

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VALTOCO nasal spray safely and effectively. See full prescribing information for VALTOCO nasal spray.

VALTOCO® (diazepam nasal spray), CIV
Initial U.S. Approval: 1963

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

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).

INDICATIONS AND USAGE

VALTOCO 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 6 years of age and older. (1)

DOSAGE AND ADMINISTRATION

Administer VALTOCO by the nasal route only. (2.3)

Dosage is dependent on the patient's age and weight. (2.2)

Initial Dose: VALTOCO 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril. Administration of 15 mg and 20 mg doses requires two nasal spray devices, one spray into each nostril. (2.2)

Second Dose: A second dose, when required, may be administered at least 4 hours after the initial dose. If administered, use a new blister pack. (2.2)

Maximum Dosage and Treatment Frequency: Do not use more than 2 doses to treat a single episode. It is recommended that VALTOCO be used to treat no more than one episode every five days and no more than five episodes per month. (2.2)

DOSAGE FORMS AND STRENGTHS

Nasal spray: 5 mg, 7.5 mg, or 10 mg of diazepam in 0.1 mL. (3)

CONTRAINDICATIONS

- Hypersensitivity to diazepam. (4)
- Acute narrow-angle glaucoma. (4)

WARNINGS AND PRECAUTIONS

- *CNS Depression:* May cause an increased CNS-depressant effect when used with alcohol or other CNS depressants. (5.2)
- *Suicidal Behavior and Ideation:* Antiepileptic drugs increase the risk of suicidal ideation and behavior. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (at least 4%) were somnolence, headache, and nasal discomfort. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurelis, Inc. at 1-866-696-3873 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *CYP2C19 and CYP3A4 Inhibitors:* Adverse reactions with VALTOCO may be increased. (7.3)
- *Inducers of CYP2C19 and CYP3A4 Inducers:* Exposure of diazepam after VALTOCO administration may be decreased. (7.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.1)*].

- 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.

1 INDICATIONS AND USAGE

VALTOCO® 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 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions Prior to Dosing

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

2.2 Dosing Information

The recommended dose of VALTOCO nasal spray is 0.2 mg/kg or 0.3 mg/kg, depending on the patient's age and weight. See Table 1 for specific recommendations.

The following table provides the acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose.

Table 1: Recommended Dosage for Adults and Pediatric Patients 6 Years of Age and Older

Dose Based on Age and Weight			Administration	
6 to 11 Years of Age (0.3 mg/kg)	12 Years of Age and Older (0.2 mg/kg)	Dose (mg)	Number of Nasal Spray Devices	Number of Sprays
Weight (kg)	Weight (kg)			
10 to 18	14 to 27	5	One 5 mg device	One spray in one nostril
19 to 37	28 to 50	10	One 10 mg device	One spray in one nostril
38 to 55	51 to 75	15	Two 7.5 mg devices	One spray in each nostril
56 to 74	76 and up	20	Two 10 mg devices	One spray in each nostril

Second Dose (if needed): A second dose, when required, may be administered after at least 4 hours after the initial dose. If the second dose is to be administered, use a new blister pack of VALTOCO.

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

It is recommended that VALTOCO be used to treat no more than one episode every five days and no more than five episodes per month.

2.3 Important Administration Instructions

VALTOCO is for intranasal use only.

No device assembly is required. VALTOCO is a ready-to-use nasal spray device. VALTOCO nasal spray delivers its entire contents upon activation. Do not prime or attempt to use for more than one administration per device.

Patients and caregivers should be counseled to read carefully the “Instructions for Use” for complete directions on how to properly administer VALTOCO.

3 DOSAGE FORMS AND STRENGTHS

VALTOCO is available in 5 mg, 7.5 mg, and 10 mg strengths. Each VALTOCO nasal spray device contains 0.1 mL solution.

4 CONTRAINDICATIONS

VALTOCO nasal spray is contraindicated in patients with:

- Known hypersensitivity to diazepam
- Acute narrow angle glaucoma [*see Warnings and Precautions (5.4)*]

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Concomitant Use with Opioids

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

5.2 CNS Depression

Benzodiazepines, including VALTOCO, may produce CNS depression. Caution patients against engaging in hazardous activities requiring mental alertness (e.g., 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 VALTOCO is indicated for use solely on an intermittent basis, the potential for synergistic CNS-depressant effects 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.

5.3 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including VALTOCO, 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/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
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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 VALTOCO 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.

5.4 Glaucoma

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

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

VALTOCO is not approved for use in neonates or infants. Serious and fatal adverse reactions including “gaspings syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including VALTOCO. The “gaspings 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 (VALTOCO contains 10.5 mg of benzyl alcohol per 0.1 mL) [see *Use in Specific Populations* (8.4)].

6 ADVERSE REACTIONS

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

- Risk of Concomitant Use with Opioids [see *Warnings and Precautions* (5.1)]
- CNS depression [see *Warnings and Precautions* (5.2)]
- Suicidal Behavior and Ideation [see *Warnings and Precautions* (5.3)]
- Glaucoma [see *Warnings and Precautions* (5.4)]
- Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative [see *Warnings and Precautions* (5.5)].

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical

studies of another drug and may not reflect the rates observed in practice. The safety of VALTOCO is supported by clinical trials using diazepam rectal gel, as well as open-label, repeat-dose studies of VALTOCO in healthy subjects and 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 4%) in the two double-blind, placebo-controlled studies were somnolence, headache, and diarrhea. Adverse events 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 More Common Than Placebo

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
Vasodilation	2	0

VALTOCO (Diazepam Nasal Spray)

Clinical studies of patients with epilepsy 6 years of age and older were conducted to support the safety and tolerability of VALTOCO for the treatment of acute repetitive seizures. A total of 190 patients 6 years of age and older received VALTOCO, of whom 114 received VALTOCO for at least 6 months, and 67 for at least 1 year. Other than adverse reactions related to local nasal administration, the adverse reactions reported in these studies were similar to those seen in the efficacy trials of diazepam rectal gel.

The most common local adverse reactions that occurred in VALTOCO-treated patients were nasal discomfort (6%), nasal congestion (3%), epistaxis (3%), and dysgeusia (2%).

Other Adverse Reactions

Diazepam rectal gel has previously been 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, 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 VALTOCO, 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 [*see Warnings and Precautions (5.1)*]. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

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 VALTOCO 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 VALTOCO 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 VALTOCO may be decreased.

7.4 Effect of VALTOCO on the Metabolism of Other Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

There are no adequate data on the use of VALTOCO in pregnant women. Available data suggest that the class of benzodiazepines is not associated with marked increases in risk for congenital anomalies. Although some early epidemiological studies suggested a relationship between benzodiazepine use in pregnancy and congenital anomalies such as cleft lip and or palate, these studies had considerable limitations. More recently completed studies of benzodiazepine use in pregnancy have not consistently documented elevated risks for specific congenital anomalies. There is insufficient evidence to assess the effect of benzodiazepine pregnancy exposure on

neurodevelopment.

There are clinical considerations regarding exposure to benzodiazepines during the second and third trimesters of pregnancy or immediately prior to or during childbirth. These risks include decreased fetal movement and/or fetal heart rate variability, floppy infant syndrome, dependence, and withdrawal (*see Clinical Considerations and 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*).

Advise a pregnant woman and women of childbearing age of the potential risk to a fetus.

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. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period. Clinical manifestations of withdrawal or neonatal abstinence syndrome may include hypertonia, hyperreflexia, hypoventilation, irritability, tremors, diarrhea, and vomiting. These complications can appear shortly after delivery to 3 weeks after birth and persist from hours to several months depending on the degree of dependence and the pharmacokinetic profile of the benzodiazepine. Symptoms may be mild and transient or severe. Standard management for neonatal withdrawal syndrome has not yet been defined. Observe newborns who are exposed to VALTOCO in utero during the later stages of pregnancy for symptoms of withdrawal and manage accordingly.

Labor and Delivery

Administration of benzodiazepines immediately prior to or during childbirth can result in a floppy infant syndrome, which is characterized by lethargy, hypothermia, hypotonia, respiratory depression, and difficulty feeding. Floppy infant syndrome occurs mainly within the first hours after birth and may last up to 14 days. Observe exposed newborns for these symptoms and manage accordingly.

Data

Human Data

Congenital Anomalies

Although there are no adequate and well-controlled studies of VALTOCO in pregnant women, there is information about benzodiazepines as a class. Dolovich et al. published a meta-analysis of 23 studies that examined the effects of benzodiazepine exposure during the first trimester of pregnancy. Eleven of the 23 studies included in the meta-analysis considered the use of chlordiazepoxide and diazepam and not other benzodiazepines. The authors considered case-control and cohort studies separately. The data from the cohort studies did not suggest an increased risk for major malformations (OR 0.90; 95% CI 0.61—1.35) or for oral cleft (OR 1.19; 95% CI 0.34—4.15). The data from the case-control studies suggested an association between benzodiazepines and major malformations (OR 3.01, 95% CI 1.32— 6.84) and oral cleft (OR 1.79; 95% CI 1.13—2.82). The limitations of this meta-analysis included the small number of reports included in the analysis, and that most cases for analyses of both oral cleft and major malformations came from only three studies. A follow up to that meta-analysis included 3 new cohort studies that examined risk for major malformations and one study that considered cardiac malformations. The authors found no new studies with an outcome of oral clefts. After the addition of the new studies, the odds ratio for major malformations with first trimester exposure to benzodiazepines was 1.07 (95% CI 0.91—1.25).

Neonatal Withdrawal and Floppy Infant Syndrome

Neonatal withdrawal syndrome and symptoms suggestive of floppy infant syndrome associated with administration of benzodiazepines during the later stages of pregnancy and peripartum period have been reported. Findings in published scientific literature suggest that the major neonatal side effects of benzodiazepines include sedation and dependence with withdrawal signs. Data from observational studies suggest that fetal exposure to benzodiazepines is associated with the neonatal adverse events of hypotonia, respiratory problems, hypoventilation, low Apgar score, and neonatal withdrawal syndrome.

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 the maximum recommended human dose [MRHD = 0.6mg/kg/day] or greater on a mg/m² 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 inhibition 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 that takes place during the third trimester of pregnancy in humans.

8.2 Lactation

Risk Summary

Diazepam is excreted in human milk.

There are no data to assess the effects of VALTOCO and/or its active metabolite(s) on the

breastfed infant or on milk production. Postmarketing experience suggests that breastfed infants of mothers taking benzodiazepines, such as VALTOCO, may have effects of lethargy, somnolence, and poor sucking.

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

8.4 Pediatric Use

Safety and effectiveness of VALTOCO have been established in pediatric patients 6 years to 16 years of age. Use of VALTOCO 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 VALTOCO with diazepam rectal gel, patient pharmacokinetic data, and an open-label safety study of VALTOCO including patients 6 years to 16 years of age [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)*].

Safety and effectiveness of VALTOCO in pediatric patients below the age of 6 have not been established.

VALTOCO 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 “gaspings 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 (VALTOCO contains 10.5 mg of benzyl alcohol per 0.1 mL) [*see Warnings and Precautions (5.5)*].

8.5 Geriatric Use

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

Therefore, in elderly patients, VALTOCO 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

VALTOCO 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

VALTOCO contains diazepam, a Schedule IV controlled substance.

9.2 Abuse

VALTOCO contains diazepam, a sedative with a known potential for abuse. VALTOCO can be abused in a similar manner as other benzodiazepines, which can lead to addiction. VALTOCO, like other benzodiazepines, can be diverted for non-medical use into illicit channels for abuse purposes.

Drug abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Whereas 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.

In the clinical studies with VALTOCO at recommended doses, abuse-related adverse events included euphoria, somnolence, sedation, anterograde amnesia, depression, anxiety, hallucinations, and restlessness.

Abuse and misuse of diazepam products, especially prolonged and at higher doses, may result in neuropsychiatric and other symptoms including: euphoria, anxiety, depression, irritability, restlessness, cognitive and psychomotor impairment, disorientation, paranoia, hallucinations, slurred speech, double vision, tremors, nausea or vomiting, loss of appetite, and muscle spasms.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic or frequent use of diazepam products. 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). 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.

It is recommended that patients be treated with VALTOCO no more frequently than every five days and no more than five times per month.

VALTOCO 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.

Withdrawal symptoms have occurred following abrupt discontinuance of diazepam. These withdrawal symptoms may consist of tremor, abdominal and muscle cramps, vomiting, sweating, headache, muscle pain, extreme anxiety, tension, restlessness, confusion, and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations, or epileptic seizures. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena.

In some patients, chronic treatment with diazepam may lead to protracted withdrawal symptoms after the drug discontinuation which is characterized by anxiety, depression, tinnitus, headache, paresthesias, motor symptoms such as weakness, tremor, muscle twitches, ataxia, cognitive dysfunction, and short-term memory loss. These withdrawal symptoms may persist for weeks and months even with taper at the end of treatment with diazepam.

10 OVERDOSAGE

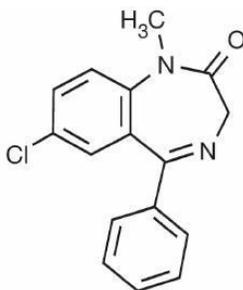
The manifestations of diazepam overdose reported are similar to those observed with other benzodiazepines, including somnolence, confusion, coma, and diminished reflexes. Respiration, pulse, and blood pressure should be monitored.

General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with VALTOCO is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients, particularly in long-term benzodiazepine users. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions, including increased seizures. Its use in patients with epilepsy is typically not recommended.

11 DESCRIPTION

Diazepam, the active ingredient of VALTOCO nasal spray, is a benzodiazepine anticonvulsant with the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. The structural formula is as follows:



The inactive ingredients in VALTOCO nasal spray include benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside, and vitamin E. VALTOCO nasal spray is a clear pale amber liquid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action for diazepam is not fully understood, but it 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

Absorption

Pharmacokinetic information for VALTOCO following nasal administration was obtained from studies conducted in healthy adult subjects, as well as adult and pediatric patients with epilepsy 6 years of age and older.

In a pharmacokinetic study in healthy adult subjects, the highest plasma diazepam concentrations after nasal administration of VALTOCO was reached in 1.5 hours. The estimated volume of distribution of diazepam at steady-state is 0.8 to 1.0 L/kg. The absolute bioavailability of VALTOCO relative to intravenous diazepam was 97%. The mean elimination half-life of diazepam following administration of a 10 mg dose of VALTOCO was found to be about 49.2 hours. In another pharmacokinetic study in healthy adult subjects, diazepam plasma exposures (C_{max} and AUC) increased approximately proportional to dose from 5 mg to 20 mg.

In a relative bioavailability study in healthy adult subjects, diazepam exposure (C_{max} and AUCs)

was evaluated following administration of 15 and 20 mg of VALTOCO nasal spray and diazepam rectal gel. The diazepam PK parameters were 2 to 4-fold less variable for VALTOCO and within the range of those seen with diazepam rectal gel.

In a pharmacokinetic study in patients with epilepsy, pharmacokinetic parameters were similar between seizure versus non-seizure states.

Distribution

Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).

Metabolism and Elimination

In vitro studies using human liver preparations suggest that CYP2C19 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of diazepam. 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.

Specific Populations

Geriatric Patients

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 [*see Use in Specific Populations (8.5)*].

Pediatric Patients

Literature review indicates that following IV administration (0.33 mg/kg), diazepam has a half-life in pediatric patients 6 to 12 years of age of approximately 15-21 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 VALTOCO 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

The carcinogenic potential of diazepam delivered by the intranasal route of administration has not been evaluated. In studies in which mice and rats were administered diazepam orally in the diet at a dose of 75 mg/kg/day (approximately 10 and 20 times, respectively, the maximum recommended human dose [MRHD=0.6 mg/kg/day] on a mg/m² 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 with orally administered 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 the MRHD on a mg/m² 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 the MRHD on a mg/m² basis).

14 CLINICAL STUDIES

The efficacy of VALTOCO is based on the relative bioavailability of VALTOCO nasal spray compared to diazepam rectal gel in healthy adults [*see Clinical Pharmacology (12.3)*].

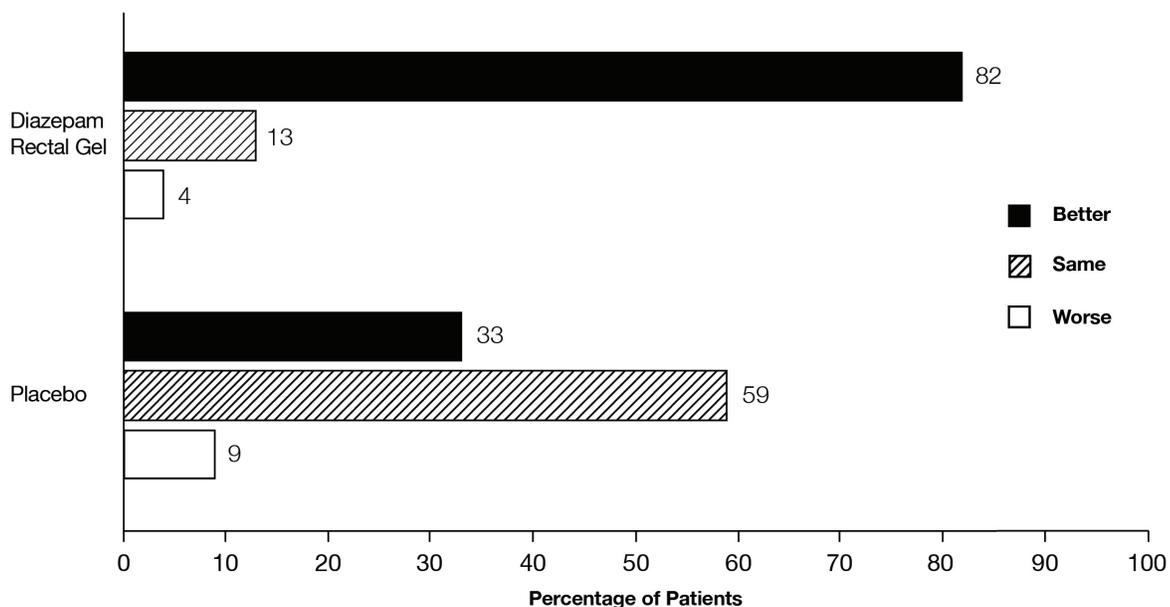
The effectiveness of diazepam rectal gel has been established in two adequate and well-controlled clinical studies in children and adults exhibiting seizure patterns.

A randomized, double-blind study compared sequential doses of diazepam rectal gel and placebo in 91 patients (47 children, 44 adults) exhibiting the appropriate seizure profile. The first dose

was given at the onset of an identified episode. Children were dosed again four hours after the first dose and were observed for a total of 12 hours. Adults were dosed at four 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.

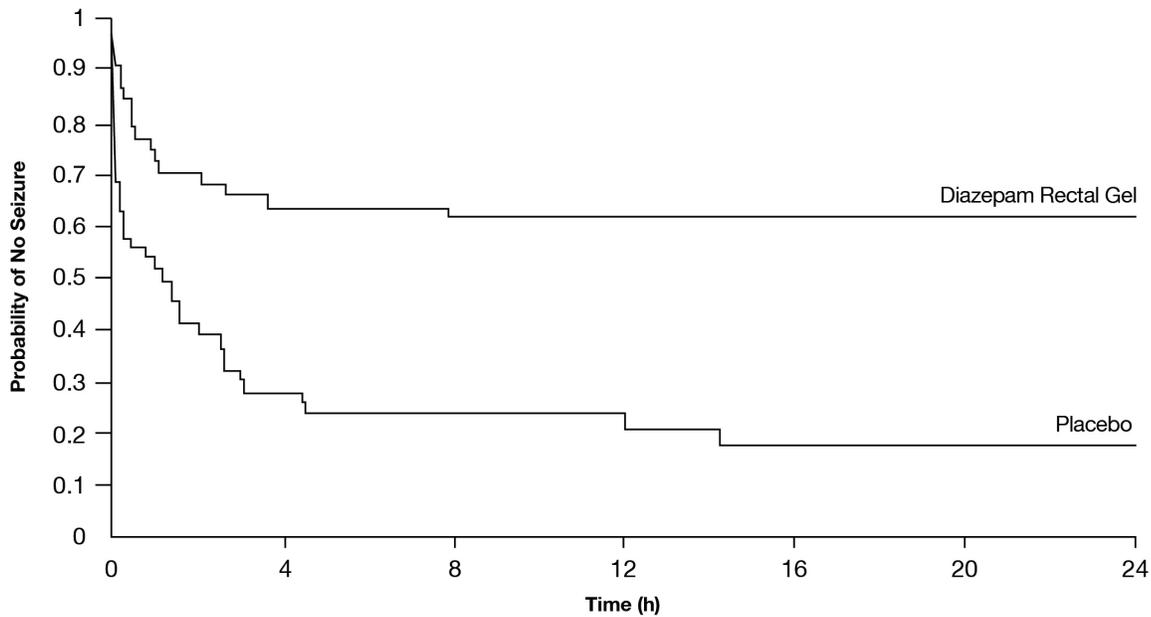
The median seizure frequency for the diazepam rectal gel treated group was zero seizures per hour, compared to a median seizure frequency of 0.3 seizures per hour for the placebo group, a difference that was statistically significant ($p < 0.0001$). All three categories of the global assessment (seizure 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

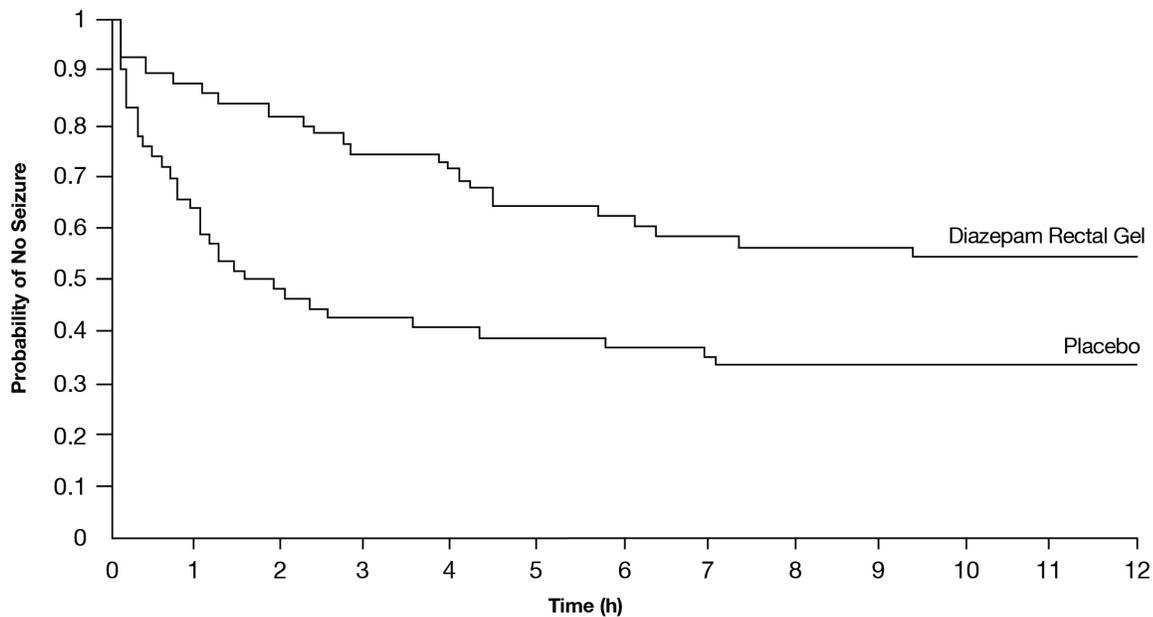


In addition, 62% of patients treated with diazepam rectal gel were seizure-free during the observation period compared to 20% of placebo patients.

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 children, 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 zero 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 centimeter 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

VALTOCO is available in 5 mg, 7.5 mg, and 10 mg strengths. VALTOCO is supplied and packaged in doses of 5 mg, 10 mg, 15 mg, or 20 mg (see Table 4).

Table 4: Available Packaging Configurations

Description	Contents	NDC
5 mg carton	2 individual blister packs, each containing one 5 mg nasal spray device	72252-505-02
10 mg carton	2 individual blister packs, each containing one 10 mg nasal spray device	72252-510-02
15 mg carton	2 individual blister packs, each containing two 7.5 mg nasal spray devices	72252-515-04
20 mg carton	2 individual blister packs, each containing two 10 mg nasal spray devices	72252-520-04

16.2 Storage and Handling

Do not open individual blister packs or test nasal spray devices before use.

Each single-dose nasal spray device sprays one (1) time and cannot be re-used.

Do not use if the nasal spray unit appears damaged.

Store VALTOCO at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see *USP Controlled Room Temperature*]. Do not freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

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

Concomitant use with Opioids

Concomitant use of benzodiazepines, including VALTOCO, and opioids may result in profound sedation, respiratory depression, coma, and death. Do not use such drugs concomitantly unless supervised by a health care provider [see *Warnings and Precautions (5.1)*].

Drug Abuse and Dependence

Diazepam is a Schedule IV controlled substance and can produce drug dependence. It is recommended that patients be treated with VALTOCO no more frequently than every five days and no more than five times per month.

Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Abrupt discontinuation of diazepam following chronic regular use has resulted in withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels for several months.

Important Treatment Instructions

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

