PRODUCT MONOGRAPH

ratio-TEMAZEPAM

Temazepam

15 mg and 30 mg capsules, USP

Hypnotic

ratiopharm inc.
Canada, J7J 1P3

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ACTIONS AND CLINICAL PHARMACOLOGY

General:

Temazepam is a benzodiazepine with hypnotic properties.

Benzodiazepines act as depressants of the central nervous system (CNS). It is believed that benzodiazepines enhance or facilitate the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

Benzodiazepines act as agonists at the benzodiazepine receptors sites. The benzodiazepine-GABA receptor-chloride ionophore complex functions mainly in the gating of the chloride channel. Benzodiazepines are thought to produce their pharmacological effects by facilitating GABA-mediated transmission in the CNS, which reportedly increase the frequency of the chloride channel opening.

In sleep laboratory studies, the effect of temazepam 15 mg and 30 mg, was compared to placebo over a two week period. There was a linear dose-response improvement in total sleep time and sleep latency with significant drug-placebo differences occurring for total sleep time at both doses, and for sleep latency at the higher dose. REM sleep was essentially unchanged and slow wave sleep was decreased.

Rebound insomnia:

A transient syndrome, known as "rebound insomnia", whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of hypnotic treatment. In the sleep laboratory studies, no measurable effects on daytime alertness or performance occurred following temazepam treatment or during the withdrawal period, even though a transient sleep disturbance in some sleep parameters was observed following the withdrawal of the higher doses.

The duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) and beta (elimination) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours. If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. However, during nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop.

If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., in relation to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night and 2) the appearance of increased day-time anxiety (see WARNINGS).

Pharmacokinetics:

Orally administered temazepam is well absorbed in man. In a single and multiple dose absorption, distribution, metabolism and excretion (ADME) study, using ^{3}H labelled drug, temazepam was 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. Oral administration of 15 to 45 mg temazepam in man resulted in

rapid absorption with significant blood levels achieved in 30 minutes and peak levels at 2-3 hours. Drug levels in blood declined in a biphasic manner with a short half-life ranging from 0.4 to 0.6 hours and a terminal half-life from 3.5 to 18 hours (mean 9 hours). The inactive O-conjugate metabolite was formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, O-conjugation is the rate limiting step in the biodisposition. In a multiple dose study, steady-state was approximated after the second daily dose with no evidence of accumulation after 5 consecutive daily doses of 30 mg temazepam. Steady-state plasma levels at 2.5 hours were 382 ± 192 ng/mL.

Approximately 96% of unchanged drug is bound to plasma protein.

Twenty-four hours after a single oral dose of temazepam approximately 80%-90% of the drug was recovered in urine, primarily as the O-conjugate. Total recovery from feces and urine in single- and multiple-dose studies was approximately 95%, with only 3-13% of the radioactivity detectable in feces. Less than 1% of the dose was excreted as unchanged drug or N-desmethyltemazepam. A dose-proportional relationship has been established for the area under the plasma concentration/time curve over the 15-30 mg dose range.

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

BIOAVAILABILITY

Randomized, two-way crossover, single-dose bioavailability studies were conducted in fasting healthy, adult male subjects. The bioavailability of **ratio-TEMAZEPAM** capsules, 15 and 30 mg, relative to Restoril® capsules, 15 and 30 mg was determined following single 1 x 15 mg and 1 x 30 mg doses. The average values of the pharmacokinetic parameters as well as ratio of means (with 90% confidence intervals) are listed in the following tables:

Table 1:

*Summary Table of the Comparative Bioavailability Study of **ratio-TEMAZEPAM** vs Restoril®, Temazepam 15 mg capsules conducted under fasting conditions in 24 healthy adult male volunteers (from measured data)*			
	Geometric Mean Arithmetic Mean (CV%)		
Parameter	***ratio-TEMAZEPAM***	*Restoril®***	*Ratio of Geometric Means (%) (90% Confidence Limits)*
AUCt	*2051.15*	*2092.97*	*98*
(ng.h/mL)	*2203.85 (40.9)*	*2277.73 (46.1)*	*(95-102)*
AUCinf	*2190.65*	*2237.77*	*98*
(ng.h/mL)	*2352.96 (41.7)*	*2459.45 (50.1)*	*(95-101)*
C_{max}	*368.18*	*322.43*	*114*
(ng/mL)	*376.72 (20.8)*	*334.76 (28.3)*	*(104-125)*
*T_{max}**	*1.18 (57.6)*	*1.51 (50.2)*	*---*
(h)			
*T½**	*10.06 (26.9)*	*10.54 (31.0)*	*---*
(h)			

**The T_{max} and T½ parameters are expressed as the arithmetic means.*

***Restoril® is manufactured by Novartis Pharmaceuticals and was purchased in Canada.*

Table 2:

*Summary Table of the Comparative Bioavailability Study of **ratio-TEMAZEPAM** vs Restoril®, Temazepam 30 mg capsules conducted under fasting conditions in 24 healthy adult male volunteers (from measured data)*			
	Geometric Mean Arithmetic Mean (CV%)		
Parameter	***ratio-TEMAZEPAM***	*Restoril®***	*Ratio of Geometric Means (%) (90% Confidence Limits)*
AUCt	*5696.11*	*5924.46*	*96*
(ng.h/mL)	*6172.59 (38.7)*	*6414.84 (39.1)*	*(92-99)*
AUCinf	*5905.83*	*6140.71*	*96*
(ng.h/mL)	*6424.72 (39.7)*	*6673.25 (40.2)*	*(92-99)*
C_{max}	*892.64*	*903.73*	*98*
(ng/mL)	*929.49 (27.7)*	*949.22 (29.8)*	*(89-109)*
T_{max}*	*1.65 (48.8)*	*1.54 (53.8)*	*---*
(h)			
*T½**	*10.34 (23.6)*	*10.60 (17.6)*	*---*
(h)			

**The T_{max} and T½ parameters are expressed as the arithmetic means.*

***Restoril® is manufactured by Novartis Pharmaceuticals and was purchased in Canada.*

Conclusion: The 90% confidence intervals for the ln-transformed parameters AUCt and AUCinf for temazepam were within the 80-125% TPD acceptance range both before and after correction for measured content. Also, the ratio of means for Cmax was within the 80-125% range. Based on these results, **ratio-TEMAZEPAM** and Restoril® (temazepam) 15 and 30 mg capsules are considered bioequivalent under single-dose fasting conditions.

INDICATIONS AND CLINICAL USE

Sleep disturbance may be the presenting manifestation of a 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.

ratio-TEMAZEPAM (temazepam) is indicated for the symptomatic relief of transient and short-term insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings.

Treatment with **ratio-TEMAZEPAM** should usually not exceed 7 to 10 consecutive days. Use for more than 2 to 3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for **ratio-TEMAZEPAM** should be written for short-term use (7 to 10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

The use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning.

CONTRAINDICATIONS

ratio-TEMAZEPAM (temazepam) is contraindicated in patients with a known hypersensitivity to the drug, any component of its formulation, or to other benzodiazepines; myasthenia gravis; sleep apnea syndrome.

ratio-TEMAZEPAM is contraindicated in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

WARNINGS

General:

Benzodiazepines should be used with extreme caution in patients with a history of substance or alcohol abuse.

The lowest possible effective dose should be prescribed for elderly patients. Inappropriate, heavy sedation in the elderly, may result in accidental events or falls.

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 or the presence of sleep state misperception.

Worsening of insomnia or the emergence of new abnormalities of thinking or behaviour may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of drugs that act at the benzodiazepine receptors.

Pregnancy:

The use of **ratio-TEMAZEPAM** (temazepam) during pregnancy is not recommended.

Benzodiazepines may cause fetal damage when administered during pregnancy. During the first trimester of pregnancy, several studies have suggested an increased risk of congenital malformations associated with the use of benzodiazepines. During the last weeks of pregnancy, ingestion of therapeutic doses of a benzodiazepine hypnotic has resulted in neonatal CNS depression due to transplacental distribution.

If the drug is prescribed to a woman of childbearing potential, the patient should be warned of the potential risk to a fetus and advised to consult her physician regarding the discontinuation of the drug if she intends to become pregnant or suspects that she is pregnant.

Memory disturbance:

Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines. The event is rare with temazepam. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk. Cases of transient global amnesia and "traveller's amnesia" have also been reported in association with benzodiazepines, the latter in individuals who have taken the drug, often in the middle of the night, to induce sleep while travelling.

Transient global amnesia and traveller's amnesia are unpredictable and not necessarily dose-related phenomena. Patients should be warned not to take temazepam under circumstances in which a full night's sleep and clearance of the drug from the body are not possible before they need again to resume full activity.

Abnormal thinking and psychotic behavioural changes have been reported to occur in association with the use of benzodiazepines including temazepam, although rarely. Some of the changes may be characterized by decreased inhibition, e.g., aggressiveness or extroversion that seem excessive, similar to that seen with alcohol and other CNS depressant (e.g., sedative/hypnotics). Particular caution is warranted in patients with a history of violent behaviour and a history of unusual reactions to sedatives including alcohol and the benzodiazepines. Psychotic behavioural changes that have been reported with benzodiazepines include bizarre behaviour, hallucinations, and depersonalization. Abnormal behaviours associated with the use of benzodiazepines have been reported more with chronic use and/or high doses but they may occur during the acute, maintenance or withdrawal phases of treatment.

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

Confusion:

The benzodiazepines affect mental efficiency, e.g., concentration, attention and vigilance. The risk of confusion is greater in the elderly and in patients with cerebral impairment.

Anxiety, restlessness:

An increase in daytime anxiety and/or restlessness have been observed during treatment with temazepam.

This may be a manifestation of interdose withdrawal due to the short elimination half-life of the drug.

Depression:

Caution should be exercised if temazepam is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g., intentional overdose) is high in patients with depression and thus, the least amount of drug that is feasible should be available to them at any one time.

Potentiation of drug effects:

Temazepam may potentiate the effects of other central nervous system depressant drugs such as alcohol, barbiturates, non-barbiturate hypnotics, antihistamines, narcotics, antipsychotic and antidepressant drugs, and anticonvulsants. Therefore, different benzodiazepines should usually not be used simultaneously and careful consideration should be given if other CNS depressants are administered in combination with temazepam. Patients should be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol because of the potentiation of effects that might occur.

Complex Sleep-Related Behaviours

Complex sleep-related behaviours 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 in patients who have taken temazepam. Other potentially dangerous

behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with “sleep-driving”, patients usually do not remember these events. The use of alcohol and other CNS-depressants with temazepam appears to increase the risk of such behaviours, as does the use of temazepam at doses exceeding the maximum recommended dose. Temazepam is not to be taken with alcohol. Caution is needed with concomitant use of other CNS depressant drugs. Due to the risk to the patient and the community, discontinuation of temazepam should be strongly considered for patients who report any such complex sleep-related behaviours.

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 temazepam. 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 throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with temazepam should not be rechallenged with the drug.

PRECAUTIONS

Drug interactions:

ratio-TEMAZEPAM (temazepam) may produce additive CNS depressant effects when co-administered with alcohol, sedative antihistamines, anticonvulsants, or psychotropic medications which themselves can produce CNS depression.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines.

Drug abuse, dependence and withdrawal:

Withdrawal symptoms, similar in characteristic to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating,

dysphoria, perceptual disturbances and insomnia) have occurred following abrupt discontinuation of benzodiazepines including temazepam.

The more severe symptoms are usually associated with higher dosages and longer usage, although patients given therapeutic dosages for as few as 1 to 2 weeks can also have withdrawal symptoms including daytime anxiety between nightly doses. Consequently, abrupt discontinuation should be avoided and a gradual dosage tapering schedule is recommended in any patient taking more than the lowest dose for more than a few weeks. The recommendation for tapering is particularly important in patients with a history of seizures.

The risk of dependence is increased in patients with a history of alcoholism, drug abuse, or in patients with marked personality disorders. Interdose daytime anxiety and rebound anxiety may increase the risk of dependency in temazepam treated patients.

As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

Patients with specific conditions

Temazepam is O-conjugated in the liver and is primarily excreted by the kidney. Hence, **ratio-TEMAZEPAM** (temazepam) should be given with caution to patients with impaired hepatic or renal function.

ratio-TEMAZEPAM (temazepam) should also be given with caution to patients with severe pulmonary insufficiency: respiratory depression has been reported in patients with compromised respiratory function.

ratio-TEMAZEPAM (temazepam) should be used 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.

Patients requiring mental alertness:

Because of temazepam's CNS depressant effect, patients receiving the drug should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be warned against the concomitant ingestion of **ratio-TEMAZEPAM** and alcohol or CNS depressant drugs.

Use in nursing mothers:

It is not known whether or not temazepam is excreted in human milk. Therefore, it should not be given to nursing mothers.

Use in pregnancy:

For teratogenic effects see **WARNINGS**. Non-teratogenic effects: a child born to a mother who is on benzodiazepines may be at risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity has been reported in an infant born to a mother who had been receiving benzodiazepines.

Use in children:

The safety and effectiveness of temazepam in children below the age of 18 have not been established.

Use in the elderly and debilitated patients:

Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Inappropriate, heavy sedation may result in accidental events/falls. Therefore, the lowest possible dose should be used in these subjects.

Debilitated patients, or those with organic brain syndrome, are prone to CNS depression after even low doses of benzodiazepines and may experience paradoxical reactions to these drugs. Therefore, **ratio-TEMAZEPAM** (temazepam) should be used only at the

lowest possible dose and adjusted when necessary under careful observation, depending on the response of the patient.

Because temazepam is eliminated by O-conjugation, minimal accumulation occurs.

ADVERSE REACTIONS

During controlled clinical trials in which 1076 patients received temazepam at bedtime, the adverse events occurring in 1% or more of patients are listed as follows:

	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 with an incidence of 0.5 - 0.9%:
Central nervous system: anorexia, ataxia, equilibrium loss, tremor, increased dreaming.
Cardiovascular: dyspnea, palpitations.
Gastrointestinal: vomiting.
Musculoskeletal: backache.
Special senses: hyperhydrosis, burning eyes.

The following adverse events have been reported with an incidence of less than 0.5%: Amnesia, hallucinations, horizontal nystagmus and paradoxical reactions including restlessness, overstimulation and agitation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations of acute overdosage of temazepam, as with other benzodiazepines, can be expected to reflect the increasing CNS effects of the drug and include somnolence, confusion and coma, with reduced or absent reflexes. With large overdoses, respiratory depression, hypotension and finally coma will result. If the patient is conscious, vomiting should be induced mechanically or with emetics (e.g., syrup of ipecac 20 to 30 mL). Gastric lavage should be employed as soon as possible, utilizing concurrently a cuffed endotracheal tube if the patient is unconscious, in order to prevent aspiration and pulmonary complications. Maintenance of adequate pulmonary ventilation is essential and fluids should be administered intravenously to encourage diuresis. The use of pressor agents, such as norepinephrine bitartrate or metaraminol, intravenously may be necessary to combat hypotension but only if considered essential. The value of dialysis in emergency therapy for benzodiazepine overdosage has not been determined. If excitation occurs, barbiturates should not be used. It should be borne in mind that multiple agents may have been ingested.

The benzodiazepine antagonist, flumazenil (Anexate), is a specific antidote in known or suspected benzodiazepine overdose. For conditions of use see flumazenil Product Monograph.

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

The lowest effective dose of ratio-TEMAZEPAM (temazepam) should be used. Treatment with ratio-TEMAZEPAM should usually not exceed 7-10 consecutive days.

Use for more than 2 to 3 consecutive weeks requires complete reevaluation of the patient.

An appropriate hypnotic dose should produce the desired hypnotic effect while avoiding oversedation and impairment of performance the next day.

Adult dose:

The recommended adult dose of **ratio-TEMAZEPAM** (temazepam) is 30 mg before retiring, **15 mg may be sufficient for some patients**.

Elderly and debilitated patients:

The recommended initial dose should not exceed 15 mg before retiring. (see **PRECAUTIONS**).

ratio-TEMAZEPAM (temazepam) is intended only for short-term use and therefore, should not be prescribed in quantities exceeding those required for that cycle of administration. Prescriptions should not be renewed without further assessment of the patient's needs.

ratio-TEMAZEPAM is not indicated in children under 18 years of age.

PHARMACEUTICAL INFORMATION

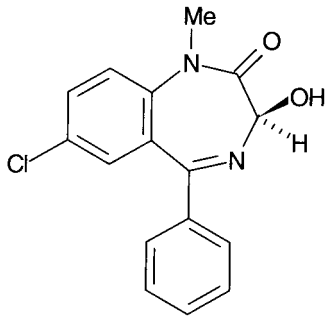
Drug substance:

Trade name: **ratio-TEMAZEPAM**

Proper name: Temazepam

Chemical name: 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one.

Structural formula:



Molecular formula: $C_{16}H_{13}ClN_2O_2$

Molecular weight: 300.74

Composition:

Each 15 mg capsule contains: 15 mg of temazepam. **Non-medicinal ingredients in alphabetical order:** Ammonium hydroxide, n-butyl alcohol, D&C red #28, D&C red #33, D&C yellow #10, FD&C blue #1, FD&C yellow #6, gelatin, isopropyl alcohol, lactose, magnesium stearate, propylene glycol, shellac, silicon dioxide, simethicone, sodium lauryl sulfate and titanium dioxide.

Each 30 mg capsule contains: 30 mg of temazepam. **Non-medicinal ingredients in alphabetical order:** Ammonium hydroxide, n-butyl alcohol, D&C red #28, D&C red #33, D&C yellow #10, FD&C blue #1, gelatin, isopropyl alcohol, lactose,

magnesium stearate, propylene glycol, shellac, silicon dioxide, simethicone, sodium lauryl sulfate and titanium dioxide.

Stability and storage recommendations: Store at controlled room temperature, between 15-30 °C. Protect from moisture and light.

AVAILABILITY OF DOSAGE FORMS

ratio-TEMAZEPAM (temazepam) 15 mg

Each maroon and peach, size 3 hard shell gelatin capsule, printed in white ink with "TEC 185A", contains: temazepam 15 mg. Also contains lactose. Bottles of 100 and 500.

ratio-TEMAZEPAM (temazepam) 30 mg

Each maroon and blue, size 3 hard shell gelatin capsule, printed in white ink with "TEC 185B", contains: temazepam 30 mg. Also contains lactose. Bottles of 100 and 500.

PHARMACOLOGY

In animals, temazepam produces sedative and muscle relaxant effects. At higher doses it has some cardiovascular depressant effects. In unanesthetized rabbits and dogs, temazepam caused slight but significant decreases in blood pressure at oral doses from 5 to 20 mg/kg.

Temazepam decreases spontaneous activity at doses of 2.5 to 5 mg/kg p.o. in the mouse, 20 mg/kg p.o. in the rat and at 10 mg/kg p.o. in the dog. It produces ataxia in the mouse and rat at 10 mg/kg p.o. and in the dog at 20 mg/kg p.o. Loss of righting reflex occurs in mouse and rat at 40 mg/kg p.o. and muscle tone is decreased in the mouse at 10 to 40 mg/kg p.o. and in the rat and dog at 20 mg/kg p.o. Ptosis, myosis and piloerection occur in the mouse at 2.5 to 5 mg/kg p.o., in the rat at 10 to 20 mg/kg p.o., and in the dog bradycardia occurs at 20 to 40 mg/kg and photophobia at 80 mg/kg p.o.

Temazepam potentiates the sleep-enhancing effects of hexabarbitone, induces sleep in cebus monkeys at the minimum effective dose of 3.75 mg/kg p.o. and blocks the lingomandibular reflex in cats at the dose of 0.1 to 1.0 mg/kg i.v. Temazepam also blocks pentylenetetrazol-induced convulsions in mice at the dose of 0.23 mg/kg p.o.

Pharmacokinetics:

Metabolism and excretion of temazepam in toxicology species (mouse, rat and dog) varied considerably from the pattern in man but the biotransformation pathways in humans also occur in all of the animals studied thus far. In the mouse, the major metabolites were N-desmethyltemazepam and its conjugates. In the rat, temazepam and the N-demethylated compound were present in equal proportions, largely unconjugated, but more than 50% was present as unidentified metabolites. In the dog, conjugated temazepam was the major metabolite, followed by free and conjugated N-desmethyltemazepam in equal proportions. In all species studied, man showed the

highest blood levels, the smallest distribution volume and the greatest proportion of urinary elimination.

TOXICOLOGY

In the acute toxicity studies the following title LD_{50} for temazepam were determined:

Species	Sex	Routes	LD_{50} mg/kg
Mouse	M & F	Oral	1963 (1813-2126)
Mouse	M	Oral	980 (860-1117)
Mouse	M & F	i.p.	1050 (967-1140)
Mouse	M	i.p.	485 (411-572)
Rat	M & F	Oral	1823 (1639-2027)
Rat	M	Oral	2800 (2059-3808)
Rat	M & F	i.p.	617 (551-690)
Rat	M	i.p.	670 (626-717)
Rabbit	M & F	Oral	$\geq$ 2400
Dog	M & F	Oral	$\geq$ 1600

Overt sedation was prominent in all acute tests and ataxia and decreased locomotion were observed in some tests.

Subacute toxicity experiments lasting from 6 to 13 weeks were conducted in rats (9-250 mg/kg/day p.o.) and dogs (80-200 mg/kg/day p.o.). In the rat changes in hepatic function were seen at the doses over 100 mg/kg/day.

In subacute studies in dogs treatment-related symptoms included decreased locomotion, sedation, abdominal distension and weight loss. Sporadic hyperexcitability was seen in some animals. Chronic toxicity studies of 6 to 12 months were performed in rats (10-160 mg/kg/day p.o.) and dogs (5-120 mg/kg/day p.o.). In the rat the major finding was a liver weight increase at high doses and minimal hepatic lipidosis at the mid and high doses. Dogs at the higher doses exhibited slight lethargy.

Two series of 18 month studies were performed in mice at doses from 11-158 mg/kg/day. In one study there was a 4% increase over controls in hepatocellular adenomas in female mice. This incidence is within that found in control groups for the species studied.

Reproductive and Teratology studies:

Rats (25-840 mg/kg/day) and rabbits (5-60 mg/kg/day) were utilized to assess potential reproductive and teratologic effects. Two segment II type studies in rats provided evidence of the possible increased incidence of **fetal** resorptions, **at doses of 30-120 mg/kg**. In perinatal and postnatal studies in rats at doses of 60 and 120 mg/kg/day, **resulted in increasing nursling mortality**. There were minimal untoward effects on the newborn survival rate. Two segment II type studies in rabbits produced no evidence of potential teratologic effects.

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III. Others:

1. Product Monograph Restoril® (temazepam) capsules - 15 mg and 30 mg. Date of revision June 26, 2009. Sepracor Pharmaceuticals Inc.

PART III: CONSUMER INFORMATION

ratio-TEMAZEPAM
(temazepam)

This leaflet is part III of a three-part "Product Monograph" published when ratio-TEMAZEPAM was approved for sale in Canada and is designed specifically for Consumers. Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets, as you may need to read it again. This leaflet should not replace a discussion between you and your doctor about the risks and benefits of ratio-TEMAZEPAM. This leaflet is a summary and will not tell you everything about ratio-TEMAZEPAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ratio-TEMAZEPAM is intended to help you sleep if you have transient and short-term insomnia. Symptoms of insomnia include difficulty falling asleep, and/or waking up often during the night or too early in the morning.

Treatment with **ratio-TEMAZEPAM** should usually not go on for more than 7-10 days and should be restricted for insomnia where disturbed sleep results in impaired daytime functioning. **ratio-TEMAZEPAM** does not treat the underlying cause of your insomnia.

What it does:
ratio-TEMAZEPAM is a benzodiazepine which acts on receptors in your brain to produce a calming effect.

ratio-TEMAZEPAM is one of several benzodiazepine sleeping pills that have generally similar properties. If you are prescribed one of these medications, you should consider both their benefits and risks.

Important risks you should consider when taking **ratio-TEMAZEPAM** are:
• the longer you use **ratio-TEMAZEPAM**, the less effective it may become,
• You may become dependent on **ratio-TEMAZEPAM**,
• **ratio-TEMAZEPAM** may affect your mental alertness or memory, particularly when not taken as prescribed (see "WARNINGS AND PRECAUTIONS")

When it should not be used:
• Patients with a known allergy to temazepam or other benzodiazepines or to any of the ingredients **ratio-TEMAZEPAM** contains (see '**What the nonmedicinal ingredients are**')
• Patients with a chronic disease characterized by weakness of the skeletal muscles (myasthenia gravis)
• Patients with a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea)
• Patients with a past history of unexpected reactions to alcohol or sedative medications, such as irritability, aggression, hallucinations, etc.

What the medicinal ingredient is:
Temazepam

What the important nonmedicinal ingredients are:
Ammonium hydroxide, n-butyl alcohol, D&C red #28, D&C red #33, D&C yellow #10, FD&C blue #1, FD&C yellow #6 (15 mg capsule only), gelatin, isopropyl alcohol, lactose, magnesium stearate, propylene glycol, shellac, silicon dioxide, simethicone, sodium lauryl sulfate and titanium dioxide.

What dosage forms it comes in:
Capsules 15 mg and 30 mg

WARNINGS AND PRECAUTIONS

Complex sleep-related behaviours
There have been reports of people getting out of bed while not fully awake after taking **ratio-TEMAZEPAM** and doing activities that they did not know they were doing. The next morning they did not remember doing these activities. This unusual behaviour is more likely to occur if **ratio-TEMAZEPAM** is taken with alcohol or other drugs that make you sleepy such as treatments for depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc.

Important:
1. Do not take more **ratio-TEMAZEPAM** than prescribed.
2. Do not take **ratio-TEMAZEPAM** if you drink alcohol.
3. Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products. Your doctor will tell you if you can take **ratio-TEMAZEPAM** with your other medicines.
4. You and people close to you should watch for the type of unusual behaviour described above. If you find out you have done *any* such activities for which you have no memory you should call your doctor immediately.

Mental Alertness
ratio-TEMAZEPAM may affect your ability to be alert. Do not operate a car or dangerous machinery while using **ratio-TEMAZEPAM** until you know how this drug affects you.

Memory problems
Sleeping pills can cause a special type of memory loss (amnesia).

You may not recall events that occurred during a period of time, usually several hours after taking the drug. This lapse can be a problem if you take the medication to induce sleep while travelling, such as during an airplane flight, as you may wake up before the effect of the drug is gone. This has been called "traveler's amnesia". Do not take **ratio-TEMAZEPAM** when a full night's sleep is not possible before you would again need to be active and functional, e.g., overnight flight of less than 8 hours. Memory lapses may occur in such situations. Your body needs time to eliminate the medication from your system.

Tolerance/Withdrawal Symptoms
After nightly use for more than a few weeks, this drug may lose some of its effectiveness to help you sleep (tolerance).

Withdrawal effects can occur when patients stop taking sleeping pills suddenly. The effects may occur following use for only a week or two but may be more common and more severe after long periods of continuous use. Symptoms may range from unpleasant feelings to a major withdrawal syndrome that may include stomach/muscle cramps, vomiting, sweating, tremors or, rarely, convulsions. The severe symptoms are uncommon.

You may develop an increase in sleep difficulties (rebound insomnia) and/or increased daytime anxiety (rebound anxiety) for one or two days after discontinuing **ratio-TEMAZEPAM**. This effect does not occur in everyone.

Also, although not common, it is possible that your body may eliminate **ratio-TEMAZEPAM** too quickly and the level of drug in your body may be too low at some point during each night's use to maintain sleep for the full night. This can lead to being awake during the last third of the night and/or increased daytime anxiety or nervousness. If this happens to you, talk to your doctor.

Dependence/Abuse
Sleeping pills can cause dependence (addiction) especially when used regularly for more than a few weeks or at higher doses. Some people develop a need to continue taking these drugs, either at the prescribed dose or higher doses – not only for continued therapeutic effect, but also to avoid withdrawal symptoms or to achieve non-therapeutic effects. Patients who depend on or have depended on alcohol or other drugs in the past may be at particular risk but ALL PEOPLE ARE AT SOME RISK. Consider this matter before you take these medications beyond a few weeks.

Mental and Behavioural Changes
A variety of abnormal thinking and behaviour changes may occur when you use benzodiazepine sleeping pills, including aggressiveness, extroversion, confusion, strange behaviour, restlessness, illusions, hallucinations, feeling like you are not yourself, worsening of insomnia or worsening of depression including suicidal thinking. It is rarely clear whether such symptoms are caused by the medication, by an illness that was present before the medication was used or are simply spontaneous happenings. If you develop any unusual disturbing thoughts or behaviour discuss the matter with your doctor immediately.

Worsening of Side Effects
Do not consume alcohol while taking **ratio-TEMAZEPAM**. Some medicines may also worsen side effects that some patients experience with **ratio-TEMAZEPAM** (see "INTERACTIONS WITH THIS MEDICATION").

Elderly
An increased risk of falls and fractures has been reported in elderly people who take benzodiazepines such as **ratio-TEMAZEPAM**.

Effects on Pregnancy
Certain benzodiazepine sleeping pills have been linked to birth defects when taken during the early months of pregnancy. In addition, benzodiazepine sleeping pills taken during the last weeks
of pregnancy have been known to sedate the baby and may also cause withdrawal symptoms after birth. **Do not take ratio-TEMAZEPAM at any time during pregnancy.**

BEFORE you use ratio-TEMAZEPAM talk to your doctor or pharmacist if:
- You have a lung disease or breathing problems
- You have liver or kidney conditions.
- You have a history of depression and/or suicide thoughts or attempts.
- You have a history of drug or alcohol abuse or addiction.
- You are pregnant, if you are planning to become pregnant, or if you become pregnant while taking this medication.
- You are breastfeeding.
- You consume alcohol.
- You are taking other medications, including drugs you can buy without a prescription and herbal products.
- You have lactose intolerance.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking any other medicines, including medicines you can buy without a prescription and herbal products.

Drugs that may interact with **ratio-TEMAZEPAM** include: alcohol, barbiturates, hypnotics (sleeping pills), antihistamines, narcotics, antipsychotics, antidepressants and anticonvulsants.

Do not take ratio-TEMAZEPAM if you drink alcohol.

Do not use **ratio-TEMAZEPAM** along with other medications without first discussing this with your doctor.

PROPER USE OF THIS MEDICATION

Benzodiazepines are effective medications and are relatively free of serious problems when used for the short term management of

insomnia. Insomnia may last only for a short time and may respond to brief treatment. The risks and benefits of prolonged use should be discussed with your doctor.

Usual dose:
Follow your doctor's advice about how to take **ratio-TEMAZEPAM**, when to take it, and how long to take it.

Adults: The recommended dose is 30 mg right before bedtime, 15 mg may be sufficient for some patients.

Elderly and debilitated patients should start with 15 mg before bedtime.

The lowest effective dose should be used. Treatment with ratio-TEMAZEPAM should usually not exceed 7-10 consecutive days.
If you still have problems sleeping after you finish your capsules, contact your doctor again.

Do not take more **ratio-TEMAZEPAM** than prescribed.
Do not take **ratio-TEMAZEPAM** if you drink alcohol.

Do not take **ratio-TEMAZEPAM** if it is not prescribed for you.

Do not take **ratio-TEMAZEPAM** when a full night's sleep is not possible before you would again need to be active and functional.

Do not drive a car or operate potentially dangerous machinery until you experience how **ratio-TEMAZEPAM** will affect you the next day.

ratio-TEMAZEPAM is not for use in children under 18 years of age.

Overdose:
Contact your doctor, regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your **ratio-TEMAZEPAM**. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick. Show your doctor your bottle of capsules.

Missed Dose:
If you miss a dose, take your usual dose the next evening. Do not double your dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common Side Effects
The most common side effects include: drowsiness, dizziness, lightheadedness and difficulty with coordination. Patients should be cautious about performing hazardous activities requiring complete mental alertness (i.e: operating machinery or driving a car).

How sleepy you are the day after you use **ratio-TEMAZEPAM** depends on your individual response and how quickly your body gets rid of the medication. Benzodiazepines, which are eliminated rapidly, tend to cause less drowsiness the next day but may cause withdrawal problems the day after use.

The larger the dose, the more likely that you will experience drowsiness, etc. the next day. For this reason, it is important that you use the lowest dose possible that will still help you sleep at night.

Elderly patients are especially susceptible to side effects. Excessive drowsiness in the elderly may result in falls and fractures.

Do not drink alcohol while using **ratio-TEMAZEPAM**. Do not use sleeping pills along with other medications without first discussing this with your doctor.

Rare cases of severe allergic reactions have been reported. Symptoms may include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you have any of these symptoms after taking **ratio-TEMAZEPAM**.

Withdrawal-related side effects: See 'WARNINGS AND PRECAUTIONS, **Tolerance/Withdrawal Symptoms'.**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek urgent medical attention
		Only if severe	In all cases	
Common	Depressed mood		✓	
Rare	Severe allergic reaction (swelling of tongue or throat, trouble breathing, nausea & vomiting)			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

		Talk with your doctor or pharmacist		
Rare	Unexpected reactions such as excitement, agitation, hyperactivity, hallucination, worsened insomnia, aggressiveness, irritability, rages, psychoses, and violent behaviour		✓	
Rare	Somnambulism (sleepwalking) – getting out of bed while not fully awake and do activities you do not remember the day after		✓	
Rare	Thoughts of death or suicide		✓	

This is not a complete list of side effects. For any unexpected effects while taking ratio-TEMAZEPAM, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15-30 ºC). Protect from moisture and light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.ratiopharm.ca

or by contacting the sponsor, ratiopharm inc., at:
1-800-337-2584

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