8299.

Sincerely,

David M. Humphrey, M.D.
Director, Clinical Affairs
Global Medical Affairs

---

1. Blayney M., et al Cardiac arrythmias in children during out-patient general anesthesia for dentistry: A prospective randomized trial. Lancet, 1999; 354; 1864-66.

Wyeth-Ayerst Laboratories
Global Product Information and Labeling Division
150-B1 Building, P.O. Box 8299
Philadelphia, PA 19101-8299

Return to Summary

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

[Code of Federal Regulations]
[Title 21, Volume 4, Parts 200 to 299]
[Revised as of April 1, 1999]
From the U.S. Government Printing Office via GPO Access
[**CITE: 21CFR200.5**]

[Page **5**-6]

TITLE 21--FOOD AND DRUGS

PART 200--GENERAL--Table of Contents

Subpart A--General Provisions

Sec. 200.**5** Mailing of important information about drugs.

Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care. In the public interest, such mail should be distinctive in appearance so that it will be promptly recognized and read. The Food and Drug Administration will make such mailings in accordance with the specifications set forth in this section. Manufacturers and distributors of drugs are asked to make such mailings as prescribed by this section and not to use the distinctive envelopes for ordinary mail.

(a) Use first class mail and No. 10 white envelopes.

(b) The name and address of the agency or the drug manufacturer or distributor is to appear in the upper left corner of the envelope.

(c) The following statements are to appear in the far left third of the envelope front, in the type and size indicated, centered in a rectangular space approximately 3 inches wide and 2\1/4\ inches high with an approximately \3/8\ inch-wide border in the color indicated:

(1) When the information concerns a significant hazard to health, the statement:

IMPORTANT

DRUG

WARNING

The statement shall be in three lines, all capitals, and centered. ``Important'' shall be in 36 point Gothic Bold type. ``Drug'' and ``Warning'' shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be red.

(2) When the information concerns important changes in drug package labeling, the statement:

IMPORTANT

PRESCRIBING

INFORMATION

The statement shall be in three lines, all capitals, and centered. ``Important'' shall be in 36 point Gothic Bold type. ``Prescribing'' and ``Information'' shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be blue.

(3) When the information concerns a correction of prescription drug advertising or labeling, the statement:

[[Page 6]]

IMPORTANT

CORRECTION

OF DRUG

INFORMATION

The statement shall be in four lines, all capitals, and centered. ``Important'' shall be in 36 point Gothic Bold type. ``Correction,'' ``Of Drug,'' and ``Information'' shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be brown.

TALK PAPERS

The following are the most recent two Talk Papers issued to communicate a safety issue. Talk Papers are sent to the consolidated press and posted on the MedWatch portion of the FDA internet site (www.fda.gov/medwatch/safety).

This is the retyped text of a letter from GlaxoWellcome, Inc. Contact the company for a copy of any referenced enclosures.

May 2000

Important Drug Warning

Re: Potential safety concerns with the large amount of propylene glycol in AGENERASE® (amprenavir) Oral Solution.

Dear Health Care Professional:

Glaxo Wellcome Inc., is writing to inform you of important changes to the labeling for AGENERASE (amprenavir) Oral Solution, a protease inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 4 years of age and older. These changes highlight the potential risks associated with the large amount of the excipient propylene glycol in AGENERASE Oral Solution.

Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. This enzyme pathway does not attain full adult activity until 12 to 30 months of age. Some patients (infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole) are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Additionally, other patient subgroups as described below may also be at risk. Although, we have received no reports of death or serious injury that have been attributed to propylene gylcol in AGENERASE Oral Solution, there are potential safety concerns regarding AGENERASE Oral Solution due to its high propylene glycol content.

To communicate this important information to health care professionals, the prescribing information for AGENERASE Oral Solution has been revised. The revised boxed warning and the additions to the sections DESCRIPTION, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION are as follows.

The following paragraphs show the complete text of the change to labeling for each section of the package insert for AGENERASE Oral Solution:

- BOXED WARNING (new statements in the box are underlined):

AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

- **DESCRIPTION:**

Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE Oral Solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

- **INDICATIONS AND USAGE:**

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

- **CONTRAINDICATIONS:**

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see WARNINGS and PRECAUTIONS).

- **WARNINGS:**

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

If patients require treatment with AGENERASE Oral Solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from AGENERASE Oral Solution to AGENERASE

Capsules as soon as they are able to take the capsule formulation.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

- **PRECAUTIONS:**

Information for Patients:

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole AGENERASE Oral Solution should be used only when AGENERASE Capsule or other protease inhibitor formulations are not therapeutic options.

Patients treated with AGENERASE Capsules should be cautioned against switching to AGENERASE Oral Solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount propylene glycol in AGENERASE Oral Solution.

Patients should be advised that drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution.

Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient propylene glycol (see CONTRAINDICATIONS and WARNINGS). Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

- **OVERDOSAGE:**

AGENERASE Oral Solution contains large amounts of propylene glycol. In the event of overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene glycol can be removed by hemodialysis.

- **DOSAGE AND ADMINISTRATION:**

Consideration should be given to switching patients from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation (see WARNINGS).

In addition to the above changes in the prescribing information, the Patient Information leaflet has been amended to address the information provided in this letter. A copy of this Patient Information is printed at the end of the enclosed package insert. This Patient Information is supplied to pharmacies with each bottle of the product for dispensing to the patient.

Glaxo Wellcome is committed to providing you with the most current product information for the management of your patients being treated with AGENERASE. You can assist us in monitoring the safety of AGENERASE by reporting adverse reactions to the Glaxo Wellcome Product Surveillance Department at 1-888-825-5249 or to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.fda.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Please refer to the enclosed revised prescribing information for AGENERASE Oral Solution. If you have questions about the new information or want additional medical information about

AGENERASE Oral Solution, please contact the Glaxo Wellcome Customer Response Center at 1-888-TALK2GW (1-888-825-5249).

Sincerely,

Marc Rubin, M.D.
Vice President, Therapeutic Development and Product Strategy
HIV, Infectious Disease and Hepatitis

Glaxo Wellcome, Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, North Carolina 27709-3398
Telephone: 919 483-2100

Return to Summary

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

This is the retyped text of a letter from Wyeth-Ayerst Laboratories. Contact the company for a copy of any referenced enclosures.

March 2000

Dear Healthcare Professional:

This letter is to inform you about changes to the prescribing information for Fluothane (halothane, U.S.P.). Many of these changes are intended to highlight and expand upon information already present in the labeling for Fluothane. Much of this information is well-known to persons familiar with the administration of halothane. However, important new information has been included to reflect current scientific opinion, accepted standards of care, and safety information in an effort to ensure the anesthesia care provider remains informed in making treatment decisions regarding the administration of Fluothane.

Arrhythmias in Children Undergoing Halothane Anesthesia for Out-patient Dental Surgery

In a prospective randomized trial conducted in the United Kingdom, the efficacy and safety of halothane and sevoflurane were compared in children undergoing dental surgery in an out-patient setting. It should be noted that in this study general inhalational anesthesia was administered by "nasal masks", and patients were not intubated. Patient end-tidal CO2, if measured in this study, was not reported. The trial demonstrated a strong association between halothane and ventricular arrhythmias, especially ventricular tachycardia.[1]

Q-T Interval Prolongation and Arrythmias

Halothane has been reported to cause prolongation of the Q-T interval. Q-T interval prolongation constitutes a risk of ventricular tachycardia, including torsade de points. This should be taken into consideration when contemplating the use of halothane in patients with existing Q-T prolongation or in patients receiving other drugs known to prolong the Q-T interval.

These reports confirm the pro-arrhythmic potential of halothane.

Revisions to Prescribing Information for Fluothane

The prescribing information for Fluothane has been revised to include information on circumstances under which Fluothane may be administered. This information is found in the beginning of the **Warnings** section of the revised Fluothane prescribing information.

> Fluothane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen

enrichment, and circulatory resuscitation must be immediately available. Unless recognized standards for anesthesia care are adhered to and qualified personnel present and equipment and drugs are on hand to manage emergencies, halothane should not be administered.

The decision to administer halothane should include an assessment of the individual patient and the safety profile of halothane (e.g., pro-arrhythmic properties, hepatotoxicity, malignant hyperthermia).

Halothane administration is commonly associated with arrhythmias, some of which may be fatal. The risk of arrhythmias during halothane anesthesia may be increased in certain procedures (e.g., dental surgery), clinical states (metabolic abnormalities, hypoxia and/or hypercapnia, pre-existing Q-T prolongation or history of arrhythmias), and populations (e.g., children).

The new prescribing information for Fluothane contains several other revisions in the **Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosing and Administration** sections. Many of these revisions have been made to reflect current scientific opinion and accepted standards of care. The major revisions include the following:

- The **Contraindications** section has been modified and expanded to include patients with known sensitivity to halothane or other halogenated anesthetics; patients with known or suspected susceptibility to malignant hyperthermia; obstetrical anesthesia except when uterine relaxation is required; and patients who have developed jaundice or acute hepatic damage from previous exposure to halothane unless other causes of liver damage were demonstrated.

- The **Warnings** section has been modified and expanded to include information moved from the previous **Precautions** section on hepatotoxicity and malignant hyperthermia. Cases of halothane-associated liver toxicity ("halothane hepatitis"), in some instances leading to liver failure and death, have been described in the literature and in spontaneous reports. Repeat exposure to halothane within a short period of time is not recommended. This expanded information on hepatotoxicity and malignant hyperthermia reflects current recommendations on diagnosis, monitoring, and treatment.

- The **Precautions** section has been modified and expanded to include new information on PEDIATRIC USE, additional information on DRUG INTERACTIONS and new subsections on GERIATRIC USE and LABORATORY TESTS.

If you are aware of any serious adverse events associated with the administration of Fluothane, we encourage you to report such information to Wyeth-Ayerst Laboratories at 1-800-934-5556 or to the Food and Drug Administration MedWatch Program by telephone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, by internet at www.FDA.gov/medwatch, or by mail to the following address: MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

A copy of the revised Fluothane prescribing information is included with this letter. If you have any questions regarding the information discussed in this letter, please call 1-800-934-5556 or write to: Wyeth-Ayerst Laboratories, Global Product Information and Labeling Division, 150-B1 Building, P.O. Box 8299, Philadelphia, PA 19101-8299.

Sincerely,

David M. Humphrey, M.D.
Director, Clinical Affairs
Global Medical Affairs

---

1. Blayney M., et al Cardiac arrythmias in children during out-patient general anesthesia for dentistry: A prospective randomized trial. Lancet, 1999; 354; 1864-66.

Wyeth-Ayerst Laboratories
Global Product Information and Labeling Division
150-B1 Building, P.O. Box 8299
Philadelphia, PA 19101-8299

Return to Summary

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

PUBLIC HEALTH ADVISORIES

The following are two of the most recently issued Public Health Advisories. Public Health Advisories are sent to major professional and patient advocacy organizations as well as the MedWatch Partners. They are also posted on the drug information portion of the CDER internet site (www.fda.gov/cder/drug/advisory).

FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH ADVISORY

SUBJECT: SAFE AND APPROPRIATE USE OF INFLUENZA DRUGS

12 January 2000

Dear Health Care Professional:

Diagnostic and therapeutic decisions for patients with symptoms of influenza involve many factors, including consideration of whether to prescribe one of the four drugs currently approved for treatment of influenza. Two of these drugs, amantadine (Symmetrel® and others) and rimantadine (Flumadine®), have been available for many years in the United States. The recent approval of, and promotional activities for, two additional drugs, zanamivir (Relenza®) and oseltamivir (Tamiflu®), have increased attention to, and interest in, the role of specific anti-viral therapy in this disease.

Given that influenza is now occurring in many areas of the country, FDA is issuing this public health advisory to health care professionals to remind prescribers of important clinical decisions that need to be made when considering use of anti-viral drugs for treatment of patients with signs and symptoms of influenza.

The following three considerations are important primarily for two reasons. First, they are important in identifying patients who are appropriate candidates for anti-viral therapy. Secondly, they are important in recognizing patients who may be at risk for serious adverse outcomes from other non-influenza diagnoses or from adverse events potentially related to anti-influenza therapy.

1. **Vaccination remains the primary method of preventing and controlling influenza.**
2. **Always consider the possibility of primary or concomitant bacterial infection when making treatment decisions for patients with suspected influenza.**

   When initiation of anti-viral therapy alone is considered on a presumptive basis, ongoing clinical assessment and diagnostic evaluation of the patient continues to be important. FDA has received several reports of patients with serious bacterial infections who initially had influenza-like symptoms and whose bacterial infections progressed during treatment with antiviral drugs alone. Prescribers should be aware that patients with severe influenza-like illness, especially patients with chronic medical conditions or complicated manifestations of acute illness, might have significant bacterial infections instead of, or in addition to, viral illness. These anti-viral products have no activity against bacterial infections. Appropriate anti-bacterial therapy should be initiated whenever bacterial infection is suspected.

3. **Use special caution if prescribing Relenza® to patients with underlying asthma or chronic obstructive pulmonary disease (COPD).**

FDA has received several reports of deterioration of respiratory function following inhalation of Relenza® in patients with underlying asthma or COPD. Causal relationships with drug therapy are extremely difficult to evaluate in the setting of complex medical processes, but the possibility can not be excluded that an acute decline in respiratory function may contribute to a fatal outcome in patients with a complicated pre-existing medical history and pulmonary compromise. The Relenza® package insert contains important precautionary information regarding risks of bronchospasm in patients with underlying airway disease and regarding the lack of proven efficacy in such persons. If a decision is made to prescribe Relenza® for a patient with underlying airway disease, this should be done with careful consideration of the potential risks and benefits. In such patients, Relenza® should be used under conditions of careful monitoring, proper observation and appropriate supportive care, including the availability of short-acting bronchodilators.

The evidence for use of anti-viral drugs to treat influenza is based principally on studies in patients with uncomplicated influenza. There is not clear evidence for safety and efficacy in persons with underlying respiratory or cardiac diseases, or in persons with complications of an acute influenza episode (for example, viral or bacterial pneumonia). Such patients may require extensive supportive and adjunctive care. Anti-viral therapy has not been shown to reduce the need for such care and monitoring.

All health care professionals are encouraged to report any serious adverse event associated with the use of anti-viral drugs for influenza to the FDA's MedWatch program at 1-800-FDA-1088 (fax 1-800-FDA-0178), or to the respective pharmaceutical manufacturers:

Flumadine® (rimantadine), Forest Pharmaceuticals, Inc., 1-800-678-1605

Relenza® (zanamivir), GlaxoWellcome, Inc. 1-800-825-5249

Symmetrel® (amantadine; also available in generic forms), Endo Pharmaceuticals, Inc., 1-800-462-3636

Tamiflu® (oseltamivir), Roche Laboratories, Inc., 1-800-526-6367

Sincerely yours,

Murry M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

FDA PUBLIC HEALTH ADVISORY
February 10, 2000

List of Drugs in the Journal of American Medical Association Article, Jane Henney (Linked 5/31/2000)

Subject: RISK OF DRUG INTERACTIONS WITH ST JOHN'S WORT AND INDINAVIR AND OTHER DRUGS

Dear Health Care Professional:
The Food and Drug Administration would like to inform you about results from a study conducted by The National Institutes of Health (NIH) that showed a significant drug interaction between St John's wort (hypericum perforatum), an herbal product sold as a dietary supplement, and indinavir, a protease inhibitor used to treat HIV infection. In this study, concomitant administration of St. John's wort and indinavir substantially decreased indinavir plasma concentrations, potentially due to induction of the cytochrome P450 metabolic pathway. For additional information on this study please refer to the February 12, 2000 Lancet publication (Piscitelli, et al).

RECOMMENDATIONS:

Indinavir and other antiretroviral agents

At this time, pharmacokinetic data are available only for concomitant administration of indinavir with St. John's wort. However, based on these results, it is expected that St John's wort may significantly decrease blood concentrations of all of the currently marketed HIV protease inhibitors (PIs) and possibly other drugs (to varying degrees) that are similarly metabolized, including the nonnucleoside reverse transcriptase inhibitors (NNRTIs). Consequently, concomitant use of St John's wort with PIs or NNRTIs is not recommended because this may result in suboptimal antiretroviral drug concentrations, leading to loss of virologic response and development of resistance or class cross-resistance.

Because herbal products are widely used in the United States and are available in various forms such as combination products and teas, it is important that health care professionals ask patients about concomitant use of products that could contain St. John's wort (hypericum perforatum).

In addition, FDA is working closely with drug manufacturers to ensure that product labeling of antiretrovirals is revised to highlight the potential for drug interactions with St. John's wort.

Other drugs

Based on this study and reports in the medical literature, St. John's wort appears to be an inducer of an important metabolic pathway, cytochrome P450. As many prescription drugs used to treat conditions such as heart disease, depression, seizures, certain cancers or to prevent conditions such as transplant rejection or pregnancy (oral contraceptives) are metabolized via this pathway,

health care providers should alert patients about these potential drug interactions to prevent loss of therapeutic effect of any drug metabolized via the cytochrome P450 pathway.

All health care professionals are encouraged to report any serious adverse event associated with the concomitant use of prescription drugs and St. John's wort products to the FDA's MedWatch program at 1-800-FDA-1088 (fax 1-800-FDA-0178).

Sincerely yours,

Murray M. Lumpkin, M.D
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

Susan Alpert, Ph.D., M.D.
Director of Food Safety
Center for Food Safety and Applied Nutrition

QUESTIONS & ANSWERS

Q&As are posted on the MedWatch portion of the FDA internet site (www.fda.gov/medwatch/safety)

U.S. Food and Drug Administration

May 6, 1998

Q & A's: LOW MOLECULAR WEIGHT HEPARINS/HEPARINOIDS AND SPINAL/EPIDURAL ANESTHESIA

The Food and Drug Administration (FDA) appreciates the communications that have been received from the healthcare community regarding the December 15, 1997 FDA Public Health Advisory related to the use of low molecular weight heparins (LMWHs)/heparinoids and spinal/epidural anesthesia.

In response to your questions and concerns, the FDA is providing updated information with respect to this important safety-related issue.

1. **What was the purpose of the December 15, 1997 FDA Public Health Advisory?**

   The purpose of the Public Health Advisory was to call attention to postmarketing reports of patients who have developed epidural or spinal hematomas with the concurrent use of LMWHs/heparinoids and spinal/epidural anesthesia or spinal puncture.

2. **How serious were the reports?**

   Many of the hematomas caused neurologic injury, including long-term or permanent paralysis. Given the potential seriousness of this complication, the Public Health Advisory was released in the belief that patients and healthcare professionals should be notified.

3. **Did these reports involve all LMWHs and heparinoids currently available on the market?**

   The four currently approved drug products are Fragmin (dalteparin sodium) Injection, Lovenox (enoxaparin sodium) Injection, Normiflo (ardeparin sodium) Injection, and Orgaran (danaparoid sodium) Injection. The postmarketing reports received at the time of the Public Health Advisory involved patients who were treated with Lovenox .

   However, the adverse event would be expected to occur with drugs with similar pharmacological activity used in the same manner. Therefore, the FDA asked all manufacturers of LMWHs and heparinoids to revise their package inserts to provide further information for the safe and effective use of these drugs.

   Since the Public Health Advisory, two Norwegian patients administered Fragmin have been reported in the literature to have developed epidural hematomas.

4. **How many reports does FDA have to date?**

   As of April 1998, there have been more than 50 spontaneous safety reports describing patients who have developed epidural or spinal hematomas with concurrent use of enoxaparin sodium

and spinal/epidural anesthesia or spinal puncture.

5. **Is the FDA contraindicating or seeking to eliminate the use of spinal/epidural anesthesia with LMWHs/heparinoids?**

   No, the FDA is **NOT** contraindicating or eliminating the use of spinal/epidural anesthesia with LMWHs/heparinoids.

   The purpose of the December 15, 1997 FDA Public Health Advisory was to inform healthcare professionals about the reporting of these serious adverse events. Further, the FDA does not regulate the practice of medicine.

6. **How frequently do these specific adverse events occur?**

   The limitations of spontaneous reports data, particularly underreporting, make it impossible to say how frequently these specific adverse events occur. Because these reports are made voluntarily, only those cases that are reported are known, and there is no definitive information as to the size of the potential patient population exposed to the agents in question.

   With respect to Lovenox Injection, millions of syringes have been distributed since its market introduction.

7. **Are there any common clinical factors among the reports?**

   Yes. Approximately 75% of the patients were women. The overall patient median age was about 75 years. The majority of patients had either knee or hip replacement surgery, and a minority had spinal surgery.

   The majority of the patients had spinal/epidural anesthesia with or without catheter placement. Five reports were for patients who had no surgery. Of these five case reports, three patients had spinal injections and two patients had no known spinal puncture/trauma.

8. **In the reports, what were the signs and symptoms of spinal/epidural hematoma?**

   The reported signs and symptoms were sensory deficits including numbness and/or paresthesias; motor deficits including leg weakness and/or paralysis; and bowel/bladder dysfunction. Back pain was NOT the typical presentation, although some patients also experienced this symptom.

   Patients with spinal/epidural hematomas may initially present with a single sign/symptom, or a combination of signs and symptoms.

9. **When did the hematomas occur?**

   The onset of signs/symptoms was generally about 2-3 days after initiation of Lovenox therapy.

   Overall, the reports did not provide sufficient information to correlate the timing of epidural/ spinal catheter removal and the onset of neurological signs/symptoms associated with spinal/ epidural hematomas.

10. **Does analysis of the reports indicate the optimal time for performing spinal/epidural procedures in patients anticoagulated or scheduled to be anticoagulated with LMWHs or heparinoids?**

The available clinical data for the reported cases of spinal/epidural hematomas do not provide adequate information to determine the optimal time for performing spinal/epidural procedures in patients anticoagulated or scheduled to be anticoagulated with LMWHs or heparinoids.

However, when performing procedures in patients anticoagulated or scheduled to be anticoagulated with LMWHs or heparinoids, including: 1) spinal anesthesia, 2) placing or removing spinal/epidural catheters, or 3) any procedure involving epidural or dural puncture, the following should be considered:

- Time of anticoagulation administration
- Dosing regimen
- Pharmacokinetic profile of the drug (see current package insert of individual agent)
- Concomitant administration of medications known to increase bleeding [e.g., non-steroidal anti-inflammatory drugs (NSAIDs) or other anticoagulants].

11. **Where can I get additional information about this risk?**

Regarding specific evidence and scientific documentation of spinal/epidural hematomas/bleeds associated with the use of LMWHs and spinal/epidural anesthesia, you can obtain the tabulation of reports in Lovenox users made to FDA through January 7, 1998 by calling either:

- *Fax-on-Demand*: 1-800-342-2722 or (301) 827-0577, enter 941
- MedWatch at 1-800-FDA-1088 (press "O")

In addition, the following literature review articles are recommended:

- Horlocker and Heit (Anesth Analg 1997;85:874-85)
- Porterfield and Wu (Journal of Clinical Anesthesia 1997;9:74-77)
- Vandermuelen, Van Aken, and Vermylen (Anesth Analg 1994;79:1165-77)

12. **What do practitioners need to be aware of when using these products?**

At this time, as stated in the Public Health Advisory, FDA believes practitioners should be aware of the following:

- When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with LMWHs or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or

spinal hematoma which can result in long-term or permanent paralysis.

- The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis, such as NSAIDs, platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

- Patients should be frequently monitored for signs and symptoms of neurological impairment, as the majority of patients presented with paresthesias, leg weakness, sensory loss, motor deficit, or bowel/bladder dysfunction. Back pain was NOT the typical presentation, although some patients also experienced this symptom.

  If neurologic compromise is noted, urgent intervention is necessary.

- Patients should be instructed to inform their healthcare provider immediately if they experience any of these signs/symptoms.

- Practitioners should consider fully the potential benefit versus risk before neuraxial intervention in patients anticoagulated or scheduled to be anticoagulated for thromboprophylaxis.

13. **Have the requested package insert revisions been made?**

Yes. The package inserts of Fragmin , Lovenox , Normiflo , and Orgaran Injections were revised in January 1998 to include additional safety information and recommendations in a Boxed Warning, with related revisions in the Warnings, Precautions, and Adverse Reactions sections. These revisions were addressed in the Public Health Advisory, and are outlined in the answer immediately above.

To further review these labeling changes, go to the MedWatch Web Site at www.fda.gov/medwatch/safety/1998/jan98.htm, or contact the following individual manufacturers for a copy of their specific revised label/package insert:

- **Fragmin** : Pharmacia & Upjohn: 1-800-253-8600, ext. 38244

- **Lovenox Injection** : Rhone-Poulenc Rorer Pharmaceuticals Inc.: 1-800-340-7502

- **Normiflo Injection** : Wyeth Laboratories Inc.: 1-800-934-5556

- **Orgaran Injection** : Organon Inc.: 1-800-631-1253

14. **What has the FDA done since releasing the Public Health Advisory?**

1. The FDA Anesthetic and Life Support Drugs Advisory Committee met on February 5, 1998 to discuss the reports of spinal/epidural hematomas with the concurrent use of approved LMWHs/heparinoids and spinal/epidural anesthesia or spinal puncture.

   The committee concluded that the current amount of data is too sparse to determine specific time intervals between the insertion and removal of the spinal/epidural catheters

and the development of spinal/epidural hematomas.

Further, the committee agreed that physicians should be given sufficient information to make an educated decision about the relative risks of different types of anesthesia, and balance the risks of perioperative thromboembolic complications and spinal or epidural hematomas.

A transcript (300+ pages) of the February 5, 1998 meeting can be easily accessed via internet at www.fda.gov/ohrms/dockets/ac/98/transcpt/3380t1.pdf .

2. FDA continues to closely monitor the postmarketing reports for additional events.

15. **How can healthcare professionals help in the ongoing study of these adverse events?**

All healthcare professionals are strongly encouraged to report any serious adverse events, including cases of epidural or spinal hematomas, occurring with the use of LMWHs, heparinoids, or other anticoagulants to either FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178) or mail (using postage-paid form) to FDA, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787, or to the respective pharmaceutical manufacturers:

- **Fragmin** : Pharmacia & Upjohn: 1-800-253-8600, ext. 38244
- **Lovenox Injection** : Rhone-Poulenc Rorer Pharmaceuticals Inc.: 1-800-340-7502
- **Normiflo Injection** : Wyeth Laboratories Inc.: 1-800-934-5556
- **Orgaran Injection** : Organon Inc.: 1-800-631-1253

MEDWATCH HOME PAGE | COMMENTS FOR MEDWATCH | SAFETY ANNOUNCEMENTS

MEDWATCH

FDA HOME PAGE

317

LIST OF MEDWATCH PARTNERS

U.S. Food and Drug Administration

MEDWATCH

The FDA Medical Products Reporting Program

MEDWATCH Partners

MEDWATCH Partners work with the FDA to help keep their members informed about the **FDA Medical Products Reporting Program** and encourage them to play an active role in postmarketing surveillance.

MedWatch Partners as of November 1, 1997

Academy of Dentistry for Persons with Disabilities
Academy of General Dentistry
Academy of Managed Care Pharmacy
Academy of Psychosomatic Medicine
Advanstar Communications
American Academy of Allergy, Asthma and Immunology
American Academy of Clinical Toxicology
American Academy of Cosmetic Surgery
American Academy of Dermatology
American Academy of Facial Plastic and Reconstructive Surgery
American Academy of Family Physicians
American Academy of Neurology
American Academy of Ophthalmology
American Academy of Optometry
American Academy of Orthopaedic Surgeons
American Academy of Otolaryngology-Head & Neck Surgery
American Academy of Pain Medicine
American Academy of Pediatric Dentistry
American Academy of Pediatrics
American Academy of Physical Medicine and Rehabilitation
American Academy of Physician Assistants
American Association for Clinical Chemistry
American Association of Endodontists
American Association of Blood Banks
American Association of Colleges of Nursing
American Association of Colleges of Pharmacy
American Association of Critical Care Nurses
American Association of Dental Schools
American Association of Hospital Dentists
American Association of Neurological Surgeons
American Association of Endodontists
American Association of Hospital Dentists

American Association of Neurological Surgeons
American Association of Nurse Anesthetists
American Association of Oral and Maxillofacial Surgeons
American Association of Physician Specialists
American Association of Poison Control Centers
American Association of Women Dentists
American College of Cardiology
American College of Clinical Engineering
American College of Clinical Pharmacology
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Legal Medicine
American College of Nuclear Physicians
American College of Nurse-Midwives
American College of Nurse Practitioners
American College of Obstetricians and Gynecologists
American College of Osteopathic Family Physicians
American College of Physicians
American College of Radiology
American College of Rheumatology
American College of Sports Medicine
American College of Surgeons
American Dental Assistants Association
American Dental Association
American Diabetes Association
American Gastroenterological Association
American Health Care Association
American Medical Association
American Medical Student Association
American Medical Women's Association
American Nephrology Nurses' Association
American Nurses Association
American Osteopathic Association
American Pharmaceutical Association
American Podiatric Medical Association
American Psychiatric Association
American Society for Aesthetic Plastic Surgery
American Society for Clinical Laboratory Science
American Society for Clinical Pharmacology and Therapeutics
American Society for Geriatric Dentistry
American Society for Microbiology
American Society for Therapeutic Radiology and Oncology
American Society of Anesthesiologists
American Society of Bariatric Physicians
American Society of Clinical Pathologists
American Society of Consultant Pharmacists
American Society of Health-System Pharmacists
American Society of Internal Medicine

American Society of Plastic and Reconstructive Surgeons
American Speech-Language-Hearing Association
American Urological Association
American Veterinary Medical Association
Association for Hospital Medical Education
Association of American Medical Colleges
Association of Military Surgeons of the United States
Association of Women's Health, Obstetric and Neonatal Nurses
College of American Pathologists
CVS Pharmacy
Emergency Nurses Association
F.A. Davis Company
Federation of Special Care Organizations in Dentistry
Food Marketing Institute
Galt Associates (informatics-online)
Generic Pharmaceutical Industry Association
Gibeck, Inc.
Infectious Diseases Society of America
Institute for Safe Medication Practices
Interamerican College of Physicians and Surgeons
International Society for Pharmacoepidemiology
Joint Commission on Accreditation of Health Care Organizations
Lippincot-Raven Publishers
Medical Economics Data
National Association of Boards of Pharmacy
National Association of Chain Drug Stores
National Association of Hispanic Nurses
National Association of Pediatric Nurse Associates & Practitioners
National Association of Pharmaceutical Manufacturers
National Community Pharmacists Association
National Black Nurses' Association
National College of Naturopathic Medicine
National Foundation for Infectious Diseases
National League for Nursing
National Medical Association
National Pharmaceutical Alliance
National Student Nurses' Association
Nonprescription Drug Manufacturers Association
Pharmaceutical and Research Manufacturers Association
Pharmaceutical Information Associates
Pharmaceutical Outcomes Research
Pharmacist's Letter
Physicians' Online
Oklahoma Osteopathic Association
Society for Biomaterials
Society of General Internal Medicine
Society of Nuclear Medicine
Society of Thoracic Surgeons

Southwestern Surgical Congress
Texas Medical Association
Texas Osteopathic Medical Association
Tri-State Nursing Computer Network
United States Pharmacopeia

MEDWATCH