HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DORAL® safely and effectively. See full prescribing information for DORAL.

DORAL (Quazepam) Tablets for oral use, C-IV
Initial U.S. Approval: 1985

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS
See full prescribing information for complete boxed warning.

- **Concomitant use of benzodiazepines 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 inadequate. Limit dosages and durations to the minimum required.Follow patients for signs and symptoms of respiratory depression and Sedation (5.1, 7).**
- **The use of benzodiazepines, including DORAL, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing DORAL and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (5.2).**
- **Abrupt discontinuation or rapid dosage reduction of DORAL after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue DORAL or reduce the dosage (2.3, 5.3).**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.9) 01/2023

---------- INDICATIONS AND USAGE----------
DORAL, a gamma-aminobutyric (GABAA) agonist, is indicated for the treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. (1)

----------DOSAGE AND ADMINISTRATION----------
Use the lowest dose effective for the patient:
- Recommended initial dose is 7.5 mg (2.1)
- Split the 15 mg tablet along the score line to achieve 7.5 mg dose (2.1)
- The elderly and debilitated may be more sensitive to benzodiazepines (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
15 mg functionally scored tablet, oral (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to DORAL or other benzodiazepines (4)
- Established or suspected sleep apnea, or chronic pulmonary insufficiency (4)

----------WARNINGS AND PRECAUTIONS----------
- CNS depressant effects: Impaired alertness and motor coordination, including risk of daytime impairment. Caution patients against driving and other activities requiring complete mental alertness (5.4)
- The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. (5.5)
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.6)
- Sleep driving and other complex behaviors while not fully awake. Risk increases with dose and concomitant CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes (5.7)
- Worsening of depression or suicidal thinking may occur: Prescribe the least number of tablets feasible to avoid intentional overdose (5.8)
- Neonatal Sedation and Withdrawal Syndrome: DORAL use during pregnancy can result in neonatal sedation and/or neonatal withdrawal (5.9, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>1%): drowsiness, headache, fatigue, dizziness, dry mouth, dyspepsia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Galt Pharmaceuticals at 1-844-416-4284 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- CNS Depressants: downward dose adjustment may be necessary due to additive effects (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation *[see Warnings and Precautions (5.1), Drug Interactions (7)]*.**

- **The use of benzodiazepines, including DORAL, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing DORAL and throughout treatment, assess each patient's risk for abuse, misuse, and addiction *[see Warnings and Precautions (5.2)]*.**

- **The continued use of benzodiazepines, including DORAL, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of DORAL after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue DORAL or reduce the dosage *[see Dosage and Administration (2.3) and Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

DORAL is indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The effectiveness of DORAL has been established in placebo-controlled clinical studies of 5 nights duration in acute and chronic insomnia. The sustained effectiveness of DORAL has been established in chronic insomnia in a sleep lab (polysomnographic) study of 28 nights duration. Because insomnia is often transient and intermittent, the prolonged administration of DORAL Tablets is generally not necessary or recommended. Since insomnia may be a symptom of several other disorders, the possibility that the complaint may be related to a condition for which there is a more specific treatment should be considered.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Recommendations

Use the lowest dose effective for the patient, as important adverse effects of DORAL are dose related. The recommended initial dose is 7.5 mg. The 7.5 mg dose can be increased to 15 mg if necessary for efficacy. The 7.5 mg dose can be achieved by splitting the 15 mg tablet along the score line.

2.2 Special Populations

Elderly and debilitated patients may be more sensitive to benzodiazepines.

2.3 Discontinuation or Dosage Reduction of DORAL

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue DORAL or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly *[see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets, 15 mg, functionally scored, capsule-shaped, light orange, slightly white speckled tablets, impressed with the product identification number 15 on one side of the tablet, and the product name (DORAL) on the other.

4 CONTRAINDICATIONS

DORAL is contraindicated in patients with known hypersensitivity to quazepam or other benzodiazepines. Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of DORAL. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Patients who develop such reactions should not be rechallenged with DORAL.

Contraindicated in patients with established or suspected sleep apnea, or with pulmonary insufficiency.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including DORAL, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe DORAL concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of DORAL than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking DORAL, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when DORAL is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined *[see Drug Interactions (7)]*.

5.2 Abuse, Misuse, and Addiction

The use of benzodiazepines, including DORAL, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death *[see Drug Abuse and Dependence (9.2)]*.

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

5.3 Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue DORAL or reduce the dosage (a patient-specific plan should be used to taper the dose) *[see Dosage and Administration (2.3)]*.

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

Acute Withdrawal Reactions
The continued use of benzodiazepines, including DORAL, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of DORAL after continued use , or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) *[see Drug Abuse and Dependence (9.3)]*.

Protracted Withdrawal Syndrome
In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months *[see Drug Abuse and Dependence (9.3)]*.

5.4 CNS-Depressant Effects and Daytime Impairment

DORAL is a central nervous system (CNS) depressant and can impair daytime function in some patients even when used as prescribed. Prescribers should monitor for excess depressant effects, but impairment can occur in the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e. less than formal psychomotor testing). While pharmacodynamics tolerance or adaptation to some adverse depressant effects of DORAL may develop, patients using DORAL should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness.

Additive effects occur with concomitant use of other CNS depressants (e.g., other benzodiazepines, opioids, tricyclic antidepressants, alcohol), including daytime use. Downward dose adjustment of DORAL and concomitant CNS depressants should be considered. The potential for adverse drug interactions continues for several days following discontinuation of DORAL, until serum levels of both active parent drug and psychoactive metabolites decline.

Use of DORAL with other sedative-hypnotics is not recommended. Alcohol generally should not be used during treatment with DORAL. The risk of next-day psychomotor impairment is increased if DORAL is taken with less than a full night of sleep remaining (7 to 8 hours); if higher than the recommended dose is taken; if co-administered with other CNS depressants *[see Dosage and Administration (2.1)]*.

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

5.5 Need to Evaluate for Co-morbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia

or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative-hypnotic drugs.

5.6 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 DORAL. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis.

Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with DORAL should not be rechallenged with the drug.

5.7 Abnormal Thinking and Behavior Changes

Abnormal thinking and behavior changes have been reported in patients treated with sedative-hypnotics including DORAL. Some of these changes include decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, and depersonalization. Visual and auditory hallucinations have also been reported. Amnesia, and other neuro-psychiatric symptoms may occur.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, and sleep disturbances may occur unpredictably.

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake, with amnesia for the event) have been reported with use of sedative-hypnotics. These behaviors can occur with initial treatment or in patients previously tolerant of DORAL or other sedative-hypnotics. Although these behaviors can occur with use at therapeutic doses, risk is increased by higher doses or concomitant use of alcohol or other CNS depressants. Due to risk to the patient and community, DORAL should be discontinued if "sleep-driving" occurs.

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

5.8 Worsening of Depression

Benzodiazepines may worsen depression. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered.

5.9 Neonatal Sedation and Withdrawal Syndrome

Use of DORAL late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate *[see Use in Specific Populations (8.1)]*. Monitor neonates exposed to DORAL during pregnancy or labor for signs of sedation and monitor neonates exposed to DORAL during pregnancy for signs of withdrawal; manage these neonates accordingly.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Risks from Concomitant Use with Opioids *[see Warnings and Precautions (5.1)]*
- Abuse, Misuse, and Addiction *[see Warnings and Precautions (5.2)]*
- Dependence and Withdrawal Reactions *[see Warnings and Precautions (5.3)]*
- CNS-depressant effects and next-day impairment *[see Warnings and Precautions (5.4)]*
- Abnormal thinking and behavior changes, and complex behaviors *[see Warnings and Precautions (5.7)]*
- Worsening of depression *[see Warnings and Precautions (5.8)]*
- Neonatal Sedation and Withdrawal Syndrome *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The table shows adverse reactions occurring at an incidence of 1% or greater in relatively short-duration, placebo-controlled clinical trials of DORAL.

	DORAL 15 mg	PLACEBO
NUMBER OF PATIENTS	267	268
	% OF PATIENTS REPORTING	
Central Nervous System		
Daytime Drowsiness	12	3

Headache	5	2
Fatigue	2	0
Dizziness	2	<1
Autonomic Nervous System		
Dry Mouth	2	<1
Gastrointestinal System		
Dyspepsia	1	<1

A double-blind, controlled sleep laboratory study (N=30) in elderly patients compared the effects of DORAL 7.5 mg and 15 mg to that of placebo over a period of 7 days. Both the 7.5 mg and 15 mg doses appeared to be well tolerated. Caution must be used in interpreting this data due to the small size of the study.

7 DRUG INTERACTIONS

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Benzodiazepines, including DORAL, produce additive CNS depressant effects when co-administered with ethanol or other CNS depressants (e.g. psychotropic medications, anticonvulsants, antihistamines). Downward dose adjustment of DORAL and/or concomitant CNS depressants may be necessary because of additive effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal *[see Warnings and Precautions (5.9) and Clinical Considerations].* Available data from published observational studies of pregnant women exposed to benzodiazepines do not report a clear association with benzodiazepines and major birth defects *(see Data).*

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia, and sedation in neonates. Monitor neonates exposed to Doral during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to Doral during pregnancy for signs of withdrawal. Manage these neonates accordingly *[see Warnings and Precautions (5.9).*

Data

Human Data

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

Animal Data

Developmental toxicity studies of DORAL in mice at doses up to 400 times the human dose (15 mg) revealed no major drug-related malformations. Minor fetal skeletal variations that occurred were delayed ossification of the sternum, vertebrae, distal phalanges and supraoccipital bones, at doses approximately 70 and 400 times the human dose. A developmental toxicity study of DORAL in New Zealand rabbits at doses up to approximately 130 times the human dose demonstrated no effect on fetal morphology or development of offspring.

8.3 Nursing Mothers

Risk Summary

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

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

DORAL may cause confusion and over-sedation in the elderly. Elderly patients generally should be started on a low dose of DORAL and observed closely. Elderly and debilitated patients may be more sensitive to benzodiazepines, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A double-blind controlled sleep laboratory study (N=30) compared the effects of DORAL 7.5 mg and 15 mg to that of placebo over a period of 7 days. Both the 7.5 mg and 15 mg doses appeared to be well tolerated. Caution must be used in interpreting this data due to the small size of the study.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DORAL contains quazepam, a Schedule IV controlled substance.

9.2 Abuse

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

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders *[see Warnings and Precautions (5.2)]*.

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

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

9.3 Dependence

Physical Dependence
DORAL may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use *[see Warnings and Precautions (5.3)]*.

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue DORAL or reduce the dosage *[see Dosage and Administration (2.3) and Warnings and Precautions (5.3)]*.

Acute Withdrawal Signs and Symptoms
Acute withdrawal signs and symptoms have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment,

muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, , mania, psychosis, seizures, and suicidality.

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

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

10 OVERDOSAGE

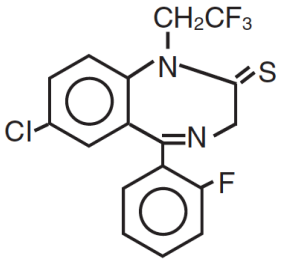
Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthia, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdosage cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal *[see Warnings and Precautions (5.2)].* Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage.

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

Consider contacting the Poison Help line (1-800-222-1222) or medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

DORAL contains quazepam, a trifluoroethyl benzodiazepine hypnotic agent, having the chemical name 7-chloro-5- (o-fluoro-phenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-thione and the following structure:



Quazepam has the empirical formula $C_{17}H_{11}ClF_4N_2S$, and a molecular weight of 386.8. It is a white crystalline compound, soluble in ethanol and insoluble in water.

Each DORAL Tablet contains 15 mg of quazepam. The inactive ingredients for DORAL Tablets include cellulose, corn starch, FD&C Yellow No. 6, lactose, magnesium stearate, silicon dioxide, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DORAL, like other central nervous system agents of the 1,4-benzodiazepine class, presumably exerts its effects by binding to stereo-specific receptors at several sites within the central nervous system (CNS). The exact mechanism of action is unknown.

12.3 Pharmacokinetics

Absorption
DORAL is rapidly (absorption half-life of about 30 minutes) and well absorbed from the gastrointestinal tract. The peak plasma concentration of quazepam is approximately 20 ng/mL after a 15 mg dose and occurs at about 2 hours.

Metabolism
Quazepam, the active parent compound, is extensively metabolized in the liver; two of the plasma metabolites are 2-oxoquazepam and N-desalkyl-2-oxoquazepam. All three compounds show CNS depressant activity.

Distribution
The degree of plasma protein binding for quazepam and its two major metabolites is greater than 95%.

Elimination
Following administration of 14C-quazepam, 31% of the dose appeared in the urine and 23% in the feces over five days; only trace amounts of unchanged drug were present in the urine.

The mean elimination half-life of quazepam and 2-oxoquazepam is 39 hours and that of N-desalkyl-2-oxoquazepam is 73 hours. Steady-state levels of quazepam and 2-oxoquazepam are attained by the seventh daily dose and that of N-desalkyl-2-oxoquazepam by the thirteenth daily dose.

Special Populations
Geriatrics: The pharmacokinetics of quazepam and 2-oxoquazepam in geriatric subjects are comparable to those seen in young adults; as with desalkyl metabolites of other benzodiazepines, the elimination half-life of N-desalkyl-2-oxoquazepam in geriatric patients is about twice that of young adults.

Drug Interactions
Bupropion (a CYP2B6 substrate): Co-administration of a single dose of 150 mg Bupropion Hydrochloride XL with steady state quazepam did not significantly affect the AUC and Cmax of bupropion or its primary metabolite, hydroxybupropion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
DORAL showed no evidence of carcinogenicity in oral carcinogenicity studies in mice and hamsters.

Mutagenesis
DORAL was negative in the bacterial reverse mutation (Ames) assay and equivocal in the mouse lymphoma tk assay.

Impairment of Fertility
Reproduction studies in mice conducted with DORAL at doses equal to 60 and 180 times the human dose of 15 mg produced slight reductions in fertility rate. Similar reductions in fertility rate have been reported in mice dosed with other benzodiazepines, and is believed to be related to the sedative effects of these drugs at high doses.

14 CLINICAL STUDIES

The effectiveness of DORAL was established in placebo-controlled clinical studies of 5 nights duration in acute and chronic insomnia. The sustained effectiveness of DORAL was established in chronic insomnia in a sleep laboratory (polysomnographic) study of 28 nights duration. In the sleep laboratory study, DORAL significantly decreased sleep latency and total wake time, and significantly increased total sleep time and percent sleep time, for one or more nights.

DORAL 15 mg was effective on the first night of administration. Sleep latency, total wake time and wake time after sleep onset were still decreased and percent sleep time was still increased for several nights after the drug was discontinued. Percent slow wave sleep was decreased, and REM sleep was essentially unchanged. No transient sleep disturbance, such as “rebound insomnia,” was observed after withdrawal of the drug in sleep laboratory studies in 12 patients using 15 mg doses.

A double-blind, controlled sleep laboratory study (N=30) in elderly patients compared the effects of DORAL 7.5 mg and 15 mg to that of placebo over a period of 7 days. Both the 7.5 mg and 15 mg doses appeared to be effective. Caution must be used in interpreting this data due to the small size of the study.

16 HOW SUPPLIED / STORAGE AND HANDLING

DORAL Tablets, 15 mg, functionally scored, capsule-shaped, light orange, slightly white speckled tablets, impressed with the product identification number 15 on one side of the tablet, and the product name (DORAL) on the other.

15 mg	Bottles of 30	NDC 61825-165-30
15 mg	Bottles of 100	NDC 61825-165-10

Store DORAL Tablets at controlled room temperature 20°-25°C (68°-77°F).

17 PATIENT COUNSELING INFORMATION

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

Risks from Concomitant Use with Opioids
Inform patients and caregivers that potentially fatal additive effects may occur if DORAL is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.1), Drug Interactions (7)]*.

Abuse, Misuse, and Addiction
Inform patients that the use of DORAL even at recommended dosages, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death, especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug *[see Warnings and Precautions (5.2) and Drug Abuse and Dependence (9.2)]*.

Withdrawal Reactions
Inform patients that the continued use of DORAL may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of DORAL may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months. Instruct patients that discontinuation or dosage reduction of DORAL may require a slow taper *[see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.3)]*.

CNS Depressant Effects and Next-Day Impairment
Tell patients that DORAL can cause next-day impairment, even in the absence of symptoms. Caution patients against driving or engaging in other hazardous activities or activities requiring complete mental alertness when using DORAL. Tell patients that daytime impairment may persist for several days following discontinuation of DORAL. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients *[see Warnings and Precautions (5.4)]*.

Severe Allergic Reactions
Inform patients that severe allergic reactions can occur from DORAL. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if these occur *[see Warnings and Precautions (5.6)]*.

Abnormal Thinking and Behavior Change
Instruct patients that sedative hypnotics can cause abnormal thinking and behavior change, including “sleep-driving” and other complex behaviors while not being fully awake (preparing and eating food, making phone calls, or having sex). Tell patients to call you immediately if they develop any of these symptoms *[see Warnings and Precautions (5.7)]*.

Suicide
Tell patients that DORAL can worsen depression, and to immediately report any suicidal thoughts *[see Warnings and Precautions (5.8)]*.

Alcohol and Other Drugs
Ask patients about alcohol consumption, medicines they are taking now, and drugs they may be taking without a prescription. Advise patients that alcohol generally should not be used during treatment with DORAL.

Pregnancy
Advise pregnant females that use of DORAL late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in newborns *[see Warnings and Precautions (5.9), Use in Specific Populations (8.1)]*. Instruct patients to inform their healthcare provider if they are pregnant.

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DORAL during pregnancy *[see Use in Specific Populations (8.1)]*.

Nursing
Instruct patients to notify their healthcare provider if they are breastfeeding or intend to breastfeed. Instruct breastfeeding patients using DORAL to monitor infants for excessive sedation, poor feeding and poor weight gain, and to seek medical attention if they notice these signs *[see Use in Specific Populations (8.3)]*.

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Atlanta, GA 30339

GALT
PHARMACEUTICALS

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MEDICATION GUIDE

DORAL (DOOR-al)

(quazepam)

tablets, C-IV

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

- **DORAL is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system (CNS) depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.** Get emergency help right away if the following happens:
  - shallow or slowed breathing
  - breathing stops (which may lead to the heart stopping)
  - excessive sleepiness (sedation)

Do not drive or operate heavy machinery until you know how taking DORAL with opioids affects you.

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

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

What is DORAL?

- DORAL is a prescription medicine used to treat certain types of insomnia including difficulty falling asleep, waking up often during the night, or waking up early in the morning
- **DORAL is a federal controlled substance (C-IV) because it contains quazepam that can be abused or lead to dependence.** Keep DORAL in a safe place to prevent misuse and abuse. Selling or giving away DORAL may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if DORAL is safe and effective in children.

Do not take DORAL if you:

- are allergic to quazepam or any of the ingredients in DORAL. See the end of this Medication Guide for a complete list of ingredients in DORAL.
- have had an allergic reaction to other sleep medicines or sedatives such as benzodiazepines Symptoms of a serious allergic reaction can include:
  - swelling of your face, lips, and throat that may cause difficulty breathing or swallowing
  - nausea and vomiting
- have sleep apnea, breathing or lung problems

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

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

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

Taking DORAL with certain other medicines can cause side effects or affect how well DORAL or the other medicines work.

Do not start or stop other medicines without talking to your healthcare provider.

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

How should I take DORAL?

- See "**What is the most important information I should know about DORAL?**"
- Take DORAL exactly as your healthcare providers tell you to take it.
- DORAL comes in 15 mg tablets. Your healthcare provider may start your DORAL dose at 7.5 mg which is half a tablet. Talk to your healthcare provider or pharmacist about your dose schedule.
- If you take too much DORAL or overdose, get emergency treatment right away.

What are the possible side effects of DORAL?

DORAL may cause serious side effects, including:

- **See "What is the most important information I should know about DORAL?"**
- **Other conditions.** Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problem.
- **Severe allergic reactions.** Symptoms include swelling of the tongue or throat, and trouble breathing. Other symptoms may include nausea and vomiting. Get emergency medical help right away if you have these symptoms after taking DORAL.
- **Abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts.
- **DORAL can make you sleepy or dizzy and can slow your thinking and motor skills.**
  - **Do not drive, operate heavy machinery, or do other dangerous activities until you know how DORAL affects you.**
  - **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking DORAL without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, DORAL may make your sleepiness or dizziness much worse**
- **Depression**. Pre-existing depression may emerge or worsen during use of benzodiazepines including DORAL.

Call your healthcare provider right away if you have any of the above side effects while taking DORAL.

The most common side effects of DORAL include:

- drowsiness
- feeling very tired
- dry mouth
- headache
- dizziness
- upset stomach

After you stop taking a sleep medicine, you may have symptoms for the next 1 to 2 days such as:

- trouble sleeping
- lightheadedness
- stomach cramps
- stomach area pain
- nausea
- uncontrolled crying
- panic attack
- flushing
- vomiting
- nervousness

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

How should I store DORAL?

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

General information about the safe and effective use of Doral.

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

What are the ingredients in DORAL?

Active Ingredient: quazepam

Inactive Ingredients: cellulose, corn starch, FD&C Yellow No.6, lactose, magnesium stearate, silicon dioxide, and sodium lauryl sulfate

Distributed by Galt Pharmaceuticals, Atlanta, GA 30339 USA. If you would like more information, call Galt Pharmaceuticals at 1-855-965-2783 or visit www.doralrx.com.

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