**Brands**  • Rohypnol
*see index for additional brand names*

**Generic?**  No

**Class**
• Neuroscience-based Nomenclature: GABA positive allosteric modulator (GABA-PAM)
• Benzodiazepine (hypnotic)

**Commonly Prescribed for** *(bold for FDA approved)*
• Short-term treatment of insomnia (severe, disabling)
• 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
• Inhibitory actions in sleep centers may provide sedative hypnotic effects

**How Long Until It Works**
• Generally takes effect in less than an hour

**If It Works**
• Improves quality of sleep
• Effects on total wake-time and number of nighttime awakenings may be decreased over time

**If It Doesn’t Work**
• If insomnia does not improve after 7–10 days, it may be a manifestation of a primary psychiatric or physical illness such as obstructive sleep apnea or restless leg syndrome, which requires independent evaluation
• Increase the dose
• Improve sleep hygiene
• Switch to another agent

**Best Augmenting Combos for Partial Response or Treatment Resistance**
• Generally, best to switch to another agent
• Trazodone

**Agents with antihistamine actions (e.g., diphenhydramine, TCAs)**

**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

**How Drug Causes Side Effects**
• Same mechanism for side effects as for therapeutic effects — namely due to excessive actions at benzodiazepine receptors
• Actions at benzodiazepine receptors that carry over to next day can cause daytime sedation, amnesia, and ataxia
• Long-term adaptations in benzodiazepine receptors may explain the development of dependence, tolerance, and withdrawal

**Notable Side Effects**
✽ Sedation, fatigue, depression
✽ Dizziness, ataxia, slurred speech, weakness
✽ Forgetfulness, confusion
✽ Hyperexcitability, nervousness
• Rare hallucinations, mania
• Rare hypotension
• Hypersalivation, dry mouth
• Rebound insomnia when withdrawing from long-term treatment

**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**
• Many experience and/or can be significant in amount
FLUNITRAZEPAM (continued)

What to Do About Side Effects
- Wait
- To avoid problems with memory, only take flunitrazepam if planning to have a full night’s sleep
- Lower the dose
- Switch to a shorter-acting sedative hypnotic
- Switch to a non-benzodiazepine hypnotic
- 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

Long-Term Use
- Not generally intended for long-term use
- Use is not recommended to exceed 4 weeks

Habit Forming
- Some patients may develop dependence and/or tolerance; risk may be greater with higher doses
- History of drug addiction may increase risk of dependence
- Currently classified as Schedule III by the World Health Organization
- Currently classified as a Schedule IV drug in the USA, but not legally available in the USA

How to Stop
- If taken for more than a few weeks, taper to reduce chances of withdrawal effects
- Patients with seizure history may seize upon sudden withdrawal
- Rebound insomnia may occur the first 1–2 nights after stopping
- For 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 and 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

Pharmacokinetics
- Elimination half-life 16–35 hours
- Half-life of active metabolite 23–33 hours

Drug Interactions
- Increased depressive effects when taken with other CNS depressants (see Warnings below)
- Cisapride may hasten the absorption of flunitrazepam and thus cause a temporary increase in the sedative effects of flunitrazepam

Other Warnings/Precautions
- Boxed warning regarding the increased risk of CNS depressant effects when benzodiazepines and opioid medications

DOSING AND USE

Usual Dosage Range
- 0.5–1 mg/day at bedtime

Dosage Forms
- Tablet 0.5 mg, 1 mg, 2 mg, 4 mg

How to Dose
- Initial 0.5–1 mg/day at bedtime; maximum generally 2 mg/day at bedtime

Dosing Tips
- Use lowest possible effective dose and assess need for continued treatment regularly
- Flunitrazepam should generally not be prescribed in quantities greater than a 1-month supply
- Patients with lower body weights may require lower doses
- Risk of dependence may increase with dose and duration of treatment
- Use doses over 1 mg only in exceptional circumstances
- Patients who request or who require doses over 1 mg may be more likely to have present or past substance abuse
- Flunitrazepam is 10 times more potent than diazepam

Overdose
- Sedation, slurred speech, poor coordination, confusion, coma, respiratory depression

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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
- Insomnia may be a symptom of a primary disorder, rather than a primary disorder itself
- 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)
- Some depressed patients may experience a worsening of suicidal ideation
- Use only with extreme caution in patients with impaired respiratory function or obstructive sleep apnea
- Flunitrazepam should be administered only at bedtime

Do Not Use

- If patient is pregnant
- If patient has severe chronic hypercapnia, myasthenia gravis, severe respiratory insufficiency, sleep apnea, or severe hepatic insufficiency
- In children
- If patient has angle-closure glaucoma
- If there is a proven allergy to flunitrazepam or any benzodiazepine

Elderly

- Initial starting dose 0.5 mg at bedtime; maximum generally 1 mg/day at bedtime
- Paradoxical reactions with restlessness and agitation are more likely to occur in the elderly

Children and Adolescents

- Safety and efficacy have not been established
- Not recommended for use in children or adolescents
- Paradoxical reactions with restlessness and agitation are more likely to occur in children

Pregnancy

- Positive evidence of risk to human fetus; contraindicated for use in pregnancy
- 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

Breast Feeding

- Unknown if flunitrazepam is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- Effects on infant have been observed and include feeding difficulties, sedation, and weight loss

SPECIAL POPULATIONS

Renal Impairment

- Drug should be used with caution

Hepatic Impairment

- Dose should be lowered
- Should not be used in patients with severe hepatic insufficiency, as it may precipitate encephalopathy

Cardiac Impairment

- Benzodiazepines have been used to treat insomnia associated with acute myocardial infarction

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- For severe, disabling insomnia unresponsive to other sedative hypnotics

Potential Disadvantages

- For those who need treatment for longer than a few weeks
- For those with current or past substance abuse

Primary Target Symptoms

- Time to sleep onset
- Total sleep time
- Nighttime awakenings
Pearls

* Psychiatric symptoms and “paradoxical” reactions may be quite severe with flunitrazepam and may be more frequent than with other benzodiazepines
* “Paradoxical” reactions include symptoms such as restlessness, agitation, irritability, aggressiveness, delusions, rage, nightmares, hallucinations, psychosis, inappropriate behavior, and other adverse behavioral effects
• Although legally available in Europe, Mexico, South America, and many other countries, it is not legally available in the USA
• Although currently classified as a Schedule IV drug, the USA drug enforcement agency is considering reclassifying it as Schedule I
* Has earned a reputation as a “date rape drug” in which sexual predators have allegedly slipped flunitrazepam into women’s drinks to induce sexual relations
* Flunitrazepam, especially in combination with alcohol, is claimed to reduce the woman’s judgment, inhibitions, or physical ability to resist sexual advances, as well as to reduce or eliminate her recall of the events
* Until 1999 was colorless, but a colorimetric compound is now added that turns the drug blue when added to a liquid, making it obvious that a drink was tampered with
• Illicit use since 1999 has fallen in part due to this additive
• Illicit use has also fallen in the USA due to the Drug-Induced Rape Prevention and Punishment act of 1996, making it punishable to commit a violent crime using a controlled substance such as flunitrazepam
• Street names for flunitrazepam, based in part upon its trade name of Rohypnol, manufacturer Roche, and the presence of RO-2 on the surface of the tablets, include “roofies,” “ruffies,” “roapies,” “la roacha,” “roach-2,” “Mexican valium,” “rope,” “roache vitamins,” and others
• If tolerance develops, it may result in increased anxiety during the day and/or increased wakefulness during the latter part of the night
• Best short-term use is for less than 10 consecutive days, and for less than half of the nights in a month
• Drug holidays may restore drug effectiveness if tolerance develops
• Though not systematically studied, benzodiazepines have been used effectively to treat catatonia and are the initial recommended treatment

Suggested Reading
