### LOFLAZEPATE

#### THERAPEUTICS

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| Generic? | No |

| Class | Benzodiazepine (anxiolytic) |

#### Commonly Prescribed for (bold for FDA approved)

- Anxiety, tension, depression, or sleep disorder in patients with neurosis
- Anxiety, tension, depression, or sleep disorder in patients with psychosomatic disease
- Catatonia

#### How the Drug Works

- Binds to benzodiazepine receptors at the GABA-A ligand-gated chloride channel complex
- Enhances the inhibitory effects of GABA
- Boosts chloride conductance through GABA-regulated channels
- Inhibits neuronal activity presumably in amygdala-centered fear circuits to provide therapeutic benefits in anxiety disorders

#### How Long Until It Works

- Some immediate relief with first dosing is common; can take several weeks with daily dosing for maximal therapeutic benefit

#### If It Works

- For short-term symptoms of anxiety – after a few weeks, discontinue use or use on an “as-needed” basis
- For chronic anxiety disorders, the goal of treatment is complete remission of symptoms as well as prevention of future relapses
- For chronic anxiety disorders, treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- For long-term symptoms of anxiety, consider switching to an SSRI or SNRI for long-term maintenance
- If long-term maintenance with a benzodiazepine is necessary, continue treatment for 6 months after symptoms resolve, and then taper dose slowly
- If symptoms reemerge, consider treatment with an SSRI or SNRI, or consider restarting the benzodiazepine; sometimes benzodiazepines have to be used in combination with SSRIs or SNRIs for best results

#### If It Doesn’t Work

- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy, especially cognitive behavioral psychotherapy
- Consider presence of concomitant substance abuse
- Consider presence of loflazepate abuse
- Consider another diagnosis, such as a comorbid medical condition

#### Best Augmenting Combos for Partial Response or Treatment Resistance

- Benzodiazepines are frequently used as augmenting agents for antipsychotics and mood stabilizers in the treatment of psychotic and bipolar disorders
- Benzodiazepines are frequently used as augmenting agents for SSRIs and SNRIs in the treatment of anxiety disorders
- Not generally rational to combine with other benzodiazepines
- Caution if using as an anxiolytic concomitantly with other sedative hypnotics for sleep

#### Tests

- In patients with seizure disorders, concomitant medical illness, and/or those with multiple concomitant long-term medications, periodic liver tests and blood counts may be prudent

### SIDE EFFECTS

#### How Drug Causes Side Effects

- Same mechanism for side effects as for therapeutic effects – namely due to excessive actions at benzodiazepine receptors
- Long-term adaptations in benzodiazepine receptors may explain the development of dependence, tolerance, and withdrawal
LOFLAZEPATE (continued)

**DOSING AND USE**

**Usual Dosage Range**
- 1 mg once or twice a day

**Dosage Forms**
- Tablet 1 mg, 2 mg

**How to Dose**
- Start at 1 mg, increase to 1 mg twice/day or 2 mg once a day in a few days if necessary

**Dosing Tips**
- Because of its long half-life, patients who require chronic treatment may need dose reduction after a few weeks due to drug accumulation
- Because of its long half-life, once daily dosing is the most frequent dosing generally necessary
- Because of its long half-life, some patients may have sustained benefits even if dosing is intermittently skipped on some days
- Use lowest possible effective dose for the shortest possible period of time (a benzodiazepine-sparing strategy)
- Assess need for continued treatment regularly
- Risk of dependence may increase with dose and duration of treatment
- For interdose symptoms of anxiety, can either increase dose or maintain same total daily dose but divide into more frequent doses
- Can also use an as-needed occasional “top up” dose for interdose anxiety
- Because panic disorder can require doses higher than 2 mg/day, the risk of dependence may be greater in these patients
- Some severely ill patients may require more than 2 mg/day
- Frequency of dosing in practice is often greater than predicted from half-life, as duration of biological activity is often shorter than pharmacokinetic terminal half-life, which is why once daily dosing is usually the favored option despite the long half-life

**Overdose**
- Sedation, confusion, poor coordination, diminished reflexes, coma

**Notable Side Effects**
- Sedation, fatigue, depression
- Dizziness, ataxia, slurred speech, weakness
- Forgetfulness, confusion
- Hyperexcitability, nervousness
- Rare hallucinations, mania
- Rare hypotension
- Hypersalivation, dry mouth

**Life-Threatening or Dangerous Side Effects**
- Respiratory depression, especially when taken with CNS depressants in overdose
- Rare hepatic dysfunction, renal dysfunction, blood dyscrasias

**Weight Gain**
- Reported but not expected

**Sedation**
- Occurs in significant minority
- Especially at initiation of treatment or when dose increases
- Tolerance often develops over time

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Lower the dose
- Take largest dose at bedtime to avoid sedative effects during the day
- Switch to another agent
- Administer flumazenil if side effects are severe or life-threatening

**Best Augmenting Agents for Side Effects**
- Many side effects cannot be improved with an augmenting agent

**Overdose**
- Sedation, confusion, poor coordination, diminished reflexes, coma
Long-Term Use
• Risk of dependence, particularly for treatment periods longer than 12 weeks and especially in patients with past or current polysubstance abuse

Habit Forming
• Patients may develop dependence and/or tolerance with long-term use

How to Stop
• Patients with history of seizures may seize upon withdrawal, especially if withdrawal is abrupt
• Taper by 0.5 mg every 3–7 days to reduce chances of withdrawal effects
• For difficult to taper cases, consider reducing dose much more slowly after reaching 3 mg/day, perhaps by as little as 0.25 mg every 7–10 days or slower
• For other patients with severe problems discontinuing a benzodiazepine, dosing may need to be tapered over many months (i.e., reduce dose by 1% every 3 days by crushing tablet or suspending or dissolving in 100 mL of fruit juice and then disposing of 1 mL while drinking the rest; 3–7 days later, dispose of 2 mL, and so on). This is both a form of very slow biological tapering and a form of behavioral desensitization
• Be sure to differentiate reemergence of symptoms requiring reinstitution of treatment from withdrawal symptoms
• Benzodiazepine-dependent anxiety patients and insulin-dependent diabetics are not addicted to their medications. When benzodiazepine-dependent patients stop their medication, disease symptoms can reemerge, disease symptoms can worsen (rebound), and/or withdrawal symptoms can emerge

Pharmacokinetics
• Elimination half-life approximately 122 hours (ultra-long half-life)

Drug Interactions
• Increased depressive effects when taken with other CNS depressants (see Warnings below)
• Cimetidine raises loflazepate plasma levels
• Rapid dose reduction or discontinuation of loflazepate during concomitant use

Other Warnings/Precautions
• Boxed warning regarding the increased risk of CNS depressant effects when benzodiazepines and opioid medications are used together, including specifically the risk of slowed or difficulty breathing and death
• If alternatives to the combined use of benzodiazepines and opioids are not available, clinicians should limit the dosage and duration of each drug to the minimum possible while still achieving therapeutic efficacy
• Patients and their caregivers should be warned to seek medical attention if unusual dizziness, lightheadedness, sedation, slowed or difficulty breathing, or unresponsiveness occur
• Dosage changes should be made in collaboration with prescriber
• Use with caution in patients with pulmonary disease; rare reports of death after initiation of benzodiazepines in patients with severe pulmonary impairment
• History of drug or alcohol abuse often creates greater risk for dependency
• Hypomania and mania have occurred in depressed patients taking loflazepate
• Use only with extreme caution if patient has obstructive sleep apnea
• Some depressed patients may experience a worsening of suicidal ideation
• Some patients may exhibit abnormal thinking or behavioral changes similar to those caused by other CNS depressants (i.e., either depressant actions or disinhibiting actions)

Do Not Use
• If patient has angle-closure glaucoma
• If patient has myasthenia gravis
• If there is a proven allergy to loflazepate or any benzodiazepine
Potential Advantages
- Patients who have interdose anxiety on shorter-acting benzodiazepines
- Patients who wish to take drug only once daily
- Patients who occasionally forget to take their dose

Potential Disadvantages
- Drug may accumulate in long-term users and require dosage reduction

Primary Target Symptoms
- Anxiety
- Tension

Pearls
- Is the only “ultra-long half-life” benzodiazepine with a half-life much longer than 24 hours
- Less interdose anxiety than other benzodiazepines
- Long half-life could theoretically reduce abuse and withdrawal symptoms
- Is a very useful adjunct to SSRIs and SNRIs in the treatment of numerous anxiety disorders
- Not effective for treating psychosis as a monotherapy, but can be used as an adjunct to antipsychotics
- Not effective for treating bipolar disorder as a monotherapy, but can be used as an adjunct to mood stabilizers and antipsychotics
- May both cause depression and treat depression in different patients
- Risk of seizure is greatest during the first 3 days after discontinuation of loflazepate, especially in those with prior seizures, head injuries or withdrawal from drugs of abuse
- Clinical duration of action may be shorter than plasma half-life, leading to dosing more frequently than 2–3 times daily in some patients
- When using to treat insomnia, remember that insomnia may be a symptom of some other primary disorder itself, and thus warrant evaluation for comorbid psychiatric and/or medical conditions
- Though not systematically studied, benzodiazepines have been used effectively to treat catatonia and are the initial recommended treatment

SPECIAL POPULATIONS

Renal Impairment
- Drug should be used with caution

Hepatic Impairment
- Drug should be used with caution

Cardiac Impairment
- Benzodiazepines have been used to treat anxiety associated with acute myocardial infarction

Elderly
- Drug should be used with caution
- Should begin with lower starting dose

Children and Adolescents
- Safety and efficacy have not been established
- Benzodiazepines are often used in children and adolescents, especially short-term and at the lower end of the dosing scale
- Long-term effects of loflazepate in children and adolescents are unknown
- Should generally receive lower doses and be more closely monitored

Pregnancy
- Possible increased risk of birth defects when benzodiazepines taken during pregnancy
- Because of the potential risks, loflazepate is not generally recommended as treatment for anxiety during pregnancy, especially during the first trimester
- Drug should be tapered if discontinued
- Infants whose mothers received a benzodiazepine late in pregnancy may experience withdrawal effects
- Neonatal flaccidity has been reported in infants whose mothers took a benzodiazepine during pregnancy
- Seizures, even mild seizures, may cause harm to the embryo/fetus

Breast Feeding
- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- Effects on infant have been observed and include feeding difficulties, sedation, and weight loss
Suggested Reading

