GlaxoWellcome

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 glycol 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 changes 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.

Glaxo Wellcome Inc.

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- **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 Capsules 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 of 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). Alcohol dehydrogenerase (ADH), which metabolizes propylene glycol, is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. 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:**

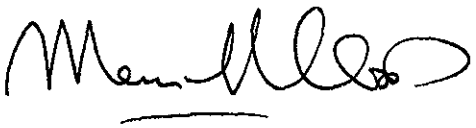
Consideration should be given to switching patients from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation (see WARNINGS).

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,



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