March 11, 2008

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IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

GlaxoSmithKline would like to advise you of a recent update to the RELENZA (zanamivir) Inhalation Powder package insert. The revision to the product label is a result of information about adverse events reported during postmarketing clinical use of RELENZA.

The revised WARNINGS AND PRECAUTIONS section of the RELENZA Inhalation Powder package insert now includes the following information and guidance under a new Neuropsychiatric Events subheading:

> **Neuropsychiatric Events**
>
> Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.
>
> There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including RELENZA. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon based on usage data for RELENZA. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of RELENZA to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

In addition, the following information has been added to the RELENZA Patient Information, in the, **What are important or common possible side effects of taking RELENZA?** section:

> People with influenza (the flu), particularly children and adolescents, may be at an increased risk of seizures, confusion, or abnormal behavior early in their illness. These events may occur after beginning RELENZA or may occur when flu is not treated. These events are uncommon but may result in accidental injury to the patient. Therefore, patients should be observed for signs of unusual behavior and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behavior.

RELENZA is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years of age and older who have been symptomatic for no more than 2 days.

- RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm.

- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- RELENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.
- RELENZA is not a substitute for early influenza vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.
- There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.
- Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

Please see page 2 of this letter for other important RELENZA safety information.

We encourage you to become familiar with these label revisions. If you have any questions or require additional information concerning RELENZA, please contact the GlaxoSmithKline Response Center at 1-888-825-5249. An updated package insert is enclosed for your information. In addition, healthcare professionals can access the revised RELENZA complete product information at

http://us.gsk.com/products/assets/us_relenza.pdf.

Additionally, we would like to direct you to the proceedings and discussion of these adverse events by the Pediatric Advisory Committee on November 27, 2007 at

http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4325t1_transcript.pdf.

GlaxoSmithKline will continue to monitor the safety of RELENZA through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. We will continue to provide you with the most current product information for RELENZA moving forward. You can assist us in monitoring the safety of RELENZA by reporting adverse reactions to us at 1-888-825-5249, or to FDA at www.fda.gov/medwatch, or by mail to MedWatch, Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd.Beltsville, MD 20705-1266.

Safety Information

RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).

Serious cases of bronchospasm, including fatalities, have been reported during treatment with RELENZA in patients with and without underlying airways disease. Many of these cases were reported during postmarketing and causality was difficult to assess.

RELENZA should be discontinued in any patient who develops bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.

Some patients without prior pulmonary disease may also have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.

Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a Phase III study in patients with acute influenza-like illness superimposed on underlying asthma or

chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22 of 237) on placebo experienced a greater than 20% decline in FEV_1 following treatment for 5 days.

If use of RELENZA is considered for a patient with underlying airways disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe RELENZA for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators.

Do not use in patients with history of allergic reaction to any ingredient of RELENZA including lactose (which contains milk proteins).

Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in postmarketing experience with RELENZA. RELENZA should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. RELENZA has not been shown to prevent such complications.

Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug. Prescribers should carefully evaluate the ability of young children to use the delivery system if use of RELENZA is considered.

The most common adverse events reported in >1.5% of patients treated with RELENZA and more commonly than in patients treated with placebo are:

- Treatment Studies – sinusitis, dizziness.
- Prophylaxis studies – fever and/or chills, arthralgia and articular rheumatism.

The concurrent use of RELENZA with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of potential interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of RELENZA, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any time relative to use of RELENZA.

Sincerely,

Judith Ng-Cashin, M.D.
Director, GlaxoSmithKline

Enclosures:

- Complete Prescribing Information for RELENZA (zanamivir) Inhalation Powder
- RELENZA Patient Information