

**IMPORTANT  
DRUG  
WARNING**

January 2017

**Subject: Serious risks from concomitant use of benzodiazepines, including KLONOPIN® (clonazepam) Tablets, KLONOPIN® (clonazepam orally disintegrating tablets)® Wafers\* or VALIUM® (diazepam) Tablets with opioids**

- **Concomitant use may result in profound sedation, respiratory depression, coma, and death**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for benzodiazepines, including KLONOPIN® (clonazepam) Tablets, KLONOPIN® (clonazepam orally disintegrating tablets) Wafers or VALIUM® (diazepam) Tablets, and concomitant use of opioids.

KLONOPIN® is indicated for the treatment of patients who have:

Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures, absence seizures (petit mal) in patients who have failed to respond to succinimides, or panic disorder, with or without agoraphobia

VALIUM® is indicated for the management of:

Anxiety disorders or for the short-term relief of the symptoms of anxiety, symptoms of acute alcohol withdrawal, adjunctively for the relief of certain types of muscle spasms, or adjunctively in convulsive disorders

VALIUM® is contraindicated in patients with severe respiratory insufficiency.

**Serious Risks With Use of KLONOPIN® or VALIUM®**

Concomitant use of benzodiazepines, including KLONOPIN® or VALIUM®, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of these drugs should be reserved for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone.

**Prescriber Action**

If a decision is made to prescribe KLONOPIN® or VALIUM®, concomitantly with opioids:

- Prescribe the lowest effective dosages and minimum durations of concomitant use.

- Follow patients closely for signs and symptoms of respiratory depression and sedation.
- Inform patients and caregivers of the risks of respiratory depression and sedation, that potentially fatal additive effects may occur if KLONOPIN® or VALIUM® is used with opioids, and not to use such drugs concomitantly unless supervised by a health care provider.
- Advise patients not to drive or operate heavy machinery until the effects of the concomitant use with the opioid have been determined.

### **Drug Interactions**

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA<sub>A</sub> sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

### **Reporting Adverse Events**

Health care providers and patients are encouraged to report adverse events in patients taking KLONOPIN® or VALIUM® to Genentech at 1-888-835-2555. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.

You may also contact the Genentech Medical Communications department at 1-800-821-8590 if you have any questions about the information contained in this letter or the safe and effective use of KLONOPIN® and/or VALIUM®.

A new Boxed Warning and new Warnings and Precautions sections have been added to the product labels to reflect these risks. This letter is not intended as a complete description of the indications, benefits and risks related to the use of KLONOPIN® and VALIUM®. Please refer to the enclosed full prescribing information, including Boxed Warning, and medication guides. These can also be found online at [https://www.gene.com/download/pdf/klonopin\\_prescribing.pdf](https://www.gene.com/download/pdf/klonopin_prescribing.pdf) and [https://www.gene.com/download/pdf/valium\\_prescribing.pdf](https://www.gene.com/download/pdf/valium_prescribing.pdf)

Sincerely,



Myriam Mendila, MD  
Senior Vice President, Head of U.S. Medical Affairs  
Genentech, Inc., a member of the Roche Group

Enclosure(s): Full Prescribing Information and Medication Guides for KLONOPIN® and VALIUM®

\*KLONOPIN Wafers (orally disintegrating tablets) are no longer manufactured or distributed by Roche.