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IMPORTANT DRUG WARNING

Subject: RELENZA[®] (zanamivir) Inhalation Powder Must Not Be Nebulized

Dear Healthcare Provider:

GlaxoSmithKline (GSK) has received a report of the death of a patient with influenza who received RELENZA (zanamivir) Inhalation Powder that was solubilized and administered by mechanical ventilation. GSK is aware that RELENZA Inhalation Powder is being removed from its FDA-approved packaging and dissolved in various solutions for the purpose of nebulizing zanamivir for inhalation by patients with influenza who are unable to take oral medications or unable to inhale RELENZA Inhalation Powder using the Diskhaler.

- **RELENZA (zanamivir) Inhalation Powder is not intended to be reconstituted in any liquid formulation and is not recommended for use in any nebulizer or mechanical ventilator.**
- **RELENZA or zanamivir for nebulization has not been approved by the FDA. The safety, effectiveness, and stability of zanamivir use by nebulization have not been established.**

The death referenced above occurred outside the US and was of a pregnant woman on mechanical ventilation who received zanamivir solution made from dry powder product from RELENZA Rotadisks via nebulizer for three days. Death was attributed to obstruction of the ventilator. The reporting physician believed that the obstruction in the ventilator was due to stickiness caused by lactose (from RELENZA Inhalation Powder) in the nebulizing solution.

RELENZA Inhalation Powder should only be used as directed in the prescribing information by using the Diskhaler device provided with the drug product. RELENZA Inhalation Powder is a mixture of zanamivir active drug substance (5 mg) and lactose drug carrier (20 mg). This formulation is not designed or intended to be administered by nebulization. There is a risk that the lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment.

Although an investigational aqueous formulation for nebulizer delivery was briefly explored during the early development of zanamivir and may be mentioned in some descriptions or publications of those early-phase studies, that formulation did not use the lactose-based powder contained in the marketed product, RELENZA.

Indications and Usage of RELENZA (zanamivir) Inhalation Powder

Treatment of Influenza

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

Prophylaxis of Influenza

RELENZA is indicated for prophylaxis of influenza in adults and pediatric patients 5 years of age and older.

Important Limitations on Use of RELENZA

- 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.
- Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use RELENZA.
- 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.

Important Safety Information About RELENZA (zanamivir) Inhalation Powder

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.

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.

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.

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.

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. If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional.

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

- 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.

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. 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.

Sincerely,

A handwritten signature in black ink, appearing to read 'JNC' followed by a stylized flourish and the letters 'MD'.

Judith Ng-Cashin, M.D.
Vice President, GlaxoSmithKline

Enclosures:

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