EFFECTIVE, LOW-DOSE THERAPY TO HELP PATIENTS FALL ASLEEP GENTLY

Restoril® 7.5 mg capsules

(temazepam) CIV

*For Transient And Short-Term Insomnia (Generally 7–10 Days' Therapy)**

- More than a decade of established RESTORIL® safety
  - Essentially no hangover effects[1–3]
  - Low potential for rebound insomnia[4] or memory loss
  - No evidence of tolerance development found after at least two weeks of nightly use (based on sleep laboratory study results)
  - Virtually no daytime anxiety or G.I. upset
- Induces sleep as effectively as RESTORIL (temazepam) 15 mg[5]
- Allows titration for greater flexibility and control†

RESTORIL therapy is contraindicated in pregnant women.

* As with all benzodiazepines, patients should be evaluated for the emergence of any abnormal thinking or behavioral changes, with appropriate consideration given to all possibilities.

† Also available in 15 mg and 30 mg capsules.

Please see adjacent page for brief summary of prescribing information.

RESTORIL® C IV

(temazepam) CAPSULES

BRIEF SUMMARY: For full prescribing information see package insert

CAUTION: Federal law prohibits dispensing without prescription.

INDICATIONS AND USAGE

Restoril® (temazepam) is indicated for the short-term treatment of insomnia (generally 7-10 days). For patients in whom the drug is used for more than 2-3 weeks, periodic reevaluation is recommended to determine whether there is a continuing need. *(See WARNINGS)*

For patients with short-term insomnia, instructions in the prescription should indicate that Restoril® (temazepam) should be used for short periods of time (7-10 days).

Restoril® (temazepam) should not be prescribed in quantities exceeding a 1-month supply.

Insomnia is characterized by complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Both sleep laboratory and outpatient studies provide support for the effectiveness of Restoril® (temazepam) administered 30 minutes before bedtime in decreasing sleep latency and improving sleep maintenance in patients with chronic insomnia. In addition, sleep laboratory studies have confirmed similar effects in normal subjects with transient insomnia.

CONTRAINDICATIONS

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

Reproduction studies in animals with temazepam were performed in rats and rabbits. In a perinatal-postnatal study in rats, oral doses of 60 mg/kg/day resulted in increasing nursling mortality. Teratology studies in rats demonstrated increased fetal resorptions at doses of 30 and 120 mg/kg in one study and increased occurrence of rudimentary ribs, which are considered skeletal variants, in a second study at doses of 240 mg/kg or higher. In rabbits, occasional abnormalities such as exencephaly and fusion or asymmetry of ribs were reported without dose relationship. Although these abnormalities were not found in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg or higher, there was an increased incidence of the 13th rib variant when compared to the incidence in concurrent and historical controls.

Restoril® (temazepam) is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving temazepam, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

WARNINGS

Sleep disturbance may be the presenting manifestation of an underlying physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.

The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness.

Worsening of insomnia may be the consequence of an unrecognized psychiatric or physical disorder as may the emergence of new abnormalities of thinking or behavior. Such abnormalities have also been reported to occur in association with the use of drugs with central nervous system depressant activity, including those of the benzodiazepine class. Some of these changes may be characterized by decreased inhibition, e.g., aggressiveness and extroversion that seem out of character, similar to that seen with alcohol. Other kinds of behavioral changes can also occur, for example, bizarre behavior, agitation, hallucinations, depersonalization, and, in primarily depressed patients, the worsening of depression, including suicidal thinking. In controlled clinical trials involving 1076 patients on Restoril® (temazepam) and 783 patients on placebo, reports of hallucinations, agitation, and overstimulation occurred at rates less than 1 in 100 patients. Hallucinations were reported in 2 Restoril® (temazepam) patients and 1 placebo patient; agitation was reported in 1 Restoril® (temazepam) patient; 2 Restoril® (temazepam) patients reported overstimulation. There were no reports of worsening of depression or suicidal ideation, aggressiveness, extroversion, bizarre behavior or depersonalization in these controlled clinical trials.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because some of the worrisome adverse effects of benzodiazepines, including Restoril® (temazepam), appear to be dose related *(see PRECAUTIONS)*, it is important to use the lowest possible effective dose. Elderly patients are especially at risk.

Patients receiving Restoril® (temazepam) should be cautioned about possible combined effects with alcohol and other CNS-depressants.

Withdrawal symptoms (of the barbiturate type) have occurred after the abrupt discontinuation of benzodiazepines.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Restoril® (temazepam) is a controlled substance in Schedule IV.

Abuse and Dependence

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal, and muscle cramps, vomiting, and sweating), have occurred following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy at doses higher than 15 mg, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. As with any hypnotic, caution must be exercised in administering Restoril® (temazepam) to individuals known to be addiction-prone or to those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeated prescriptions without adequate medical supervision.

PRECAUTIONS

General

Since the risk of the development of oversedation, dizziness, confusion, and/or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients, 7.5 mg of Restoril® (temazepam) is recommended as the initial dosage for such patients.

Restoril® (temazepam) should be administered with caution in severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

The usual precautions should be observed in patients with impaired renal or hepatic function and in patients with chronic pulmonary insufficiency.

If Restoril® (temazepam) is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, consideration should be given to potential additive effects.

The possibility of a synergistic effect exists with the co-administration of Restoril® (temazepam) and diphenhydramine. One case of stillbirth at term has been reported 8 hours after a pregnant patient received Restoril® (temazepam) and diphenhydramine. A cause and effect relationship has not yet been determined. *(See CONTRAINDICATIONS)*

Information for Patients

Please consult package insert for full prescribing information.

Laboratory Tests

The usual precautions should be observed in patients with impaired renal or hepatic function and in patients with chronic pulmonary insufficiency. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Drug Interactions

The pharmacokinetic profile of temazepam does not appear to be altered by orally administered cimetidine dosed according to labeling.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in rats at dietary temazepam doses up to 160 mg/kg/day for 24 months and in mice at dietary dose of 160 mg/kg/day for 18 months. No evidence of carcinogenicity was observed although hyperplastic liver nodules were observed in female mice exposed to the highest dose. The clinical significance of this finding is not known.

Fertility in male and female rats was not adversely affected by Restoril® (temazepam).

No mutagenicity tests have been done with temazepam.

Pregnancy

Pregnancy Category X *(see CONTRAINDICATIONS)*.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Restoril® (temazepam) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS

During controlled clinical studies in which 1076 patients received Restoril® (temazepam) at bedtime, the drug was well tolerated. Side effects were usually mild and transient. Adverse reactions occurring in 1% or more of patients are presented in the following table:

	Restoril® (temazepam) % Incidence (n=1076)	Placebo % Incidence (n=783)
Drowsiness	9.1	5.6
Headache	8.5	9.1
Fatigue	4.8	4.7
Nervousness	4.6	8.2
Lethargy	4.5	3.4
Dizziness	4.5	3.3
Nausea	3.1	3.8
Hangover	2.5	1.1
Anxiety	2.0	1.5
Depression	1.7	1.8
Dry Mouth	1.7	2.2
Diarrhea	1.7	1.1
Abdominal Discomfort	1.5	1.9
Euphoria	1.5	0.4
Weakness	1.4	0.9
Confusion	1.3	0.5
Blurred Vision	1.3	1.3
Nightmares	1.2	1.7
Vertigo	1.2	0.8

The following adverse events have been reported less frequently (0.5-0.9%):

Central Nervous System - anorexia, ataxia, equilibrium loss, tremor, increased dreaming
Cardiovascular - dyspnea, palpitations
Gastrointestinal - vomiting
Musculoskeletal - backache
Special Senses - hyperhidrosis, burning eyes

Amnesia, hallucinations, horizontal nystagmus, and paradoxical reactions including restlessness, overstimulation and agitation were rare (less than 0.5%).

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[REV: OCTOBER, 1992 RES-Z15]

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Sex bias should be avoided and gender-inclusive language used whenever possible.

References

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Morrow JD, Margolies GR, Rowland J, Roberts LJ 2nd. Evidence that histamine is the causative toxin of scombroid-fish poisoning. N Engl J Med 1991; 324:716-20.

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Schwartz JL. Review and evaluation of smoking cessation methods: the United States and Canada, 1978-1985. Bethesda, MD: Department of Health and Human Services, 1987. (NIH publication no. 87-2940.)

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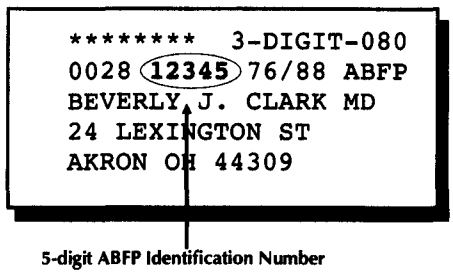

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