PRODUCT MONOGRAPH

RESTORIL®

Temazepam Capsules USP

15 mg and 30 mg Capsules

Hypnotic

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PRODUCT MONOGRAPH

RESTORIL®

Temazepam Capsules USP

THERAPEUTIC CLASSIFICATION

Hypnotic

ACTIONS AND CLINICAL PHARMACOLOGY

General

Restoril (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 Restoril 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, Restoril 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 biodispositon. 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.

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.

Restoril (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 Restoril should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for Restoril should be written for short-term use (7-10 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.

Geriatrics:
Long-term use of RESTORIL should be avoided in elderly patients. Enhanced monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Falls and fractures; DOSAGE AND ADMINISTRATION, Dosing considerations**).

CONTRAINDICATIONS

Restoril (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.

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

WARNINGS

Serious Warnings and Precautions

Addiction, Abuse and Misuse

Use of RESTORIL, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing RESTORIL
- Monitor all patients regularly for the development of these behaviours or conditions.
- RESTORIL should be stored securely to avoid theft or misuse.

Withdrawal
Benzodiazepines, like RESTORIL, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of RESTORIL.
- Terminate treatment with RESTORIL by gradually tapering the dosage schedule under close monitoring.

(see **WARNINGS AND PRECAUTIONS, Dependence/Tolerance)**

Risks from Concomitant use with Opioids
Concomitant use of RESTORIL and opioids may result in profound sedation, respiratory

depression, coma and death (see **WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids**).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

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 7-10 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.

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 for use in patients for whom alternative treatment options are not possible (see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; DRUG INTERACTIONS, Serious Drug Interactions**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If a decision is made to prescribe RESTORIL concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of RESTORIL than indicated, and titrate based on

clinical response. If an opioid analgesic is initiated in a patient already taking RESTORIL, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see **OVERDOSE).**

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 of the opioid have been determined.

Pregnancy

The use of Restoril (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 Restoril. 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 Restoril 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 behavioral changes have been reported to occur in association with the use of benzodiazepines including Restoril, 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 behavioral 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 behavioral 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 Restoril. This may be a manifestation of interdose withdrawal due to the short elimination half-life of the drug.

Depression

Caution should be exercised if Restoril 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.

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Potentiation of Drug Effects

Restoril 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 Restoril. 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 RESTORIL. 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 RESTORIL appears to increase the risk of such behaviours, as does the use of RESTORIL at doses exceeding the maximum recommended dose. RESTORIL 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 RESTORIL 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 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 throat, 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.

PRECAUTIONS

Drug interactions

Serious Drug Interactions

Concomitant use of RESTORIL and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see **WARNINGS AND PRECAUTIONS BOX, General, Risks from Concomitant use with Opioids)**

Restoril (temazepam) may produce additive CNS depressant effects when coadministered 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.

Dependence/Tolerance

Use of benzodiazepines, such as RESTORIL, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use (days to weeks) at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with RESTORIL with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing RESTORIL. In individuals prone to substance use disorder, RESTORIL should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- RESTORIL should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving opioids should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

<u>Drug abuse, dependence and withdrawal</u>

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 Restoril.

The more severe symptoms are usually associated with higher dosages and longer usage, although patients given therapeutic dosages for as few as 1-2 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 Restoril treated patients.

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

Withdrawal
Benzodiazepines, such as RESTORIL, can produce withdrawal symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use (days to weeks) at recommended therapeutic doses.

The onset of withdrawal symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), homicidal thoughts, mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behavior.

Other withdrawal symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

(see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; DOSAGE AND ADMINISTRATION, Dosing Considerations**)

Special Populations

Patients with specific conditions

Temazepam is O-conjugated in the liver and is primarily excreted by the kidney. Hence, Restoril should be given with caution to patients with impaired hepatic or renal function. Restoril should also

be given with caution to patients with severe pulmonary insufficiency: respiratory depression has been reported in patients with compromised respiratory function.

Restoril 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 Restoril'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 Restoril and alcohol or CNS depressant drugs.

Use in nursing mothers

It is not known whether or not Restoril 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 Restoril in children below the age of 18 have not been established.

Geriatrics:

Long-term use of RESTORIL should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

Use in 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, Restoril should be used only at the lowest possible dose and adjusted when necessary under careful observation, depending on the response of the patient.

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

ADVERSE REACTIONS

During controlled clinical trials in which 1076 patients received Restoril at bedtime, the Adverse Events occurring in 1% or more of patients are listed below.

	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 with an incidence of 0.5 - 0.9%:

Central Nervous System: anorexia, ataxia, equilibrium loss, tremor, increased dreaming.

Cardiovascular: dyspnea, palpitations.

Gastrointestinal: vomiting.

Muskuloskeletal: 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.

Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal: Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as Restoril. Severe and life-threatening symptoms have been reported. (see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; WARNINGS AND PRECAUTIONS, Dependence/Tolerance**)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations of acute overdosage of Restoril (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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- RESTORIL should always be prescribed at the lowest effective dose for the shortest duration possible.
- RESTORIL can produce withdrawal symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; WARNINGS AND PRECAUTIONS, Dependence/Tolerance**). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the

benzodiazepine to the previous dosage prior to proceeding with a gradual taper.

- Geriatric patients in particular may be more sensitive to benzodiazepines (see **WARNINGS AND PRECAUTIONS, Falls and Fractures**).
- Long-term use of RESTORIL should be avoided in elderly patients. Enhanced monitoring is recommended.

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

Use for more than 2-3 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 Restoril is 30 mg before retiring, **15 mg may be sufficient for some patients.**

Elderly and debilitated patients: the initial dose should not exceed 15 mg before retiring (see PRECAUTIONS).

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

Restoril is not indicated in children under 18 years of age.

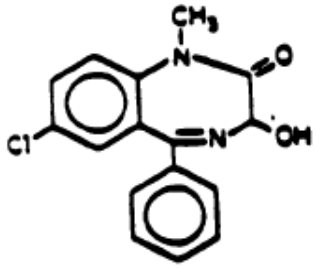
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: temazepam

Chemical Name: 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one

Structural Formula:



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

Molecular Weight: 300.74

Composition

Each 15 and 30 mg capsule contains 15 mg and 30 mg of temazepam respectively, and the inactive ingredients (alphabetical): ammonium hydroxide, croscarmellose sodium, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, lactose anhydrous, magnesium stearate, microcrystalline cellulose, propylene glycol, red iron oxide (15 mg capsules only), shellac glaze, talc, simethicone, sodium lauryl sulfate and titanium dioxide.

Stability and storage recommendations

Store at room temperature 15°C-25°C, in well-closed, light-resistant containers.

AVAILABILITY OF DOSAGE FORMS

Restoril 15 mg (temazepam) 15 mg:

Hard gelatin capsule with pink opaque body and maroon opaque cap imprinted 'TM 15' in white ink, filled with white powder.

Available in bottles of 100.

Restoril 30 mg (temazepam) 30 mg:

Hard gelatin capsule with light blue opaque body and maroon opaque cap, imprinted 'TM 30' in white ink, filled with white powder.

Available in bottles of 100.

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 hexobarbitone, 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 LD_{50} for temazepam were determined:

TABLE 1

ACUTE LD_{50} (mg/kg) OF TEMAZEPAM

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	∃2400
Dog	M & F	Oral	∃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 employed 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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PART III: CONSUMER INFORMATION

RESTORIL®
Temazepam Capsules, USP

This leaflet is part III of a three-part "Product Monograph" published when RESTORIL 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 RESTORIL. This leaflet is a summary and will not tell you everything about RESTORIL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RESTORIL 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 RESTORIL 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. RESTORIL does not treat the underlying cause of your insomnia.

If you are 65 years or older, talk to your doctor before starting RESTORIL. RESTORIL may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

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

RESTORIL 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 RESTORIL are:
- the longer you use RESTORIL, the less effective it may become,
- You may become dependent on RESTORIL,
- RESTORIL 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 RESTORIL 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 nonmedicinal ingredients are (alphabetical):
Ammonium hydroxide croscarmellose sodium, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, lactose anhydrous, magnesium stearate, microcrystalline cellulose, propylene glycol, red iron oxide (15 mg capsules only), shellac glaze, talc, simethicone, sodium lauryl sulfate and titanium dioxide

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Taking RESTORIL can lead to physical dependence, abuse and misuse, even if you take it as directed. This can result in an overdose or death, especially if it is taken with:
- **opioids**
- **alcohol or**
- **illicit drugs**

Your doctor should:
- **talk to you about the risks of treatment with RESTORIL as well as other treatment (including non-drug) options**
- **assess your risk for these behaviours before prescribing RESTORIL**
- **monitor you while you are taking RESTORIL for the signs and symptoms of misuse and abuse. If you feel like you are craving RESTORIL, or not using it as directed, talk to your doctor right away.**

Store RESTORIL in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking RESTORIL, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about)
- **Always contact your doctor before stopping, or lowering your dose of RESTORIL or changing your medicine.**

RESTORIL with Opioids: Taking RESTORIL with opioid medicines can cause:
- **severe drowsiness,**
- **decreased awareness**
- **breathing problems,**
- **coma**
- **death.**

Complex sleep-related behaviours
There have been reports of people getting out of bed while not fully awake after taking RESTORIL 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 RESTORIL 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 RESTORIL than prescribed.
2. Do not take RESTORIL 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 RESTORIL 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

RESTORIL may affect your ability to be alert. Do not operate a car or dangerous machinery while using RESTORIL 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 RESTORIL 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

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop RESTORIL.

Your risk of going through withdrawal is higher if you are taking RESTORIL for a long time or at high doses. However, symptoms can still occur if you are taking RESTORIL as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:
- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide
- thoughts of killing someone else

For other symptoms of withdrawal, see the Serious side effects and what to do about them table (below).

To reduce your chances of going through withdrawal:
- always contact your doctor before stopping or reducing your dose of RESTORIL or changing medications
- always follow your doctor's instructions on how to reduce your dose carefully and safely
- tell your doctor right away if you experience any unusual symptoms after changing or stopping your treatment

RESTORIL with Opioids: Taking RESTORIL with opioid medicines can cause severe drowsiness and breathing problems.

Tell your doctor if you:
- are taking opioid medicines
- are prescribed an opioid medicine after you start taking RESTORIL

Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and RESTORIL affects you.

Falls and Fractures: there have been reports of falls and fractures in people who take benzodiazepines such as RESTORIL. You have a greater risk of falling, which can cause fractures or other fall related-injuries if you:
- are talking other sedatives (including alcohol),
- are elderly or
- have a condition that causes weakness or frailty

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 RESTORIL. This effect does not occur in everyone.

Also, although not common, it is possible that your body may eliminate RESTORIL 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 RESTORIL. Some medicines may also worsen side effects that some patients experience with RESTORIL (see "INTERACTIONS WITH THIS MEDICATION").

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

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 RESTORIL at any time during pregnancy.**

BEFORE you use RESTORIL 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.
- have ever had a problem with:
- substance use, including prescribed or illegal drugs, or
- alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)
- have ever had a problem with:
  - substance use, including prescribed or illegal drugs, or
  - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

Taking RESTORIL and opioids may cause:
- **severe drowsiness**
- **trouble breathing**
- **coma**
- **death**

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 RESTORIL include: alcohol, barbiturates, hypnotics (sleeping pills), antihistamines, narcotics, antipsychotics, antidepressants and anticonvulsants.

Do not take RESTORIL if you drink alcohol.

Do not use RESTORIL 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.

- Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Usual dose:
Follow your doctor's advice about how to take RESTORIL, 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 RESTORIL 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 RESTORIL than prescribed.
Do not take RESTORIL if you drink alcohol.

Do not take RESTORIL if it is not prescribed for you.

Do not take RESTORIL 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 RESTORIL will affect you the next day.

RESTORIL 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 RESTORIL. 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, light headedness 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 RESTORIL 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 RESTORIL. 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 RESTORIL.

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

- **Falls and fractures**

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

Symptom / effect		Talk with your Health Care Professional		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Common	Depressed mood		✓	
Rare	Severe allergic reaction (swelling of tongue or throat, trouble breathing, nausea & vomiting)			✓
	Unexpected reactions such as excitement, agitation, hyperactivity, hallucination, worsened insomnia, aggressiveness, irritability, rages, psychoses, and violent behaviour		✓	
	Somnambulism (sleepwalking) – getting out of bed while not fully awake and do activities you do not remember the day after		✓	
	Thoughts of death or suicide		✓	
Unknown	**Overdose:** extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓

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

Symptom / effect	Talk with your Health Care Professional		Stop taking drug and seek immediate emergency help
	Only if severe	In all cases	
Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Thoughts of killing someone else** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating.		✓	

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

HOW TO STORE IT

Store at room temperature 15ºC-25ºC in well-closed, light-resistant containers.

Keep out of reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about RESTORIL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (https://www.aapharma.ca/en/products) or by calling 1-877-998-9097.

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