

Restoril™
(temazepam)
Capsules USP



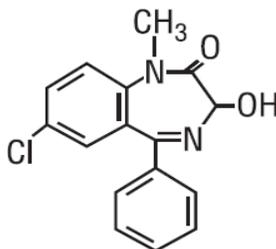
Rx only

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation (see **WARNINGS and PRECAUTIONS**).
- The use of benzodiazepines, including Restoril, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing Restoril and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see **WARNINGS**).
- The continued use of benzodiazepines, including Restoril, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of Restoril after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Restoril or reduce the dosage (see **DOSAGE AND ADMINISTRATION and WARNINGS**).

DESCRIPTION

Restoril™ (temazepam) is a benzodiazepine hypnotic agent. The chemical name is 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, and the structural formula is:



C₁₆H₁₃ClN₂O₂

MW = 300.74

Temazepam is a white, crystalline substance, very slightly soluble in water and sparingly soluble in alcohol USP.

Restoril™ (temazepam) Capsules USP, 7.5 mg, 15 mg, 22.5 mg, and 30 mg, are for oral administration.

7.5 mg, 15 mg, 22.5 mg, and 30 mg Capsules

Active Ingredient: temazepam USP

7.5 mg Capsules

Inactive Ingredients: FD&C Blue #1, FD&C Red #3, gelatin, lactose, magnesium stearate, red iron oxide, titanium dioxide.

May also include: n-butyl alcohol, iron oxide red, shellac, shellac glaze, SD-35A alcohol.

15 mg Capsules

Inactive Ingredients: FD&C Blue #1, FD&C Red #3, gelatin, lactose, magnesium stearate, red iron oxide, titanium dioxide.

May also include: n-butyl alcohol, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, iron oxide red, isopropyl alcohol, propylene glycol, shellac, shellac glaze, SD-35A alcohol, SD-45 alcohol.

22.5 mg Capsules

Inactive Ingredients: FD&C Blue #1, FD&C Red #3, gelatin, lactose, magnesium stearate, red iron oxide, titanium dioxide.

May also include: n-butyl alcohol, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, iron oxide red, isopropyl alcohol, propylene glycol, shellac, shellac glaze, SD-35A alcohol, SD-45 alcohol.

30 mg Capsules

Inactive Ingredients: FD&C Blue #1, FD&C Red #3, gelatin, lactose, magnesium stearate, red iron oxide, titanium dioxide.

May also include: n-butyl alcohol, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, iron oxide red, isopropyl alcohol, propylene glycol, shellac, shellac glaze, SD-35A alcohol, SD-45 alcohol.

CLINICAL PHARMACOLOGY

Pharmacokinetics

In a single and multiple dose absorption, distribution, metabolism, and excretion (ADME) study, using ³H labeled drug, Restoril was well absorbed and found to have minimal (8%) first pass metabolism. There were no active metabolites formed and the

only significant metabolite present in blood was the O-conjugate. The unchanged drug was 96% bound to plasma proteins. The blood level decline of the parent drug was biphasic with the short half-life ranging from 0.4 to 0.6 hours and the terminal half-life from 3.5 to 18.4 hours (mean 8.8 hours), depending on the study population and method of determination. Metabolites were formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, formation of the major metabolite is the rate limiting step in the biodisposition of temazepam. There is no accumulation of metabolites. A dose-proportional relationship has been established for the area under the plasma concentration/time curve over the 15 to 30 mg dose range.

Temazepam was completely metabolized through conjugation prior to excretion; 80% to 90% of the dose appeared in the urine. The major metabolite was the O-conjugate of temazepam (90%); the O-conjugate of N-desmethyl temazepam was a minor metabolite (7%).

Bioavailability, Induction, and Plasma Levels

Following ingestion of a 30 mg Restoril capsule, measurable plasma concentrations were achieved 10 to 20 minutes after dosing with peak plasma levels ranging from 666 to 982 ng/mL (mean 865 ng/mL) occurring approximately 1.2 to 1.6 hours (mean 1.5 hours) after dosing.

In a 7 day study, in which subjects were given a 30 mg Restoril capsule 1 hour before retiring, steady-state (as measured by the attainment of maximal trough concentrations) was achieved by the third dose. Mean plasma levels of temazepam (for days 2 to 7) were 260 ± 210 ng/mL at 9 hours and 75 ± 80 ng/mL at 24 hours after dosing. A slight trend toward declining 24 hour plasma levels was seen after day 4 in the study, however, the 24 hour plasma levels were quite variable.

At a dose of 30 mg once-a-day for 8 weeks, no evidence of enzyme induction was found in man.

Elimination Rate of Benzodiazepine Hypnotics and Profile of Common Untoward Effects

The type and duration of hypnotic effects and the profile of unwanted effects during administration of benzodiazepine hypnotics may be influenced by the biologic half-life of the administered drug and for some hypnotics, the half-life of any active metabolites formed. Benzodiazepine hypnotics have a spectrum of half-lives from short (<4 hours) to long (>20 hours). When half-lives are long, drug (and for some drugs their active metabolites) may accumulate during periods of nightly administration and be associated with impairments of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are shorter, drug (and, where appropriate, its active metabolites) will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. However, during nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short elimination

half-life, it is possible that a relative deficiency of the drug, or, if appropriate, its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for 2 clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety.

Controlled Trials Supporting Efficacy

Restoril improved sleep parameters in clinical studies. Residual medication effects ("hangover") were essentially absent. Early morning awakening, a particular problem in the geriatric patient, was significantly reduced.

Patients with chronic insomnia were evaluated in 2 week, placebo controlled sleep laboratory studies with Restoril at doses of 7.5 mg, 15 mg, and 30 mg, given 30 minutes prior to bedtime. There was a linear dose-response improvement in total sleep time and sleep latency, with significant drug-placebo differences at 2 weeks occurring only for total sleep time at the 2 higher doses, and for sleep latency only at the highest dose.

In these sleep laboratory studies, REM sleep was essentially unchanged and slow wave sleep was decreased. No measurable effects on daytime alertness or performance occurred following Restoril treatment or during the withdrawal period, even though a transient sleep disturbance in some sleep parameters was observed following withdrawal of the higher doses. There was no evidence of tolerance development in the sleep laboratory parameters when patients were given Restoril nightly for at least 2 weeks.

In addition, normal subjects with transient insomnia associated with first night adaptation to the sleep laboratory were evaluated in 24 hour, placebo controlled sleep laboratory studies with Restoril at doses of 7.5 mg, 15 mg, and 30 mg, given 30 minutes prior to bedtime. There was a linear dose-response improvement in total sleep time, sleep latency and number of awakenings, with significant drug-placebo differences occurring for sleep latency at all doses, for total sleep time at the 2 higher doses and for number of awakenings only at the 30 mg dose.

INDICATIONS AND USAGE

Restoril™ (temazepam) is indicated for the short-term treatment of insomnia (generally 7 to 10 days).

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

The clinical trials performed in support of efficacy were 2 weeks in duration with the final formal assessment of sleep latency performed at the end of treatment.

WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Restoril, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs 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. If a decision is made to prescribe Restoril concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Restoril than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking Restoril, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Restoril is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **PRECAUTIONS, Drug Interactions**).

Abuse, Misuse, and Addiction

The use of benzodiazepines, including Restoril, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death (see **DRUG ABUSE AND DEPENDENCE, Abuse**).

Before prescribing Restoril and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of Restoril, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of Restoril along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Restoril or reduce the dosage (a patient-specific plan should be used to taper the dose) (see

DOSAGE AND ADMINISTRATION, Discontinuation or Dosage Reduction of Restoril).

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including Restoril, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of Restoril after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) (see **DRUG ABUSE AND DEPENDENCE, Dependence**).

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months (see **DRUG ABUSE AND DEPENDENCE, Dependence**).

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 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.** 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. Because some of the worrisome adverse effects of benzodiazepines, including Restoril, appear to be dose related (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION**), it is important to use the lowest possible effective dose. Elderly patients are especially at risk.

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, and depersonalization. Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” may occur with Restoril alone at therapeutic doses, the use of alcohol and other CNS depressants with Restoril appears to increase the risk of such behaviors, as does the use of Restoril at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Restoril should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or

having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events. Amnesia and other neuro-psychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking has been reported in association with the use of sedative/hypnotics.

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 Restoril can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.

Severe Anaphylactic and Anaphylactoid Reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including Restoril. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with Restoril should not be rechallenged with the drug.

Neonatal Sedation and Withdrawal Syndrome

Use of Restoril late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate (see **PRECAUTIONS, Pregnancy**). Monitor neonates exposed to Restoril during pregnancy or labor for signs of sedation and monitor neonates exposed to Restoril during pregnancy for signs of withdrawal; manage these neonates accordingly.

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 is recommended as the initial dosage for such patients.

Restoril 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 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 and diphenhydramine. One case of stillbirth at term has been reported 8 hours after a pregnant patient received Restoril and diphenhydramine. A cause and effect relationship has not yet been determined (see **CONTRAINDICATIONS**).

Information for Patients

Advise the patient to read the FDA approved patient labeling (Medication Guide).

Risks from Concomitant Use with Opioids

Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when Restoril is used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **WARNINGS, Risks from Concomitant Use with Opioids and PRECAUTIONS, Drug Interactions**).

Abuse, Misuse, and Addiction

Inform patients that the use of Restoril, even at recommended dosages, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death, especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug (see **WARNINGS, Abuse, Misuse, and Addiction and DRUG ABUSE AND DEPENDENCE**).

Withdrawal Reactions

Inform patients that the continued use of Restoril may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of Restoril may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months. Instruct patients that discontinuation or dosage reduction of Restoril may require a slow taper (see **WARNINGS, Dependence and Withdrawal Reactions and DRUG ABUSE AND DEPENDENCE**).

“Sleep-Driving” and Other Complex Behaviors

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since “sleep-driving” can be dangerous. This behavior is more likely to occur when Restoril is taken with alcohol or other central nervous system depressants

(see **WARNINGS**). Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events.

Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.

Pregnancy

Advise pregnant females that use of Restoril late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in newborns (see **WARNINGS, Neonatal Sedation and Withdrawal Syndrome** and **PRECAUTIONS, Pregnancy**). Instruct patients to inform their healthcare provider if they are pregnant.

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Restoril during pregnancy (see **PRECAUTIONS, Pregnancy**).

Nursing

Instruct patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed. Instruct breastfeeding patients using Restoril to monitor infants for excessive sedation, poor feeding and poor weight gain, and to seek medical attention if they notice these signs (see **PRECAUTIONS, Nursing Mothers**).

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 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 GABAA 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. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

The benzodiazepines, including temazepam, produce additive CNS-depressant effects when co-administered with other CNS depressants such as alcohol, barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anesthetics.

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 doses 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.

No mutagenicity tests have been done with temazepam.

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to psychiatric medications, including Restoril, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/pregnancyregistry/>.

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal (see **WARNINGS, Neonatal Sedation and Withdrawal Syndrome and Clinical Considerations**). Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects (see *Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia and sedation in neonates. Monitor neonates exposed to Restoril during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to Restoril during pregnancy for signs of withdrawal. Manage these neonates accordingly (see **WARNINGS, Neonatal Sedation and Withdrawal Syndrome**).

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of more recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco and other medications, have not confirmed these findings.

Animal Data

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 nursing 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.

Nursing Mothers

Risk Summary

Temazepam is present in breast milk. There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk. The effects of temazepam on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Restoril and any potential adverse effects on the breastfed infant from Restoril or from the underlying maternal condition.

Clinical Considerations

Infants exposed to Restoril through breast milk should be monitored for sedation, poor feeding and poor weight gain.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Restoril did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater

frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy commonly observed in this population. Restoril 7.5 mg is recommended as the initial dosage for patients aged 65 and over since the risk of the development of oversedation, dizziness, confusion, ataxia and/or falls increases substantially with larger doses of benzodiazepines in elderly and debilitated patients.

ADVERSE REACTIONS

During controlled clinical studies in which 1076 patients received Restoril 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 % 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% to 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%).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Restoril contains temazepam, a Schedule IV controlled substance.

Abuse

Restoril is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders (see **WARNINGS, Abuse, Misuse, and Addiction**).

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

Dependence

Physical Dependence

Restoril may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt

discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use (see **WARNINGS, Dependence and Withdrawal Reactions**).

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Restoril or reduce the dosage (see **DOSAGE and ADMINISTRATION, Discontinuation or Dosage Reduction of Restoril and WARNINGS, Dependence and Withdrawal Reactions**).

Acute Withdrawal Signs and Symptoms

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to Restoril may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of Restoril may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

OVERDOSAGE

Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include

drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdose cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal (see **WARNINGS, Abuse, Misuse, and Addiction**). Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdose.

In managing benzodiazepine overdose, employ general supportive measures, including intravenous fluids and airway management. Flumazenil, a specific benzodiazepine receptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdose, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdose with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazepine for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, supportive management of benzodiazepine overdose. See the flumazenil injection Prescribing Information.

Consider contacting the Poison Help line (1-800-221-2222) or a medical toxicologist for additional overdose management recommendations.

DOSAGE AND ADMINISTRATION

While the recommended usual adult dose is 15 mg before retiring, 7.5 mg may be sufficient for some patients, and others may need 30 mg. In transient insomnia, a 7.5 mg dose may be sufficient to improve sleep latency. In elderly or debilitated patients, it is recommended that therapy be initiated with 7.5 mg until individual responses are determined.

Discontinuation or Dosage Reduction of Restoril

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Restoril or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly (see **WARNINGS, Dependence and Withdrawal Reactions** and **DRUG ABUSE AND DEPENDENCE: Dependence**).

HOW SUPPLIED

Restoril™ (temazepam) Capsules USP

7.5 mg

Blue and pink capsules, with the pink body imprinted “FOR SLEEP” on one side and  on the other side in red, and a blue cap imprinted “RESTORIL 7.5 mg” twice in red.

Bottle of 30 NDC 0406-9915-03

Bottle of 100 NDC 0406-9915-01

15 mg

Maroon and pink capsules, with the pink body imprinted “FOR SLEEP” on one side and  on the other side in red, and a maroon cap imprinted “RESTORIL 15 mg” twice in white.

Bottle of 100 NDC 0406-9916-01

22.5 mg

Opaque blue capsules, with the opaque blue body imprinted “FOR SLEEP” on one side and  on the other side in red, and an opaque blue cap imprinted “RESTORIL 22.5 mg” twice in red.

Bottle of 30 NDC 0406-9914-03

30 mg

Maroon and blue capsules, with the blue body imprinted “FOR SLEEP” on one side and  on the other side in red, and a maroon cap imprinted “RESTORIL 30 mg” twice in white.

Bottle of 100 NDC 0406-9917-01

Dispense in a well-closed, light-resistant container with a child-resistant closure.

Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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An electronic copy of this medication guide can be obtained from www.mallinckrodt.com/Medguide/L20R02.pdf or by calling 1-800-778-7898 for alternate delivery options.

MEDICATION GUIDE
RESTORIL™ (res-tə-ril)
(temazepam)
capsules, C-IV

What is the most important information I should know about RESTORIL?

- **RESTORIL is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system (CNS) depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.** Get emergency help right away if any of the following happens:
 - shallow or slowed breathing
 - breathing stops (which may lead to the heart stopping)
 - excessive sleepiness (sedation)
- Do not drive or operate heavy machinery until you know how taking RESTORIL and opioids affects you.
 - **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines including RESTORIL which can lead to overdose and serious side effects including coma and death.
 - **Serious side effects including coma and death have happened in people who have abused or misused benzodiazepines, including RESTORIL.** These serious side effects may also include delirium, paranoia, suicidal thoughts or actions, seizures, and difficulty breathing. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these serious side effects.**
 - **You can develop an addiction even if you take RESTORIL as prescribed by your healthcare provider.**
 - **Take RESTORIL exactly as your healthcare provider prescribed.**
 - Do not share your RESTORIL with other people.
 - Keep RESTORIL in a safe place and away from children.
- **Physical dependence and withdrawal reactions.** RESTORIL can cause physical dependence and withdrawal reactions.
 - **Do not suddenly stop taking RESTORIL.** Stopping RESTORIL suddenly can cause serious and life-threatening side effects, including, unusual movements, responses, or expressions, seizures, sudden and severe mental or nervous system changes, depression, seeing or hearing things that others do not see or hear, an extreme increase in activity or talking, losing touch with reality, and suicidal thoughts or actions. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these symptoms.**
 - **Some people who suddenly stop benzodiazepines have symptoms that can last for several weeks to more than 12 months,** including, anxiety, trouble remembering, learning, or concentrating, depression, problems sleeping, feeling like insects are crawling under your skin, weakness, shaking, muscle twitching, burning or prickling feeling in your hands, arms, legs or feet, and ringing in your ears.
 - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
 - Do not take more RESTORIL than prescribed or take RESTORIL for longer than prescribed.
- After taking RESTORIL, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with RESTORIL. Reported activities include:
 - driving a car (“sleep-driving”)
 - making and eating food
 - talking on the phone
 - having sex
 - sleep-walking

Call your healthcare provider right away if you find out that you have done any of the above activities after taking RESTORIL.

What is RESTORIL?

- RESTORIL is a prescription sleep medicine. RESTORIL is used in adults for the short-term (usually 7 to 10 days) treatment of a sleep problem called insomnia. Symptoms of insomnia include trouble falling asleep and waking up often during the night.
- **RESTORIL is a federal controlled substance (C-IV) because it contains temazepam that can be abused or lead to dependence.** Keep RESTORIL in a safe place to prevent misuse and abuse. Selling or giving away RESTORIL may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if RESTORIL is safe and effective in children.
- It is not known if RESTORIL is safe and effective for use longer than 2 weeks.

Do not take RESTORIL if you

- are allergic to temazepam or any of the ingredients in RESTORIL. See the end of this Medication Guide for a complete list of ingredients in RESTORIL.

Before you take RESTORIL, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of depression, mental illness or, suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have lung disease or breathing problems
- are pregnant or plan to become pregnant.
 - Taking RESTORIL late in pregnancy may cause your baby to have symptoms of sedation (breathing problems, sluggishness, low muscle tone), and/or withdrawal symptoms (jitteriness, irritability, restlessness, shaking, excessive crying, feeding problems).
 - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with RESTORIL.
 - There is a pregnancy registry for women who take RESTORIL during pregnancy. The purpose of the registry is to collect information about the health of women and their babies exposed to RESTORIL. If you become pregnant during treatment with RESTORIL, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychiatric Medications. You can register by calling 1-866-961-2388 or visiting <https://womensmentalhealth.org/research/pregnancyregistry/>.
- are breastfeeding, or plan to breastfeed. RESTORIL can pass through your breast milk.
 - Breastfeeding during treatment with RESTORIL may cause your baby to have sleepiness, feeding problems, and decreased weight gain.
 - Talk to your healthcare provider about the best way to feed your baby if you take RESTORIL.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking RESTORIL with certain other medicines can cause side effects or affect how well RESTORIL or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

Do not take RESTORIL with other medicines that can make you sleepy unless your healthcare provider tells you to.

How should I take RESTORIL?

- **See “What is the most important information I should know about RESTORIL?”**
- Take RESTORIL exactly as your healthcare providers tell you to take it. Take RESTORIL right before you get into bed.
- Do not take RESTORIL unless you are able to get a full night’s sleep before you must be active again.
- If you take too much RESTORIL or overdose, get emergency treatment right away.

What are the possible side effects of RESTORIL?

RESTORIL may cause serious side effects, including:

- **See “What is the most important information I should know about RESTORIL?”**
- **Abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts.
- **Severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help right away if you have these symptoms after taking RESTORIL.
- **RESTORIL can make you sleepy or dizzy and can slow your thinking and motor skills.**
 - Do not drive, operate heavy machinery, or do other dangerous activities until you know how RESTORIL affects you.
 - **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking RESTORIL without first talking to your healthcare provider.** When taken with alcohol or other drugs that cause sleepiness or dizziness, RESTORIL may make your sleepiness or dizziness much worse.

The most common side effects of RESTORIL include:

- | | |
|--------------|---------------|
| • drowsiness | • headache |
| • tiredness | • nervousness |
| • dizziness | • nausea |

You may still feel drowsy the next day after taking RESTORIL. **Do not drive or do other dangerous activities after taking RESTORIL until you feel fully awake.**

These are not all the possible side effects of RESTORIL. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RESTORIL?

- Store RESTORIL at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep RESTORIL and all medicines out of the reach of children.**

General information about the safe and effective use of RESTORIL.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RESTORIL for a condition for which it was not prescribed. Do not give RESTORIL to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about RESTORIL that is written for healthcare professionals.

What are the ingredients in RESTORIL?

Active Ingredient: temazepam

Inactive Ingredients: gelatin, lactose, magnesium stearate, red iron oxide, titanium dioxide

Manufactured by SpecGx LLC

Webster Groves, MO 63119

If you would like more information, call Mallinckrodt Inc. at 1-800-778-7898 or visit www.mallinckrodt.com.

Mallinckrodt™

This Medication Guide has been approved by the U.S. Food and Drug Administration

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