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

LIBERVANT (diazepam) buccal film, C-IV
Initial U.S. Approval: 1963

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. (**5.1, 7.1**)**
- **LIBERVANT is approved for use in pediatric patients 2 to 5 years of age. The unapproved use of LIBERVANT exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing LIBERVANT and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. (**5.2**)**
- **Although LIBERVANT is indicated only for intermittent use (**1, 2**), if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of LIBERVANT may precipitate acute withdrawal reactions, which can be life-threatening. For patients using LIBERVANT more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue LIBERVANT. (**5.3**)**

INDICATIONS AND USAGE

LIBERVANT is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age. (1)

DOSAGE AND ADMINISTRATION

The recommended dose of LIBERVANT is dependent on the patient's weight. See dosing table for specific recommendations. (2.2)

DOSAGE FORMS AND STRENGTHS

Buccal film: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to diazepam (4)
- Acute-narrow angle glaucoma (4, 5.4)

WARNINGS AND PRECAUTIONS

- CNS Depression: Monitor for central nervous system (CNS) depression. Risk may be increased with concomitant use of alcohol or other CNS depressants. (5.2, 5.4, 7.2)
- Suicidal Behavior and Ideation: Antiepileptic drugs increase the risk of suicidal thoughts and behavior. (5.5)
- Glaucoma: Can increase intraocular pressure; use in patients with open-angle glaucoma only if receiving appropriate therapy. (4, 5.6)

ADVERSE REACTIONS

- The most common adverse reactions (> 4%) were somnolence and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Aquestive Therapeutics, Inc. at 1-877-394-5045 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2C19 and CYP3A4 Inhibitors: Could decrease the rate of diazepam elimination; adverse reactions may be increased. (7.3)
- CYP2C19 and CYP3A4 Inducers: Exposure of diazepam after LIBERVANT administration may be decreased; efficacy may be decreased. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2024

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 for 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 (7.1)]*.**
- **LIBERVANT is approved for use in pediatric patients 2 to 5 years of age. The unapproved use of LIBERVANT 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 *[see Warnings and Precautions (5.2)]*.**
- **The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although LIBERVANT is indicated only for intermittent use *[see Indications and Usage (1) and Dosage and Administration (2)]*, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of LIBERVANT may precipitate acute withdrawal reactions, which can be life-threatening. For patients using LIBERVANT more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue LIBERVANT *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

LIBERVANT is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions Prior to Dosing

Prior to treatment, healthcare professionals should instruct the individual administering LIBERVANT on how to identify seizure clusters and use the product appropriately *[see Dosage and Administration (2.3) and Patient Counseling Information (17)]*.

2.2 Dosage Information

The recommended dose of LIBERVANT is dependent on the patient's weight and is provided in *Table 1*.

Table 1: Recommended Dosage for Pediatric Patients 2 to 5 Years of Age

Weight	Libervant Dose
6 kg to 10 kg	5 mg
11 kg to 15 kg	7.5 mg
16 kg to 20 kg	10 mg
21 kg to 25 kg	12.5 mg
26 kg to 30 kg	15 mg

Second Dose (if needed): A second dose, when required, may be administered at least 4 hours after the first dose.

Maximum Dosage and Treatment Frequency: Do not use more than 2 doses of LIBERVANT to treat a single episode.

Do not use LIBERVANT to treat more than one episode every five days or more than five episodes per month.

2.3 Important Administration Instructions

Caregivers should be counseled to read carefully the "Instructions for Use" for complete directions on how to properly administer LIBERVANT.

LIBERVANT is a rectangular green buccal film that dissolves when applied on the inside of the mouth on top of the surface of the cheek. Do not split LIBERVANT, the entire dose should be applied and allowed to dissolve *[see Dosage and Administration (2.1)]*. Do not administer LIBERVANT buccal film with liquids.

LIBERVANT dosing may be administered without regard to food *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

LIBERVANT buccal film: green, rectangular, orally dissolving film strips:

- 5 mg film imprinted with D5
- 7.5 mg film imprinted with D7•5
- 10 mg film imprinted with D10
- 12.5 mg film imprinted with D12•5
- 15 mg film imprinted with D15

4 CONTRAINDICATIONS

LIBERVANT is contraindicated in patients with:

- Hypersensitivity to diazepam
- Acute narrow-angle glaucoma *[see Warnings and Precautions (5.6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including LIBERVANT, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for 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 LIBERVANT 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. Advise caregivers about the risks of respiratory depression and sedation when LIBERVANT is used with opioids *[see Drug Interactions (7.1)]*.

5.2 Abuse, Misuse, and Addiction

LIBERVANT is approved for use in pediatric patients 2 to 5 years of age. The unapproved use of LIBERVANT 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)]*.

5.3 Dependence and Withdrawal Reactions After Use of LIBERVANT More Frequently Than Recommended

For patients using LIBERVANT more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue LIBERVANT (a patient-specific plan should be used to taper the dose).

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 may lead to clinically significant physical dependence. Although LIBERVANT is indicated only for intermittent use *[see Indications and Usage (1) and Dosage and Administration (2)]*, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of LIBERVANT, 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 Central Nervous System (CNS) Depression

Because LIBERVANT produces CNS depression, patients receiving this drug, who are otherwise capable and qualified to do so should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle, until the effects of the drug, such as drowsiness, have subsided, and as their medical condition permits.

Although LIBERVANT is indicated for use solely on an intermittent basis, the potential for a synergistic CNS-depressant effect when used simultaneously with alcohol or other CNS depressants must be considered by the prescriber, and appropriate recommendations made to the patient and/or caregiver.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including LIBERVANT, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. ***Table 2*** shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients / Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing LIBERVANT, or any other AED, must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.6 Glaucoma

Benzodiazepines, including LIBERVANT, can increase intraocular pressure in patients with glaucoma. LIBERVANT may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. LIBERVANT is contraindicated in patients with narrow-angle glaucoma.

5.7 Neonatal Sedation and Withdrawal Syndrome

LIBERVANT is not approved for use in adolescents and adults. Unapproved use of LIBERVANT in adolescents and adults 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 LIBERVANT during pregnancy or labor for signs of sedation and monitor neonates exposed to LIBERVANT during pregnancy for signs of withdrawal; manage these neonates accordingly.

5.8 Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative

LIBERVANT is not approved for use in neonates or infants. Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including LIBERVANT. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (LIBERVANT contains 3.96 to 11.87 mg of benzyl alcohol per buccal film) *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Risk of Concomitant Use with Opioids *[see Warnings and Precautions (5.1)]*
- Abuse, Misuse, and Addiction *[see Warnings and Precautions (5.2)]*
- Dependence and Withdrawal Reactions After Use of LIBERVANT More Frequently Than Recommended *[see Warnings and Precautions (5.3)]*
- CNS depression *[see Warnings and Precautions (5.4)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Glaucoma *[see Warnings and Precautions (5.6)]*
- Neonatal Sedation and Withdrawal Syndrome *[see Warnings and Precautions (5.7)]*
- Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative *[see Warnings and Precautions (5.8)]*

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 safety of LIBERVANT is supported by clinical trials using diazepam rectal gel; pharmacokinetic studies of LIBERVANT in healthy subjects and epilepsy patients; and an open-label long-term safety and tolerability study of LIBERVANT in epilepsy patients.

Diazepam Rectal Gel

In studies previously conducted with diazepam rectal gel, adverse event data were collected from double-blind, placebo-controlled studies and open-label studies. The majority of adverse events were mild to moderate in severity and transient in nature.

Two patients who received diazepam rectal gel died seven to 15 weeks following treatment; neither of these deaths was deemed related to diazepam rectal gel.

The most frequent adverse reactions (at least 5%) in the two double-blind, placebo-controlled studies were somnolence and headache. ***Table 3*** lists adverse reactions that occurred in greater than 1% of patients enrolled in parallel-group, placebo-controlled trials and were numerically more common in the diazepam rectal gel group than placebo. Adverse reactions were usually mild or moderate in intensity.

Approximately 1.4% of the 573 patients who received diazepam rectal gel in clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse reaction most frequently associated with discontinuation (occurring in three patients) was somnolence. Other adverse reactions most commonly associated with discontinuation and occurring in two patients were hypoventilation and rash. Adverse reactions associated with discontinuation occurring in one patient were asthenia, hyperkinesia, incoordination, vasodilatation, and urticaria.

In the two double-blind, placebo-controlled, parallel-group studies *[see Clinical Studies (14)]*, the proportion of patients who discontinued treatment because of adverse events was 2% for the

group treated with diazepam rectal gel, versus 2% for the placebo group. In the diazepam rectal gel group, one patient discontinued because of rash and one patient discontinued because of lethargy.

Table 3: Adverse Reactions That Occurred in Greater Than 1% Of Patients in Parallel-Group, Placebo-Controlled Trials with Diazepam Rectal Gel and Were More Common Than in the Placebo Group

Adverse Reaction	Diazepam Rectal Gel N = 101 %	Placebo N = 104 %
Somnolence	23	8
Headache	5	4
Diarrhea	4	<1
Ataxia	3	<1
Dizziness	3	2
Euphoria	3	0
Incoordination	3	0
Rash	3	0
Asthma	2	0
Vasodilatation	2	0

LIBERVANT (Diazepam Buccal Film)

Clinical studies, which included patients with epilepsy 2 to 5 years of age, were conducted to support the safety and tolerability of LIBERVANT for the treatment of acute repetitive seizures. A total of 197 patients received LIBERVANT, of whom 107 received LIBERVANT for at least 6 months, and 48 for at least 1 year. The adverse reactions reported in these studies were similar to those seen in efficacy trials of diazepam rectal gel.

Other Adverse Reactions

Diazepam rectal gel was administered to 573 patients with epilepsy during all clinical trials, only some of which were placebo-controlled. All of the events listed below occurred in at least 1% of the 573 individuals exposed to diazepam rectal gel.

Body as a Whole: Asthenia

Cardiovascular: Hypotension, vasodilatation

Nervous: Agitation, confusion, convulsion, dysarthria, emotional lability, speech disorder, thinking abnormal, vertigo

Respiratory: Hiccup

The following infrequent adverse events have been reported previously with diazepam use: depression, slurred speech, syncope, constipation, changes in libido, urinary retention, bradycardia, cardiovascular collapse, nystagmus, urticaria, neutropenia, and jaundice.

Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported with other diazepam products. If these events occur with the use of LIBERVANT, the prescriber should consider discontinuation of use.

7 DRUG INTERACTIONS

7.1 Effect of Concomitant Use of Benzodiazepines and Opioids

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 $GABA_A$ 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 follow patients closely for respiratory depression and sedation *[see Warnings and Precautions (5.1)]*.

7.2 CNS Depressants and Alcohol

Coadministration of other CNS depressants (e.g., valproate) or consumption of alcohol may potentiate the CNS-depressant effects of diazepam *[see Warnings and Precautions (5.2)]*.

7.3 Effect of Other Drugs on LIBERVANT Metabolism

Potential interactions may occur when diazepam is given concurrently with agents that affect CYP2C19 and CYP3A4 activity.

Inhibitors of CYP2C19 and CYP3A4

Inhibitors of CYP2C19 (e.g., cimetidine, quinidine, and tranylcypromine) and CYP3A4 (e.g., ketoconazole, troleandomycin, and clotrimazole) could decrease the rate of diazepam elimination; therefore, adverse reactions to LIBERVANT may be increased.

Inducers of CYP2C19 and CYP3A4

Inducers of CYP2C19 (e.g., rifampin) and CYP3A4 (e.g., carbamazepine, phenytoin, dexamethasone, and phenobarbital) could increase the rate of diazepam elimination; therefore, efficacy of LIBERVANT may be decreased.

7.4 Effect of LIBERVANT on the Metabolism of Other Drugs

Diazepam is a substrate for CYP2C19 and CYP3A4; therefore, it is possible that LIBERVANT may interfere with the metabolism of drugs which are substrates for CYP2C19, (e.g. omeprazole, propranolol, and imipramine) and CYP3A4 (e.g. cyclosporine, paclitaxel, theophylline, and warfarin) leading to a potential drug-drug interaction *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

LIBERVANT is indicated for treatment in patients 2 to 5 years of age *[see Indications and Usage (1)]*. LIBERVANT is not approved for use in adolescents and adults.

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as LIBERVANT, during pregnancy. Healthcare providers are encouraged to recommend that pregnant women who are taking LIBERVANT during pregnancy enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

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 (5.7) 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 Human Data).*

In animal studies, administration of diazepam during the organogenesis period of pregnancy resulted in increased incidences of fetal malformations at doses greater than those used clinically. Data for diazepam and other benzodiazepines suggest the possibility of increased neuronal cell death and long-term effects on neurobehavioral and immunological function based on findings in animals following prenatal or early postnatal exposure at clinically relevant doses (*see Animal 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 background risk of major birth defects and 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 LIBERVANT during pregnancy or labor for signs of sedation, respiratory depression, hypotonia, and feeding problems. Monitor neonates exposed to LIBERVANT during pregnancy for signs of withdrawal. Manage these neonates accordingly *[see Warnings and Precautions (5.7)].*

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

Diazepam has been shown to produce increased incidences of fetal malformations in mice and hamsters when given orally at single doses of 100 mg/kg or greater (approximately 13 times a human dose of 0.6 mg/kg/day or greater on a mg/m^2 basis). Cleft palate and exencephaly are the most common and consistently reported malformations produced in these species by administration of high, maternally toxic doses of diazepam during organogenesis.

In published animal studies, administration of benzodiazepines or other drugs that enhance GABAergic neurotransmission to neonatal rats has been reported to result in widespread apoptotic neurodegeneration in the developing brain at plasma concentrations relevant for seizure control in humans. The window of vulnerability to these changes in rats (postnatal days 0-14) includes a period of brain development corresponding to that taking place during the third trimester of pregnancy in humans.

8.2 Lactation

LIBERVANT is indicated for treatment in patients 2 to 5 years of age *[see Indications and Usage (1)]*. LIBERVANT is not approved for use in adolescents and adults.

Risk Summary

Diazepam is excreted in human milk.

There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk. There are no data to assess the effects of diazepam and/or its active metabolite(s) on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LIBERVANT and any potential adverse effects on the breastfed infant from LIBERVANT or from the underlying maternal condition.

Clinical Considerations

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

8.4 Pediatric Use

Safety and effectiveness of LIBERVANT have been established in pediatric patients 2 to 5 years of age. Use of LIBERVANT in this age group is supported by evidence from adequate and well-controlled studies of diazepam rectal gel in adult and pediatric patients, adult bioavailability studies comparing LIBERVANT with diazepam rectal gel, pediatric and adult LIBERVANT pharmacokinetic data, and an open-label safety study of LIBERVANT including patients 2 years to 5 years of age *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Safety and effectiveness of LIBERVANT in pediatric patients below the age of 2 and above the age of 5 have not been established.

LIBERVANT is not approved for use in neonates or infants.

- Prolonged CNS depression has been observed in neonates treated with diazepam.
- Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and low-birth-weight infants in the neonatal intensive care unit

who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low - birth-weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (LIBERVANT contains 3.96 to 11.87 mg of benzyl alcohol per buccal film *[see Warnings and Precautions (5.8)]*.

8.5 Geriatric Use

LIBERVANT is indicated for treatment in patients 2 to 5 years of age *[see Indications and Usage (1)]*. LIBERVANT is not approved for use in adults.

Clinical studies of LIBERVANT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

A study of single dose IV administration of diazepam (0.1 mg/kg) indicates that the elimination half-life of diazepam increases linearly with age, ranging from about 15 hours at 18 years (healthy young adults) to about 100 hours at 95 years (healthy elderly) with a corresponding decrease in clearance of free diazepam.

If used in elderly patients, LIBERVANT should be used with caution because of an increase in half-life with a corresponding decrease in the clearance of free diazepam *[see Clinical Pharmacology (12.3)]*. It is also recommended that the dosage be decreased to reduce the likelihood of ataxia or oversedation.

8.6 Compromised Respiratory Function

LIBERVANT should be used with caution in patients with compromised respiratory function related to a concurrent disease process (e.g., asthma, pneumonia) or neurologic damage.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LIBERVANT contains diazepam, a Schedule IV controlled substance.

9.2 Abuse

LIBERVANT is a benzodiazepine and a CNS depressant with a potential for abuse and addiction with unapproved use in adolescents and adults. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a 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 After Use of LIBERVANT More Frequently Than Recommended

LIBERVANT may produce physical dependence if used more frequently than recommended. 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. Although LIBERVANT is indicated only for intermittent use *[see Indications and Usage (1) and Dosage and Administration (2)]*, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction 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)]*.

For patients using LIBERVANT more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue LIBERVANT *[see Warnings and Precautions (5.3)]*.

Acute Withdrawal Signs and Symptoms

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

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome 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 LIBERVANT may develop after use more frequently than recommended. 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 benzodiazepines may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

It is recommended that patients be treated with LIBERVANT no more frequently than one episode every five days and no more than five episodes per month.

LIBERVANT is not recommended for chronic, daily use as an anticonvulsant. Chronic daily use of diazepam may increase the frequency and/or severity of tonic-clonic seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic diazepam may also be associated with a temporary increase in the frequency and/or severity of seizures.

10 OVERDOSAGE

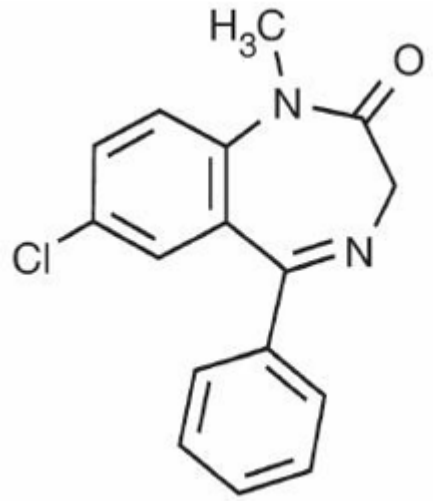
Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe 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 maintenance. 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 a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

Diazepam, the active ingredient of LIBERVANT, is a benzodiazepine anticonvulsant with the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one; its empirical formula is $C_{16}H_{13}ClN_2O$ and its molecular weight is 284.7 g/mol. It is an odorless, white to practically white crystalline powder with a pKa of 3.4 and a partition coefficient of 2.9. It is practically insoluble in water and soluble in 96% ethanol, chloroform, and alcohol. The melting range for diazepam is 131°C to 135°C.The structural formula is as follows:



LIBERVANT is a buccal film that contains the active ingredient diazepam. Each film strip contains 5, 7.5, 10, 12.5, or 15mg of diazepam and the following inactive ingredients: benzyl alcohol, clove oil, EDTA disodium salt, FD&C Green #3, glycerol monooleate, hypromellose, peppermint oil, polyethylene oxide, polyvinylpyrrolidone, sodium phosphate, sucralose, vanillin, xanthan gum, water, and white ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action for diazepam is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

12.2 Pharmacodynamics

The effects of diazepam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications.

12.3 Pharmacokinetics

The pharmacokinetics of diazepam and desmethyldiazepam following administration of LIBERVANT were investigated in adult healthy subjects and in pediatric and adult patients with epilepsy. The pharmacokinetics of diazepam were linear and dose-proportional in the

recommended dose range *[see Dosage and Administration (2.2)]*. In pediatric patients 2 to 5 years of age, median maximum plasma concentration (C_{max}) and median area under the plasma concentration curve for 4 hours after dosing (AUC_{0-4}) of diazepam are approximately 2- to 3-times greater than in adults. The higher C_{max} and higher AUC_{0-4} in pediatric patients 2 to 5 years of age are expected to provide adequate therapeutic exposures under both fed and fasted states.

Absorption

Following single doses of LIBERVANT administered to healthy adults under fasting conditions, diazepam peak concentration (C_{max}) was reached in approximately 1 hour.

In pharmacokinetic studies of patients with epilepsy, pharmacokinetic parameters were similar between seizure state and non-seizure state.

Effect of Food

The pharmacokinetics of LIBERVANT were characterized under fasting, moderate fat, and high fat fed conditions in three clinical studies in adults. Under fed conditions, a 33%-47% decrease in C_{max}, but no significant change in AUC, was observed relative to fasting state. The recommended dosage of LIBERVANT *[see Dosage and Administration (2.3)]* considers the impact of food on pharmacokinetics of diazepam. As such, LIBERVANT may be administered without regard to food.

Distribution

The volume of distribution of diazepam was calculated to be approximately 1.46 L/kg. Both diazepam and its major active metabolite, desmethyldiazepam, bind extensively to plasma proteins (95%-98%).

Elimination

Metabolism

It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are “poor metabolizers”) and CYP3A4. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2E1, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.

Excretion

The mean elimination half-lives of diazepam and desmethyldiazepam were found to be approximately 86 hours and 147 hours, respectively.

Specific Populations

Pediatric Patients

Literature reviews indicate that following IV administration (0.33 mg/kg), the half-life of diazepam in pediatric patients 2 to 5 years of age is approximately 15 to 21 hours.

Patients with Renal Impairment

The pharmacokinetics of diazepam have not been studied in subjects with renal impairment.

Patients with Hepatic Impairment

No pharmacokinetic studies were conducted with LIBERVANT in subjects with hepatic impairment. Literature review indicates that following administration of 0.1 to 0.15 mg/kg of diazepam intravenously, the half-life of diazepam was prolonged by two to five-fold in subjects with alcoholic cirrhosis (n=24) compared to age-matched control subjects (n=37) with a corresponding decrease in clearance by half. However, the exact degree of hepatic impairment in these subjects was not characterized in this literature.

Effect of Gender, Race, and Cigarette Smoking

No targeted pharmacokinetic studies have been conducted to evaluate the effect of gender, race, and cigarette smoking on the pharmacokinetics of diazepam. However, covariate analysis of a population of treated patients following administration of diazepam rectal gel, indicated that neither gender nor cigarette smoking had any effect on the pharmacokinetics of diazepam.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In studies in which mice and rats were administered diazepam in the diet at a dose of 75 mg/kg/day (approximately 10 and 20 times, respectively, a human dose of 0.6 mg/kg/day on a mg/m^2 basis) for 80 and 104 weeks, respectively, an increased incidence of liver tumors was observed in males of both species.

Mutagenesis

The data currently available are inadequate to determine the mutagenic potential of diazepam.

Impairment of Fertility

Reproduction studies of diazepam in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of an oral dose of 100 mg/kg/day (approximately 27 times a human dose of 0.6 mg/kg/day on a mg/m^2 basis) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted at a dose of 80 mg/kg/day (approximately 22 times a human dose of 0.6 mg/kg/day on a mg/m^2 basis).

14 CLINICAL STUDIES

Safety and effectiveness of LIBERVANT in pediatric patients 2 to 5 years of age are supported by evidence from adequate and well-controlled studies of diazepam rectal gel in adult and

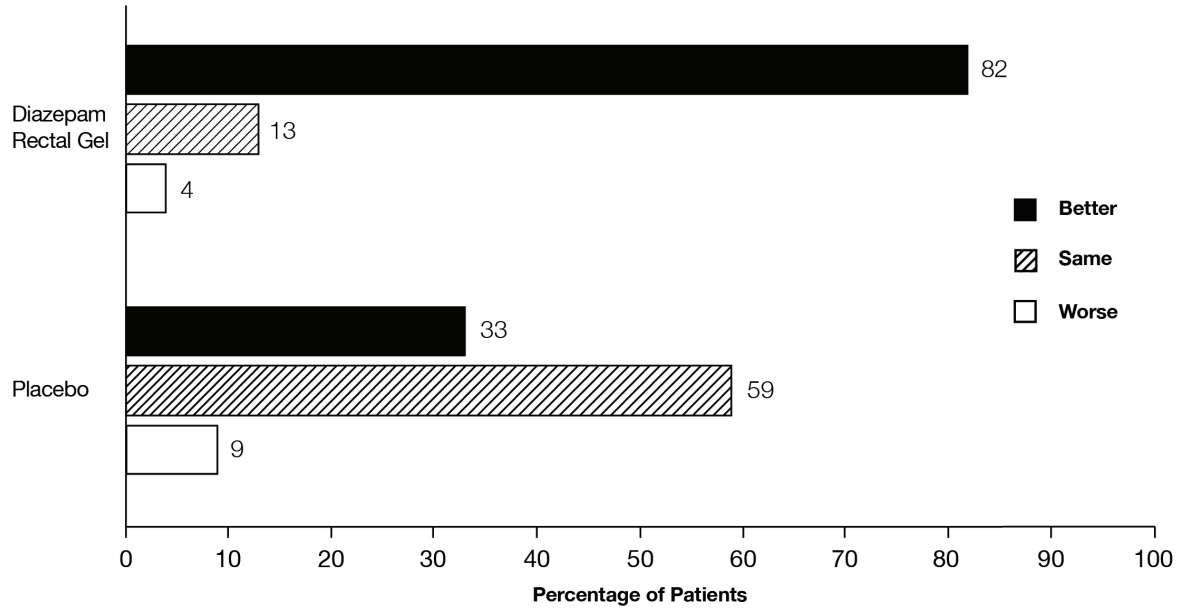
pediatric patients, adult bioavailability studies comparing LIBERVANT with diazepam rectal gel, adult and pediatric LIBERVANT pharmacokinetic data, and an open-label safety study of LIBERVANT including patients 2 years to 5 years of age *[see Clinical Pharmacology (12.3)]*.

The effectiveness of diazepam rectal gel has been established in two adequate and well-controlled clinical studies in pediatric patients 2 years of age and older and adults exhibiting intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern.

A randomized, double-blind study compared sequential doses of diazepam rectal gel and placebo in 91 patients (47 pediatric patients 2 years of age and older, 44 adults) exhibiting the appropriate seizure profile. The first dose was given at the onset of an identified episode. Pediatric patients 2 years of age and older were dosed again 4 hours after the first dose and were observed for a total of 12 hours. Adults were dosed at 4 and 12 hours after the first dose and were observed for a total of 24 hours. Primary outcomes for this study were seizure frequency during the period of observation and a global assessment that took into account the severity and nature of the seizures as well as their frequency.

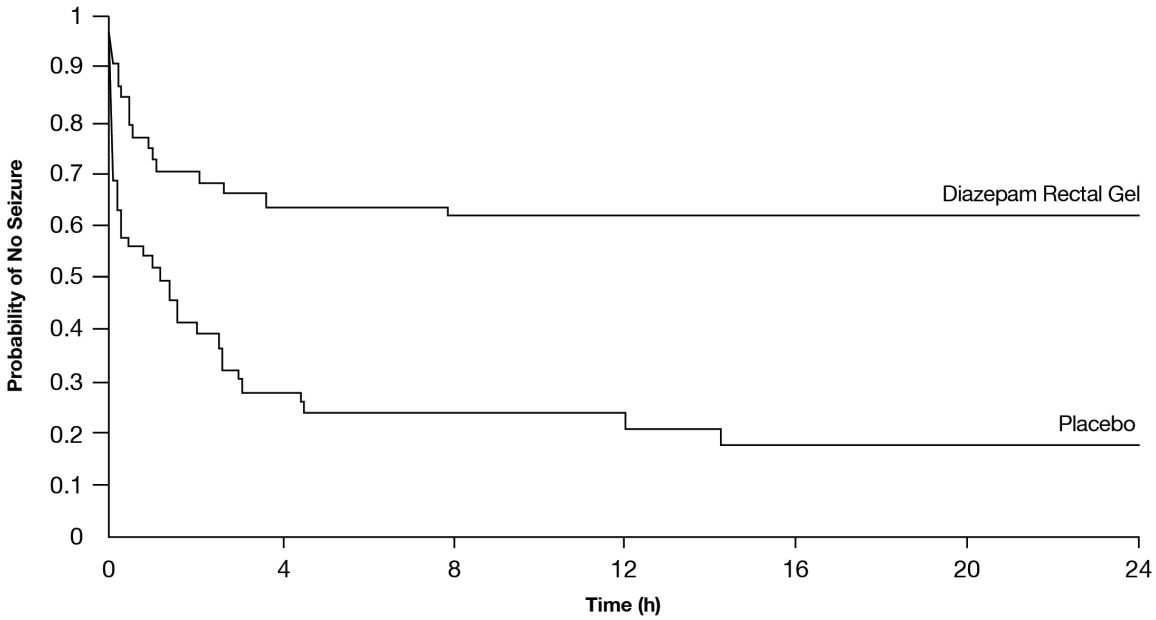
The median seizure frequency for the diazepam rectal gel treated group was zero seizures per hour, compared to a median seizure frequency of 0.3 seizures per hour for the placebo group, a difference that was statistically significant ($p < 0.0001$). All three categories of the global assessment (seizure frequency, seizure severity, and "overall") were also found to be statistically significant in favor of diazepam rectal gel ($p < 0.0001$). The following histogram displays the results for the "overall" category of the global assessment.

Figure 1: Caregiver Overall Global Assessment of the Efficacy of Diazepam Rectal Gel



Patients treated with diazepam rectal gel experienced prolonged time-to-next-seizure compared to placebo ($p = 0.0002$) as shown in the following graph.

Figure 2: Kaplan-Meier Survival Analysis of Time-to-Next-Seizure - First Study

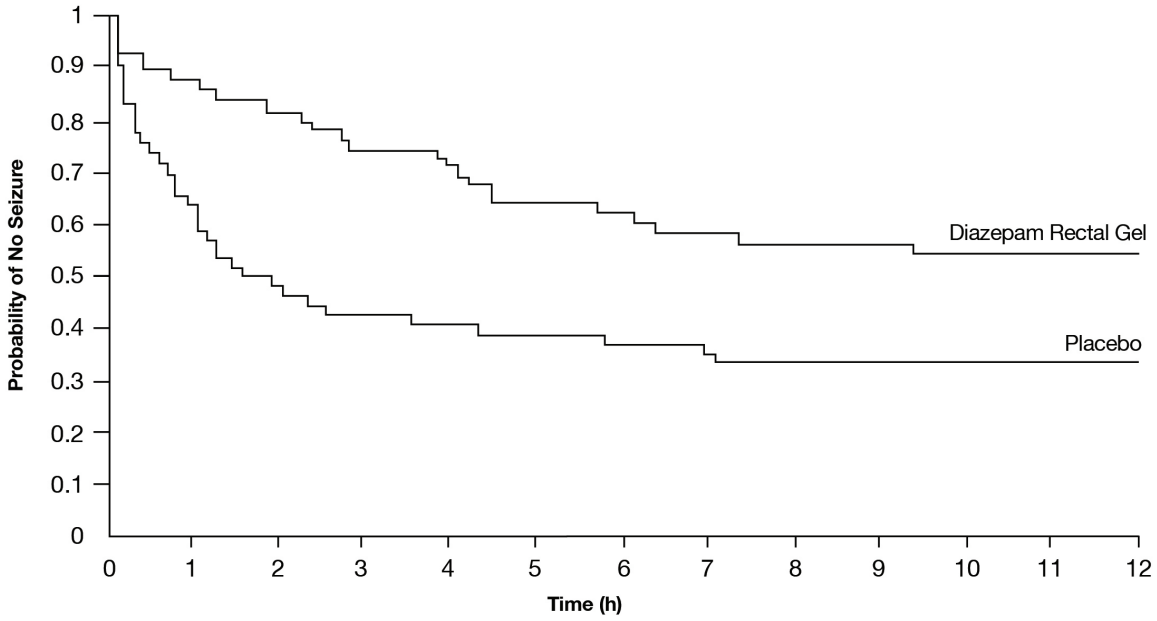


In addition, 62% of patients treated with diazepam rectal gel were seizure-free during the observation period compared to 20% of placebo patients.

Analysis of response by gender and age revealed no substantial differences between treatment in either of these subgroups. Analysis of response by race was considered unreliable, due to the small percentage of non-Caucasians.

A second double-blind study compared single doses of diazepam rectal gel and placebo in 114 patients (53 pediatric patients 2 years of age and older, 61 adults). The dose was given at the onset of the identified episode and patients were observed for a total of 12 hours. The primary outcome in this study was seizure frequency. The median seizure frequency for the diazepam rectal gel-treated group was 0 seizures per 12 hours, compared to a median seizure frequency of 2.0 seizures per 12 hours for the placebo group, a difference that was statistically significant ($p < 0.03$). Patients treated with diazepam rectal gel experienced prolonged time-to-next-seizure compared to placebo ($p = 0.0072$) as shown in Figure 3.

Figure 3: Kaplan-Meier Survival Analysis of Time-to-Next-Seizure - Second Study



In addition, 55% of patients treated with diazepam rectal gel were seizure-free during the observation period compared to 34% of patients receiving placebo. Overall, caregivers judged diazepam rectal gel to be more effective than placebo ($p = 0.018$), based on a 10 cm visual analog scale. In addition, investigators also evaluated the effectiveness of diazepam rectal gel and judged diazepam rectal gel to be more effective than placebo ($p < 0.001$).

An analysis of response by gender revealed a statistically significant difference between treatments in females but not in males in this study, and the difference between the 2 genders in response to the treatments reached borderline statistical significance. Analysis of response by race was considered unreliable, due to the small percentage of non-Caucasians.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LIBERVANT (diazepam buccal film) is supplied as five strengths of a rectangular green film imprinted in white ink according to their respective strengths and packaged in individual child-resistant polyester/foil laminated pouches (see **Table 4**).

Table 4: Available Packaging Configurations

Description	Contents	NDC
5 mg carton	5 mg film strip imprinted with D5	NDC 10094-305-01 (Individual pouch) NDC 10094-305-02 (Carton of 2 pouches)
7.5 mg carton	7.5 mg film strip imprinted with D7●5	NDC 10094-307-01 (Individual pouch) NDC 10094-307-02 (Carton of 2 pouches)
10 mg carton	10 mg film strip imprinted with D10	NDC 10094-310-01 (Individual pouch) NDC10094-310-02 (Carton of 2 pouches)

12.5 mg carton	12.5 mg film strip imprinted with D12●5	NDC 10094-312-01 (Individual pouch) NDC 10094-312-02 (Carton of 2 pouches)
15 mg carton	15 mg film strip imprinted with D15	NDC 10094-315-01 (Individual pouch) NDC 10094-315-02 (Carton of 2 pouches)

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the caregivers to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risks from Concomitant Use with Opioids

Inform caregivers that concomitant use of benzodiazepines, including LIBERVANT, and opioids may result in profound sedation, respiratory depression, coma, and death and not to use such drugs concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Abuse, Misuse, and Addiction

Inform caregivers that the use of LIBERVANT more frequently than recommended, 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 caregivers 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 caregivers that the use of LIBERVANT more frequently than recommended may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of LIBERVANT may precipitate acute withdrawal reactions, which can be life-threatening. Inform caregivers that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months *[see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.2)]*.

Important Treatment Instructions

Instruct caregivers on what is and is not an intermittent and stereotypic episode of increased seizure activity (i.e., seizure cluster) that is appropriate for treatment, and the timing of administration in relation to the onset of the episode.

Instruct caregivers on what to observe following administration, and what would constitute an outcome requiring immediate medical attention.

Instruct caregivers not to administer a second dose of LIBERVANT if they are concerned by the patient's breathing, the patient requires emergency rescue treatment with assisted breathing or intubation, or there is excessive sedation *[see Use in Specific Populations (8.6)]*.

Advise caregivers on how frequently they can treat successive seizure cluster episodes over time.

CNS Depression

Advise caregivers to check with their healthcare provider before LIBERVANT is taken with other CNS depressants, such as other benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or alcohol *[see Warnings and Precautions (5.4)]*.

If applicable, caution patients and caregivers about operating hazardous machinery, including driving a motor vehicle, or riding a bicycle, until they are reasonably certain that LIBERVANT does not affect them adversely (e.g., impair judgment, thinking or motor skills).

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that AEDs, including LIBERVANT, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Caregivers should report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.5)]*.

Proper Administration

Discuss the steps involved in the administration of LIBERVANT with the caregiver. The steps are described in the Medication Guide and Instruction for Use.

Manufactured by:

Aquestive Therapeutics

Warren, NJ