

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SYMPAZAN<sup>TM</sup> safely and effectively. See full prescribing information for SYMPAZAN<sup>TM</sup>.

SYMPAZAN<sup>TM</sup> (clobazam) oral film, CIV  
Initial U.S. Approval: 2011

### **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)

- 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.

### INDICATIONS AND USAGE

SYMPAZAN<sup>TM</sup> is a benzodiazepine indicated for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older (1)

### DOSAGE AND ADMINISTRATION

- For doses above 5 mg/day, administer in two divided doses (2.1)
- Patients weighing 30 kg or less: Initiate at 5 mg daily, and titrate as tolerated up to 20 mg daily (2.1)
- Patients weighing greater than 30 kg: Initiate at 10 mg daily, and titrate as tolerated up to 40 mg daily (2.1)
- Dosage adjustment is needed in following groups:
  - Geriatric patients (2.4, 8.5)
  - Known CYP2C19 poor metabolizers (2.5)
  - Mild or moderate hepatic impairment; no information for severe hepatic impairment (2.6, 8.8)
- Reduce dose, or discontinue drug gradually (2.2)
- Can be taken with or without food (2.3)
- Do not administer with liquids (2.3)

### DOSAGE FORMS AND STRENGTHS

Oral Film: 5 mg, 10 mg and 20 mg (3)

### CONTRAINDICATIONS

History of hypersensitivity to the drug or its ingredients (4)

### WARNINGS AND PRECAUTIONS

- Somnolence or Sedation: Monitor for central nervous system (CNS) depression. Risk may be increased with concomitant use of other CNS depressants (5.2, 5.3)
- Withdrawal: Symptoms may occur with rapid dose reduction or discontinuation. Discontinue SYMPAZAN<sup>TM</sup> gradually (5.4)
- Serious Dermatological Reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis): Discontinue SYMPAZAN<sup>TM</sup> at first sign of rash unless the rash is clearly not drug-related (5.5)
- Physical and Psychological Dependence: Monitor patients with a history of substance abuse for signs of habituation and dependence (5.6, 9)
- Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behaviors (5.7)

### ADVERSE REACTIONS

Adverse reactions that occurred at least 10% more frequently than placebo in any clobazam dose included constipation, somnolence or sedation, pyrexia, lethargy, and drooling (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aquestive Therapeutics at 1-877-394-5045 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Alcohol: Increases blood levels of clobazam by about 50% (7.2)
- Drugs metabolized by CYP2D6: Lower doses of these drugs may be required when used concomitantly with SYMPAZAN<sup>TM</sup> (7.3)
- Strong or Moderate CYP2C19 Inhibitors: Dosage adjustment of SYMPAZAN<sup>TM</sup> may be necessary (7.4)

### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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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)*, *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

SYMPAZAN™ is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Information

A daily dose of SYMPAZAN™ greater than 5 mg should be administered in divided doses twice daily; a 5 mg daily dose can be administered as a single dose. Dose patients according to body weight. Individualize dosing within each body weight group, based on clinical efficacy and tolerability. Each dose in Table 1 (e.g., 5 to 20 mg in 30 kg or less weight group) has been shown to be effective, although effectiveness increases with increasing dose [see *Clinical Studies (14)*]. Do not proceed with dose escalation more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady-state.

**Table 1: Recommended Total Daily Dosing by Weight Group**

	30 kg or Less Body Weight	Greater than 30 kg Body Weight
Starting Dose	5 mg	10 mg
Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

## 2.2 Gradual Withdrawal

Avoid abrupt withdrawal from SYMPAZAN™ in order to minimize the risk of increased seizure frequency, status epilepticus, and other adverse reactions [see *Warnings and Precautions (5.4)*]. Taper by decreasing the total daily dosage by 5-10 mg/day on a weekly basis until discontinued.

## 2.3 Important Administration Instructions

Instruct patients and/or caregivers to read the “Instruction for Use” carefully for complete directions on how to properly dose and administer SYMPAZAN™ oral films.

Apply SYMPAZAN™ on top of the tongue where it adheres and dissolves.

SYMPAZAN™ oral film can be taken with or without food [see *Clinical Pharmacology (12.3)*]. Do not administer with liquids. As the film dissolves, saliva should be swallowed in a normal manner, but the patient should refrain from chewing, spitting or talking.

Only one oral film should be taken at a time; if a second film is needed to complete the dosage, it should not be taken until the first film has completely dissolved.

## 2.4 Dosage Adjustments in Geriatric Patients

Plasma concentrations at any given dose are generally higher in geriatric patients [see *Clinical Pharmacology (12.3)*]. Therefore, the starting dosage should generally be 5 mg/day for all geriatric patients. Then proceed slowly with dose escalation; titrate according to weight, but to half the dosage presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dosage (20 mg/day or 40 mg/day, depending on weight) may be started on day 21 [see *Use in Specific Populations (8.5)*].

## 2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers

In CYP2C19 poor metabolizers, levels of N-desmethyloclobazam, clobazam's active metabolite, will be increased [see *Clinical Pharmacology (12.4)*]. Therefore, the starting dosage should be 5 mg/day in patients known to be CYP2C19 poor metabolizers. Then proceed slowly with dose escalation; titrate according to weight, but to half the dosage presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dosage (20 mg/day or 40 mg/day, depending on weight) may be started on day 21 [see *Use in Specific Populations (8.6)*].

## 2.6 Dosage Adjustments in Patients with Hepatic Impairment

SYMPAZAN™ is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of SYMPAZAN™. For patients with mild to moderate hepatic impairment (Child-Pugh score 5-9), the starting dosage should be 5 mg/day (regardless of weight). Then proceed slowly with dosing escalations; titrate patients according to weight, but to half the dosage presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dosage (20 mg/day or 40 mg/day, depending on weight) may be started on day 21. There is inadequate information about metabolism of clobazam in patients with severe hepatic

impairment. Therefore, no dosing recommendation can be given for those patients [see *Use in Specific Populations* (8.8), *Clinical Pharmacology* (12.3)].

### 3 DOSAGE FORMS AND STRENGTHS

SYMPAZAN™ Oral Film: Thin, white, rectangular, orally dissolving film strips:

- 5 mg imprinted with C5
- 10 mg imprinted with C10
- 20 mg imprinted with C20

### 4 CONTRAINDICATIONS

SYMPAZAN™ is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients. Hypersensitivity reactions have included serious dermatological reactions [see *Warnings and Precautions* (5.5)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including SYMPAZAN™, and opioids may result in profound sedation, respiratory depression, coma, and death. 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 SYMPAZAN™ 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 SYMPAZAN™ is used with opioids [see *Drug Interactions* (7.1)].

#### 5.2 Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants

Since SYMPAZAN™ has a central nervous system (CNS) depressant effect, patients or their caregivers should be cautioned against simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated [see *Drug Interactions* (7.2)].

#### 5.3 Somnolence or Sedation

SYMPAZAN™ causes somnolence and sedation. In clinical trials, somnolence or sedation was reported at all effective doses and was dose-related [see *Adverse Reactions* (6.1)].

In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of SYMPAZAN™ is known.

## 5.4 Withdrawal Symptoms

Abrupt discontinuation of SYMPAZAN™ should be avoided. SYMPAZAN™ should be tapered by decreasing the dosage every week by 5-10 mg/day until discontinuation [*see Dosage and Administration (2.2)*].

Withdrawal symptoms occurred following abrupt discontinuation of SYMPAZAN™; the risk of withdrawal symptoms is greater with higher doses.

As with most antiepileptic drugs, SYMPAZAN™ should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus.

Withdrawal symptoms (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to patients who received excessive doses over an extended period of time, followed by an abrupt discontinuation. Generally milder withdrawal symptoms (e.g., dysphoria, anxiety, and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic doses for several months.

## 5.5 Serious Dermatological Reactions

Serious skin reactions, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing period. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. SYMPAZAN™ should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered [*see Contraindications (4)*].

## 5.6 Physical and Psychological Dependence

Patients with a history of substance abuse should be under careful surveillance when receiving SYMPAZAN™ or other psychotropic agents because of the predisposition of such patients to habituation and dependence [*see Drug Abuse and Dependence (9)*].

## 5.7 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including SYMPAZAN™, 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% confidence interval [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.

<b>Indication</b>	<b>Placebo Patients with Events per 1000 Patients</b>	<b>Drug Patients with Events per 1000 Patients</b>	<b>Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients</b>	<b>Risk Difference: Additional Drug Patients with Events per 1000 Patients</b>
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 SYMPAZAN™ or any other AED must balance the risk of suicidal thoughts or behavior 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.

## 6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include the following:

- Risks from Concomitant Use with Opioids [*see Warnings and Precautions (5.1)*]
- Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants [*see Warnings and Precautions (5.2)*]
- Somnolence or Sedation [*see Warnings and Precautions (5.3)*]
- Withdrawal Symptoms [*see Warnings and Precautions (5.4)*]
- Serious Dermatological Reactions [*see Contraindications (4), Warnings and Precautions (5.5)*]
- Physical and Psychological Dependence [*see Warnings and Precautions (5.6)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.7)*]

### 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 following adverse events have been reported in clinical trials of patients treated with clobazam, the active ingredient of SYMPAZAN™.

During its development for the adjunctive treatment of seizures associated with LGS, clobazam was administered to 333 healthy volunteers and 300 patients with a current or prior diagnosis of LGS, including 197 patients treated for 12 months or more. The conditions and duration of exposure varied greatly and included single- and multiple-dose clinical pharmacology studies in healthy volunteers and two double-blind studies in patients with LGS (Study 1 and 2) [*see Clinical Studies (14)*]. Only Study 1 included a placebo group, allowing comparison of adverse reaction rates on clobazam at several doses to placebo.

#### Adverse Reactions Leading to Discontinuation in an LGS Placebo Controlled Clinical Trial (Study 1)

The adverse reactions associated with clobazam treatment discontinuation in  $\geq 1\%$  of patients in decreasing order of frequency included lethargy, somnolence, ataxia, aggression, fatigue, and insomnia.

#### Most Common Adverse Reactions in an LGS Placebo Controlled Clinical Trial (Study 1)

Table 3 lists the adverse reactions that occurred in  $\geq 5\%$  of clobazam-treated patients (at any dose), and at a rate greater than placebo-treated patients, in the randomized, double-blind, placebo-controlled, parallel group clinical study of adjunctive AED therapy for 15 weeks (Study 1).



<b>Table 3: Adverse Reactions Reported for <math>\geq 5\%</math> of Patients and More Frequently than Placebo in Any Treatment Group</b>					
	<b>Placebo N=59 %</b>	<b>Clobazam Dose Level</b>			<b>All Clobazam N=179 %</b>
		<b>Low<sup>a</sup> N=58 %</b>	<b>Medium<sup>b</sup> N=62 %</b>	<b>High<sup>c</sup> N=59 %</b>	
<b>Gastrointestinal Disorders</b>					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
<b>General Disorders and Administration Site Conditions</b>					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
<b>Infections and Infestations</b>					
Upper respiratory tract infection	10	10	13	14	12
Pneumonia	2	3	3	7	4
Urinary tract infection	0	2	5	5	4
Bronchitis	0	2	0	5	2
<b>Metabolism and Nutrition Disorders</b>					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
<b>Nervous System Disorders</b>					
Somnolence or Sedation	15	17	27	32	26
Somnolence	12	16	24	25	22
Sedation	3	2	3	9	5
Lethargy	5	10	5	15	10
Drooling	3	0	13	14	9
Ataxia	3	3	2	10	5

Psychomotor hyperactivity	3	3	3	5	4
Dysarthria	0	2	2	5	3
<b>Psychiatric Disorders</b>					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
<b>Respiratory Disorders</b>					
Cough	0	3	5	7	5

<sup>a</sup> Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight

<sup>b</sup> Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight

<sup>c</sup> Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clobazam tablets. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions are categorized by system organ class.

**Blood Disorders:** Anemia, eosinophilia, leukopenia, thrombocytopenia

**Eye Disorders:** Diplopia, vision blurred

**Gastrointestinal Disorders:** Abdominal distention

**General Disorders and Administration Site Conditions:** Hypothermia

**Investigations:** Hepatic enzyme increased

**Musculoskeletal:** Muscle spasms

**Psychiatric Disorders:** Agitation, anxiety, apathy, confusional state, depression, delirium, delusion, hallucination

**Renal and Urinary Disorders:** Urinary retention

**Respiratory Disorders:** Aspiration, respiratory depression

**Skin and Subcutaneous Tissue Disorders:** Rash, urticaria, angioedema, and facial and lip edema

## 7 DRUG INTERACTIONS

### 7.1 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<sub>A</sub> 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

Concomitant use of SYMPAZAN™ with other CNS depressants may increase the risk of sedation and somnolence [*see Warnings and Precautions (5.2)*].

Alcohol, as a CNS depressant, will interact with SYMPAZAN™ in a similar way and also increases clobazam's maximum plasma exposure by approximately 50%. Therefore, caution patients or their caregivers against simultaneous use with other CNS depressant drugs or alcohol, and caution that the effects of other CNS depressant drugs or alcohol may be potentiated [*see Warnings and Precautions (5.2)*].

## 7.3 Effect of SYMPAZAN™ on Other Drugs

### Hormonal Contraceptives

SYMPAZAN™ is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with SYMPAZAN™. Additional non-hormonal forms of contraception are recommended when using SYMPAZAN™ [*see Clinical Pharmacology (12.3), Patient Counseling Information (17)*].

### Drugs Metabolized by CYP2D6

SYMPAZAN™ inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary [*see Clinical Pharmacology (12.3)*].

## 7.4 Effect of Other Drugs on SYMPAZAN™

### Strong and Moderate Inhibitors of CYP2C19

Coadministration with strong or moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam, the active metabolite of clobazam. This may increase the risk of dose-related adverse reactions. Dosage adjustment of SYMPAZAN™ may be necessary when co-administered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole) [*see Clinical Pharmacology (12.3)*].

## 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 AEDs, such as SYMPAZAN™, during pregnancy. Physicians are advised to recommend that pregnant patients taking SYMPAZAN™ enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334 and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

## Risk Summary

There are no adequate and well-controlled studies of SYMPAZAN™ 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 drug 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 trimester 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*]. Administration of clobazam to pregnant rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation resulted in developmental toxicity, including increased incidences of fetal malformations and mortality, at plasma exposures for clobazam and its major active metabolite, N-desmethyloclobazam, below those expected at therapeutic doses in patients [*see Animal Data*].

Data for other benzodiazepines suggest the possibility of long-term effects on neurobehavioral and immunological function in animals following prenatal exposure to benzodiazepines at clinically relevant doses.

SYMPAZAN™ should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Advise pregnant women 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%-4% and to 15% to 20%, respectively. The 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 SYMPAZAN™ *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 SYMPAZAN<sup>TM</sup> in pregnant women, there is information about benzodiazepines as a class. Dolovich et al. published a metaanalysis 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 clobazam during the later stages of pregnancy and peripartum period have been reported in the postmarketing experience. 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*

In a study in which clobazam (0, 150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryofetal mortality and incidences of fetal skeletal variations were increased at all doses. The low-effect dose for embryofetal developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, lower than those in humans at the maximum recommended human dose (MRHD) of 40 mg/day.

Oral administration of clobazam (0, 10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryofetal mortality at the high dose. Incidences of fetal variations were increased at all doses. The highest dose tested was associated with maternal toxicity (ataxia and decreased activity). The low effect dose for embryofetal developmental toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethyloclobazam lower than those in humans at the MRHD.

Oral administration of clobazam (0, 50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryofetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behavior (locomotor activity) at all doses. The low-effect dose for adverse effects on pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethyloclobazam lower than those in humans at the MRHD.

## **8.2 Lactation**

### Risk Summary

SYMPAZAN™ is excreted in human milk. Postmarketing experience suggests that breastfed infants of mothers taking benzodiazepines, such as SYMPAZAN™, may have effects of lethargy, somnolence and poor sucking. The effect of SYMPAZAN™ on milk production is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SYMPAZAN™ and any potential adverse effects on the breastfed infant from SYMPAZAN™ or from the underlying maternal condition. If exposing a breastfed infant to SYMPAZAN™, observe for any potential adverse effects.

### Clinical Considerations

#### *Monitoring for Adverse Reactions*

Adverse reactions such as somnolence and difficulty feeding have been reported in infants during breastfeeding in postmarketing experience with clobazam. Monitor breastfed infants for possible sedation and poor sucking. Data Scientific literature on clobazam use during lactation is limited. After short-term administration, clobazam and N-desmethyloclobazam are transferred into breast milk.

## **8.3 Females and Males of Reproductive Potential**

Administration of clobazam to rats prior to and during mating and early gestation resulted in adverse effects on fertility and early embryonic development at plasma exposures for clobazam and its major active metabolite, N-desmethyloclobazam, below those in humans at the MRHD [*see Nonclinical Toxicology (13.1)*].

## 8.4 Pediatric Use

Safety and effectiveness for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in pediatric patients 2 years of age and older have been established in two adequate and well-controlled studies [see *Clinical Studies (14)*].

Safety and effectiveness in patients less than 2 years of age have not been established.

### Juvenile Animal Data

In a study in which clobazam (0, 4, 36, or 120 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 14 to 48), adverse effects on growth (decreased bone density and bone length) and behavior (altered motor activity and auditory startle response; learning deficit) were observed at the high dose. The effect on bone density, but not on behavior, was reversible when drug was discontinued. The no-effect level for juvenile toxicity (36 mg/kg/day) was associated with plasma exposures (AUC) to clobazam and its major active metabolite, N-desmethyclobazam, less than those expected at therapeutic doses in pediatric patients.

## 8.5 Geriatric Use

Clinical studies of clobazam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly subjects appear to eliminate clobazam more slowly than younger subjects based on population pharmacokinetic analysis. For these reasons, dosage modification is recommended [see *Dosage and Administration (2.4)*, *Clinical Pharmacology (12.3)*].

## 8.6 CYP2C19 Poor Metabolizers

Concentrations of clobazam's active metabolite, N-desmethyclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended [see *Dosage and Administration (2.5)*, *Clinical Pharmacology (12.3)*].

## 8.7 Renal Impairment

The pharmacokinetics of clobazam were evaluated in patients with mild and moderate renal impairment. There were no significant differences in systemic exposure (AUC and  $C_{max}$ ) between patients with mild or moderate renal impairment and healthy subjects. No dose adjustment is required for patients with mild and moderate renal impairment. There is essentially no experience with SYMPAZAN™ in patients with severe renal impairment or ESRD. It is not known if clobazam or its active metabolite, N-desmethyclobazam, is dialyzable [see *Clinical Pharmacology (12.3)*].

## 8.8 Hepatic Impairment

SYMPAZAN™ is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. For this reason, dosage adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9) [see *Dosage and Administration (2.6)*]. There is inadequate information about metabolism of SYMPAZAN™ in patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

SYMPAZAN™ contains clobazam which is a Schedule IV controlled substance.

### 9.2 Abuse

SYMPAZAN™ can be abused in a similar manner as other benzodiazepines, such as diazepam.

The pharmacological profile of SYMPAZAN™ is similar to that of other benzodiazepines listed in Schedule IV of the Controlled Substance Act, particularly in its potentiation of GABAergic transmission through its action on GABA<sub>A</sub> receptors, which leads to sedation and somnolence.

The World Health Organization epidemiology database contains reports of drug abuse, misuse, and overdoses associated with clobazam.

Drug abuse is the intentional non-therapeutic use of a drug, repeatedly or even sporadically, for its rewarding psychological or physiological effects.

### 9.3 Dependence

#### Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist. In clinical trials, cases of dependency were reported following abrupt discontinuation of clobazam.

The risk of dependence is present even with use of SYMPAZAN™ at the recommended dose range over periods of only a few weeks. The risk of dependence increases with increasing dose and duration of treatment. The risk of dependence is increased in patients with a history of alcohol or drug abuse.

#### Withdrawal

Abrupt discontinuation of SYMPAZAN™ causes withdrawal symptoms. As with other benzodiazepines, SYMPAZAN™ should be withdrawn gradually [*see Dosage and Administration (2.2), Warnings and Precautions (5.4)*].

In clobazam clinical pharmacology trials in healthy volunteers, the most common withdrawal symptoms after abrupt discontinuation were headache, tremor, insomnia, anxiety, irritability; drug withdrawal syndrome, palpitations, and diarrhea [*see Warnings and Precautions (5.4)*].

Other withdrawal reactions to clobazam reported in the literature include restlessness, panic attacks, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, blurred vision, photophobia, and muscle pain and stiffness. In general, benzodiazepine withdrawal may cause seizures, psychosis, and hallucinations [*see Warnings and Precautions (5.4)*].



## 10 OVERDOSAGE

### 10.1 Signs and Symptoms of Overdosage

Overdose and intoxication with benzodiazepines, including SYMPAZAN™, may lead to CNS depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, respiratory depression, hypotension, and, rarely, coma or death. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants, including opioid and alcohol.

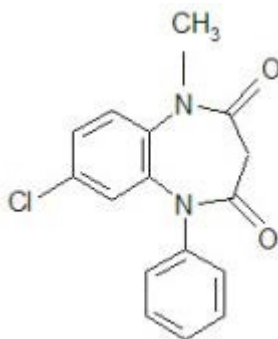
### 10.2 Management of Overdosage

The management of SYMPAZAN™ overdose may include gastric lavage and/or administration of activated charcoal, intravenous fluid replenishment, early control of airway and general supportive measures, in addition to monitoring level of consciousness and vital signs. Hypotension can be treated by replenishment with plasma substitutes and, if necessary, with sympathomimetic agents.

The efficacy of supplementary administration of physostigmine (a cholinergic agent) or of flumazenil (a benzodiazepine antagonist) in clobazam overdose has not been assessed. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions. Its use in patients with epilepsy is typically not recommended.

## 11 DESCRIPTION

SYMPAZAN™ contains clobazam, a benzodiazepine derivative, which is chemically known as 7-Chloro-1-methyl-5-phenyl-1*H*-1,5 benzodiazepine-2,4(3*H*,5*H*)-dione with a molecular formula of C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>, molecular weight of 300.74, and it has the following structural formula:



Clobazam is a white or almost white, crystalline powder with a slightly bitter taste. It is slightly soluble in water and sparingly soluble in ethanol.

Each SYMPAZAN™ Oral Film contains 5 mg, 10 mg or 20 mg of clobazam and the following inactive ingredients: artificial cooling flavor, citric acid, glycerol monooleate, hypromellose, maltitol, natural and artificial bitter masker, natural raspberry type flavor, polyethylene oxide, purified water, sodium phosphate dibasic, and sucralose.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABA<sub>A</sub> receptor.

### 12.2 Pharmacodynamics

#### Effects on Electrocardiogram

The effect of clobazam 20 mg and 80 mg administered twice daily on QTc interval was evaluated in a randomized, evaluator-blinded, placebo-, and active-controlled (moxifloxacin 400 mg) parallel thorough QT study in 280 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on the Fridericia correction method was below 10 ms, the threshold for regulatory concern. Thus, at a dose two times the maximum recommended dose, clobazam did not prolong the QTc interval to any clinically relevant extent.

### 12.3 Pharmacokinetics

SYMPAZAN™ Oral Films at single doses of 10 mg and 20 mg clobazam have been shown to be bioequivalent ( $C_{max}$  and AUC) to clobazam tablets at equivalent doses. Following single-dose administration of SYMPAZAN™, peak plasma levels ( $C_{max}$ ) and the area under the curve (AUC) of clobazam are dose-proportional over the dose range of 10-20 mg. Based on a population pharmacokinetic analysis with clobazam tablets, the pharmacokinetics of clobazam are linear from 5-160 mg/day. Clobazam is converted to N-desmethyloclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives ( $t_{1/2}$ ) of clobazam and N-desmethyloclobazam were 36-42 hours and 71-82 hours, respectively.

#### Absorption

The time to peak concentrations ( $T_{max}$ ) of SYMPAZAN™ clobazam oral film under fasted conditions ranged from 0.33 to 4.0 hours after single-dose administration. The administration of clobazam tablets with food does not affect absorption. Although not studied, the oral bioavailability of SYMPAZAN™ oral film is unlikely to be affected under fed conditions.

#### Distribution

Clobazam is lipophilic and distributes rapidly throughout the body. The apparent volume of distribution at steady state was approximately 100 L. The *in vitro* plasma protein binding of clobazam and N-desmethyloclobazam is approximately 80-90% and 70%, respectively.

#### Metabolism and Excretion

Clobazam is extensively metabolized in the liver, with approximately 2% of the dose recovered in urine and 1% in feces as unchanged drug. The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-desmethyloclobazam, an active metabolite, is the major circulating metabolite in humans, and at

therapeutic doses, plasma concentrations are 3-5 times higher than those of the parent compound. Based on animal and *in vitro* receptor binding data, estimates of the relative potency of N-desmethyloclobazam compared to parent compound range from 1/5 to equal potency. N-desmethyloclobazam is extensively metabolized, mainly by CYP2C19. N-desmethyloclobazam and its metabolites comprise ~94% of the total drug-related components in urine. Following a single oral dose of radiolabeled drug, approximately 11% of the dose was excreted in the feces and approximately 82% was excreted in the urine.

The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethyloclobazam [see *Clinical Pharmacology (12.4)*]. In CYP2C19 poor metabolizers, levels of N-desmethyloclobazam were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.

### Pharmacokinetics in Specific Populations

#### *Age*

Population pharmacokinetic analyses showed that the clearance of clobazam is lower in elderly subjects compared to other age groups (ages less than 64). Dosing should be adjusted in the elderly [see *Dosage and Administration (2.4)*].

#### *Sex*

Population pharmacokinetic analyses showed no difference in the clearance of clobazam between women and men.

#### *Race*

Population pharmacokinetic analyses including Caucasian (75%), African American (15%), and Asian (9%) subjects showed that there is no evidence of clinically significant effect of race on the clearance of clobazam.

#### *Renal Impairment*

The effect of renal impairment on the pharmacokinetics of clobazam was evaluated in patients with mild (creatinine clearance [ $CL_{CR}$ ] >50 to 80 mL/min; N=6) and moderate ( $CL_{CR}$ =30 to 50 mL/min; N=6) renal dysfunction, with matching healthy controls (N=6), following administration of multiple doses of clobazam 20 mg/day. There were insignificant changes in  $C_{max}$  (3-24%) and AUC ( $\leq$ 13%) for clobazam or N-desmethyloclobazam in patients with mild or moderate renal impairment compared to patients with normal renal function. Patients with severe renal impairment or ESRD were not included in this study.

#### *Hepatic Impairment*

There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. In a small study, the pharmacokinetics of a 20 mg single oral dose of clobazam in 9 patients with liver impairment were compared to healthy controls (N=6). The  $C_{max}$  and the mean plasma clearance of clobazam, as well as the  $C_{max}$  of N-desmethyloclobazam, showed no significant change compared to the healthy controls. The AUC values of N-desmethyloclobazam in these patients were not available. Adjust dosage in patients with hepatic impairment [see *Dosage and Administration (2.6)*].

### Drug Interaction Studies

#### *In vitro studies:*

Clobazam did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A4, UGT1A6, or UGT2B4 *in vitro*. N-desmethyloclobazam showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4.

Clobazam and N-desmethyloclobazam did not significantly increase CYP1A2 or CYP2C19 activities, but did induce CYP3A4 activity in a concentration-dependent manner. Clobazam and N-desmethyloclobazam

also increased UGT1A1 mRNA but at concentrations much higher than therapeutic levels. The potential for clobazam or N-desmethyclobazam to induce CYP2B6 and CYP2C8 has not been evaluated.

Clobazam and N-desmethyclobazam do not inhibit P-glycoprotein (P-gp), but are P-gp substrates.

#### *In vivo studies:*

##### *Potential for Clobazam to Affect Other Drugs*

The effect of repeated 40 mg once-daily doses of clobazam on the pharmacokinetic profiles of single-dose dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), and tolbutamide (CYP2C9 substrate), was studied when these probe substrates were given as a drug cocktail (N=18).

Clobazam increased AUC and  $C_{max}$  of dextromethorphan by 90% and 59%, respectively, reflecting its inhibition of CYP2D6 *in vivo*. Drugs metabolized by CYP2D6 may require dose adjustment when used with clobazam.

Clobazam decreased the AUC and  $C_{max}$  of midazolam by 27% and 24%, respectively, and increased the AUC and  $C_{max}$  of the metabolite 1-hydroxymidazolam by 4-fold and 2-fold, respectively. This level of induction does not call for dosage adjustment of drugs that are primarily metabolized by CYP3A4 when used concomitantly with clobazam. Some hormonal contraceptives are metabolized by CYP3A4 and their effectiveness may be diminished when given with SYMPAZAN<sup>TM</sup> [see *Drug Interactions (7.3)*]. Repeated clobazam doses had no effect on caffeine and tolbutamide.

A population pharmacokinetic analysis indicated clobazam did not affect the exposure of valproic acid (a CYP2C9/2C19 substrate) or lamotrigine (a UGT substrate).

##### *Potential for Other Drugs to Affect SYMPAZAN<sup>TM</sup>*

Co-administration of ketoconazole (a strong CYP3A4 inhibitor) 400 mg once-daily for 5 days increased clobazam AUC by 54%, with an insignificant effect on clobazam  $C_{max}$ . There was no significant change in AUC and  $C_{max}$  of N-desmethyclobazam (N=18).

Strong (e.g., fluconazole, fluvoxamine, ticlopidine) and moderate (e.g., omeprazole) inhibitors of CYP2C19 may result in up to a 5-fold increase in exposure to N-desmethyclobazam, the active metabolite of clobazam, based on extrapolation from pharmacogenomic data [see *Clinical Pharmacology (12.4)*]. Dosage adjustment of SYMPAZAN<sup>TM</sup> may be necessary when co-administered with strong or moderate CYP2C19 inhibitors [see *Drug Interactions (7.4)*].

The effects of concomitant antiepileptic drugs that are CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C19 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C19 inhibitors (felbamate and oxcarbazepine) were evaluated using data from clinical trials. Results of population pharmacokinetic analysis show that these concomitant antiepileptic drugs did not significantly alter the pharmacokinetics of clobazam or N-desmethyclobazam at steady-state.

Alcohol has been reported to increase the maximum plasma exposure of clobazam by approximately 50%. Alcohol may have additive CNS depressant effects when taken with SYMPAZAN<sup>TM</sup> [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.2)*].

## **12.4 Pharmacogenomics**

The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethyclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethyclobazam AUC and

C<sub>max</sub> are approximately 3-5 times higher in poor metabolizers (e.g., subjects with \*2/\*2 genotype) and 2 times higher in intermediate metabolizers (e.g., subjects with \*1/\*2 genotype). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted [see *Dosage and Administration* (2.5)].

The systemic exposure of clobazam is similar for both CYP2C19 poor and extensive metabolizers.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

In mice, oral administration of clobazam (0, 6, 12, or 24 mg/kg/day) for 2 years did not result in an increase in tumors. The highest dose tested was approximately 3 times the maximum recommended human dose (MRHD) of 40 mg/day, based on body surface area (mg/m<sup>2</sup>).

In rats, oral administration of clobazam for 2 years resulted in increases in tumors of the thyroid gland (follicular cell adenoma and carcinoma) and liver (hepatocellular adenoma) at the mid and high doses. The low dose, not associated with an increase in tumors, was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethyloclobazam, less than that in humans at the MRHD.

#### Mutagenesis

Clobazam and the major active metabolite, N-desmethyloclobazam, were negative for genotoxicity, based on data from a battery of *in vitro* (bacteria reverse mutation, mammalian clastogenicity) and *in vivo* (mouse micronucleus) assays.

#### Impairment of Fertility

In a fertility study in which clobazam (50, 350, or 750 mg/kg/day, corresponding to 12, 84, and 181 times the oral Maximum Recommended Human Dose, MRHD, of 40mg/day based on mg/m<sup>2</sup> body surface) was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6, increases in abnormal sperm and pre-implantation loss were observed at the highest dose tested. The no-effect level for fertility and early embryonic development in rats was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethyloclobazam, less than those in humans at the maximum recommended human dose of 40 mg/day.

## 14 CLINICAL STUDIES

### 14.1 Demonstration of Pharmacokinetic Equivalence between SYMPAZAN<sup>TM</sup> and clobazam tablets

The efficacy of SYMPAZAN<sup>TM</sup> is based upon bioavailability studies comparing clobazam tablets to SYMPAZAN<sup>TM</sup> [see *Clinical Pharmacology* (12.3)].

### 14.2 Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS)

The effectiveness of clobazam for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome was established in two multicenter controlled studies (Study 1 and Study 2). Both studies were similar in terms of disease characteristics and concomitant AED treatments. The most common concomitant AED treatments at baseline included: valproate, lamotrigine, levetiracetam, and topiramate.

Study 1

Study 1 (N=238) was a randomized, double-blind, placebo-controlled study consisting of a 4-week baseline period followed by a 3-week titration period and 12-week maintenance period. Patients age 2-54 years with a current or prior diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30 kg) and then randomized to placebo or one of three target maintenance doses of clobazam according to [Table 5](#).

**Table 5: Study 1 Total Daily Dose**

	<b>≤30 kg Body Weight</b>	<b>&gt;30 kg Body Weight</b>
Low Dose	5 mg daily	10 mg daily
Medium Dose	10 mg daily	20 mg daily
High Dose	20 mg daily	40 mg daily

Doses above 5 mg/day were administered in two divided doses.

The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to 12-week maintenance period.

The pre-dosing baseline mean weekly drop seizure frequency was 98, 100, 61, and 105 for the placebo, low-, medium-, and high-dose groups, respectively. [Figure 1](#) presents the mean percent reduction in weekly drop seizures from this baseline. All dose groups of clobazam were statistically superior ( $p \leq 0.05$ ) to the placebo group. This effect appeared to be dose dependent.

**Figure 1: Mean Percent Reduction from Baseline in Weekly Drop Seizure Frequency (Study 1)**

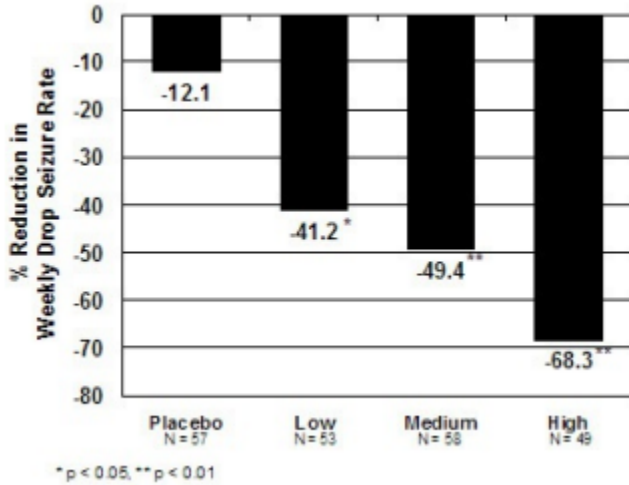
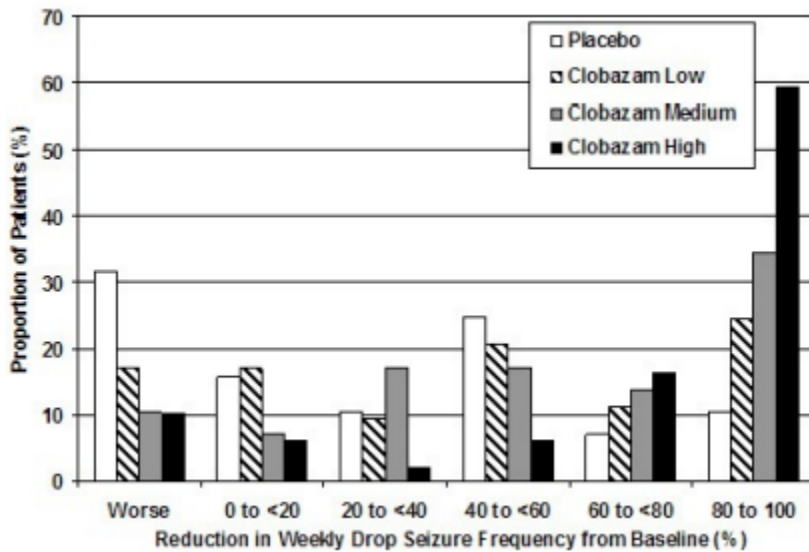


Figure 2 shows changes from baseline in weekly drop seizure frequency by category for patients treated with clobazam and placebo in Study 1. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

**Figure 2: Drop Seizure Response by Category for Clobazam and Placebo (Study 1)**



There was no evidence that tolerance to the therapeutic effect of clobazam developed during the 3-month maintenance period.

Study 2

Study 2 (N=68) was a randomized, double-blind comparison study of high- and low-dose clobazam, consisting of a 4-week baseline period followed by a 3-week titration period and 4-week maintenance period. Patients age 2-25 years with a current or prior diagnosis of LGS were stratified by weight, then randomized to either a low or high dose of clobazam, and then entered a 3-week titration period.

The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to the 4-week maintenance period.

A statistically significantly greater reduction in seizure frequency was observed in the high-dose group compared to the low-dose group (median percent reduction of 93% vs 29%;  $p < 0.05$ ).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Each SYMPAZAN™ oral film is a white rectangular film that contains 5 mg, 10 mg or 20 mg of clobazam and printed in black ink either "C5," "C10" or "C20" on the strip according to their respective strengths and each film is packaged in a pouch (sachet).

NDC 10094-205-60: 5 mg oral film, Package of 60

NDC 10094-210-60: 10 mg oral film, Package of 60

NDC 10094-220-60: 20 mg oral film, Package of 60

Store SYMPAZAN oral film pouches (sachets) 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 patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Risks from Concomitant Use with Opioids

Inform patients and caregivers that potentially fatal additive effects may occur if SYMPAZAN™ is used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider [*see Warnings and Precautions (5.1), Drug Interactions (7.1)*].

### Somnolence or Sedation

Advise patients or caregivers to check with their healthcare provider before SYMPAZAN™ is taken with other CNS depressants such as other benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or alcohol [*see Warnings and Precautions (5.2, 5.3)*].

If applicable, caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMPAZAN™ does not affect them adversely (e.g., impair judgment, thinking or motor skills).

### Increasing or Decreasing the SYMPAZAN™ Dose

Inform patients or caregivers to consult their healthcare provider before increasing the SYMPAZAN™ dose or abruptly discontinuing SYMPAZAN™. Advise patients or caregivers that abrupt withdrawal of AEDs may increase their risk of seizure [*see Dosage and Administration (2.2), Warnings and Precautions (5.4)*].



### Hypersensitivity

Inform patients or caregivers that SYMPAZAN™ is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients [see *Warnings and Precautions (5.5)*].

### Interactions with Hormonal Contraceptives

Counsel women to also use non-hormonal methods of contraception when SYMPAZAN™ is used with hormonal contraceptives and to continue these alternative methods for 28 days after discontinuing SYMPAZAN™ to ensure contraceptive reliability [see *Drug Interactions (7.3)*, *Clinical Pharmacology (12.3)*].

### Serious Dermatological Reactions

Advise patients or caregivers that serious skin reactions have been reported in patients taking clobazam. Serious skin reactions, including SJS/TEN, may need to be treated in a hospital and may be life-threatening. If a skin reaction occurs while taking SYMPAZAN™, patients or caregivers should consult with healthcare providers immediately [see *Warnings and Precautions (5.5)*].

### Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that AEDs, including SYMPAZAN™, 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. Patients should report behaviors of concern immediately to healthcare providers [see *Warnings and Precautions (5.7)*].

### Use in Pregnancy

Advise pregnant women and women of childbearing potential that the use of ONFI during pregnancy can cause fetal harm which may occur early in pregnancy before many women know they are pregnant. Instruct patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy. When appropriate, prescribers should counsel pregnant women and women of childbearing potential about alternative therapeutic options.

Advise patients that there is a pregnancy registry that collects information about the safety of antiepileptic drugs during pregnancy [see *Use in Specific Populations (8.1)*].

### Use in Lactation

Counsel patients that SYMPAZAN™ is excreted in breast milk. Instruct patients to notify their physician if they are breast feeding or intend to breast feed during therapy and counsel nursing mothers to observe their infants for poor sucking and somnolence [see *Use in Specific Populations (8.2)*].

Manufactured by: Aquestive Therapeutics  
Warren, NJ 07059



**MEDICATION GUIDE**  
**SYMPAZAN™ (SYM-pa-zan)**  
**(clobazam)**  
**oral film, CIV**

**What is the most important information I should know about SYMPAZAN?**

- **Do not stop taking SYMPAZAN without first talking to your healthcare provider.** Stopping SYMPAZAN suddenly can cause serious side effects.
- **SYMPAZAN is a benzodiazepine medicine. Benzodiazepines can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.**
- **SYMPAZAN can make you sleepy or dizzy and can slow your thinking and motor skills. This may get better over time.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how SYMPAZAN affects you.
  - SYMPAZAN may cause problems with your coordination, especially when you are walking or picking things up.
- **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking SYMPAZAN until you talk to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, SYMPAZAN may make your sleepiness or dizziness much worse.
- **SYMPAZAN can cause withdrawal symptoms.**
  - Do not stop taking SYMPAZAN all of a sudden without first talking to a healthcare provider. Stopping SYMPAZAN suddenly can cause seizures that will not stop (status epilepticus), hearing or seeing things that are not there (hallucinations), shaking, nervousness, and stomach and muscle cramps.
  - Talk to your healthcare provider about slowly stopping SYMPAZAN to avoid withdrawal symptoms.
- **SYMPAZAN can be abused and cause dependence.**
  - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
- **SYMPAZAN is a federally controlled substance (CIV) because it can be abused or lead to dependence.** Keep SYMPAZAN in a safe place to prevent misuse and abuse. Selling or giving away SYMPAZAN may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- **Serious skin reactions have been seen when SYMPAZAN is taken with other medicines and may require stopping its use.** Do not stop taking SYMPAZAN without first talking to your healthcare provider.
  - A serious skin reaction can happen at any time during your treatment with SYMPAZAN, but is more likely to happen within the first 8 weeks of treatment. These skin reactions may need to be treated right away.
  - Call your healthcare provider immediately if you have skin blisters, rash, sores in mouth, hives or any other allergic reaction.
- **Like other antiepileptic drugs, SYMPAZAN may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

**Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**How can I watch for early symptoms of suicidal thoughts and actions?**

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or

actions, your healthcare provider may check for other causes.

### **What is SYMPAZAN?**

SYMPAZAN is a prescription medicine used along with other medicines to treat seizures associated with Lennox-Gastaut Syndrome in people 2 years of age or older.

It is not known if SYMPAZAN is safe and effective in children less than 2 years old.

### **Do not take SYMPAZAN if you:**

- are allergic to clobazam or any of the ingredients in SYMPAZAN. See the end of this Medication Guide for a complete list of ingredients in SYMPAZAN.

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

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- use birth control medicine. SYMPAZAN may cause your birth control medicine to be less effective. Talk to your healthcare provider about the best birth control method to use.
- are pregnant or plan to become pregnant. **SYMPAZAN may harm your unborn baby.**
  - Tell your healthcare provider right away if you become pregnant while taking SYMPAZAN. You and your healthcare provider will decide if you should take SYMPAZAN while you are pregnant.
  - Babies born to mothers receiving benzodiazepine medications (including SYMPAZAN) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, dangerously low body temperature, and withdrawal symptoms.
- If you become pregnant while taking SYMPAZAN, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. For more information about the registry go to <http://www.aedpregnancyregistry.org>. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- SYMPAZAN can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take SYMPAZAN. You and your healthcare provider should decide if you will take SYMPAZAN or breast feed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking SYMPAZAN with certain other medicines can cause side effects or affect how well SYMPAZAN or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

### **How should I take SYMPAZAN?**

- Take SYMPAZAN exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much SYMPAZAN to take and when to take it.
- Place the entire SYMPAZAN oral film on top of the tongue.
- SYMPAZAN oral films can be taken with or without food.
- **Do not** take liquids with SYMPAZAN oral films.
- Take only 1 SYMPAZAN oral film at a time.
- Read the **Instructions for Use** at the end of this Medication Guide for information on the right way to take SYMPAZAN™ oral films.
- Your healthcare provider may change your dose if needed. **Do not** change your dose of SYMPAZAN without talking to your healthcare provider.
- **Do not** stop taking SYMPAZAN without first talking to your healthcare provider.
- Stopping SYMPAZAN suddenly can cause serious problems.
- If you take too much SYMPAZAN, call your healthcare provider or go to the nearest hospital emergency room right away.

**What should I avoid while taking SYMPAZAN?**

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how SYMPAZAN affects you.
- Do not drink alcohol or take other medicines that may make you sleepy or dizzy while taking SYMPAZAN until you talk to your healthcare provider. When taken with alcohol or medicines that cause sleepiness or dizziness, SYMPAZAN may make your sleepiness or dizziness much worse.

**What are the possible side effects of SYMPAZAN?****SYMPAZAN may cause serious side effects, including:**

- See "What is the most important information I should know about SYMPAZAN?"

**The most common side effects of SYMPAZAN include:**

- sleepiness
- drooling
- constipation
- cough
- pain with urination
- fever
- acting aggressive, being angry, or violent
- difficulty sleeping
- slurred speech
- tiredness
- problems with breathing

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

**How should I store SYMPAZAN?**

- Store SYMPAZAN oral film between 68°F to 77°F (20°C to 25°C).

**Keep SYMPAZAN and all medicines out of the reach of children.****General Information about the safe and effective use of SYMPAZAN.**

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

**What are the ingredients in SYMPAZAN?**

**Active ingredient:** clobazam

**Inactive ingredients:** artificial cooling flavor, citric acid, glycerol monooleate, hypromellose, maltitol, natural and artificial bitter masker, natural raspberry type flavor, polyethylene oxide, purified water, sodium phosphate dibasic, and sucralose.

Manufactured by:  
Aquestive Therapeutics  
Warren, NJ 07059

SYMPAZAN™ is a trademark of Aquestive Therapeutics

For more information, go to [www.SYMPAZAN.com](http://www.SYMPAZAN.com) or call the Aquestive Therapeutics Rx Patient and Caregiver Support Line at 1-833-AQUESTV (1-833-278-3788).

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued:11/2018

**Instructions for Use  
SYMPAZAN (SIM-pa-zan)  
(clobazam)  
oral film, CIV**

Read this Instructions for Use before you start using SYMPAZAN and each time you get a refill. There may be new information. The information does not take the place of talking with your healthcare provider about your medical condition or treatment.

**Important Information for Patient and Caregiver:**

- **Do not take SYMPAZAN** until:
  - you have read and understand these instructions.
  - you have reviewed the steps with your healthcare provider on how to take it.
  - you know the right time, how often, and the dose to take.
  - you feel comfortable with how to use SYMPAZAN.
- If you are not sure about giving treatment or when to give treatment, **call your healthcare provider** before using **SYMPAZAN**.

**How should I store SYMPAZAN?**

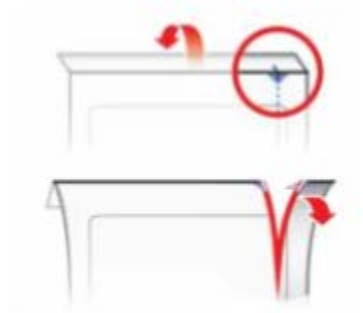
- Store SYMPAZAN at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep SYMPAZAN in the foil pouch until you are ready to use. Use right away after opening foil pouch.
- **Keep SYMPAZAN and all medicines out of the reach of children.**

**How to Use SYMPAZAN:**

- Take only 1 SYMPAZAN film at a time unless instructed differently by your healthcare provider. If a second film is needed to get a full dose of SYMPAZAN, do not take the second film until the first film has completely dissolved.
- **Place the entire SYMPAZAN oral film on top of the tongue.** Check your prescription or contact your healthcare provider if you are not sure about the amount to take.
- Make sure your hands are clean and dry before handling the SYMPAZAN film.
- Check the expiration date printed on the foil pouch. **Do not** use SYMPAZAN if expired.

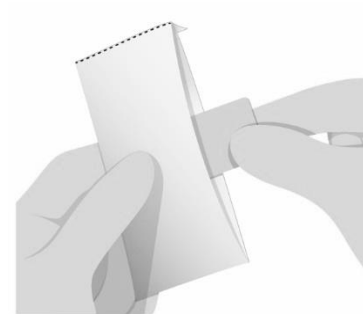
### Step 1. Open Pouch

- Fold foil pouch along solid line.
- Note where the slit is and carefully tear it to open pouch.



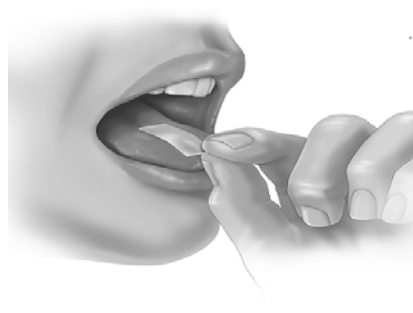
### Step 2. Remove Film

- Remove the SYMPAZAN from the foil pouch.



### Step 3. Place on Tongue

- Place SYMPAZAN on top of the tongue. The film will stick to the tongue and begin to dissolve.



### Step 4. Close Mouth and Swallow Saliva Normally

- Close mouth.
- Swallow saliva normally as SYMPAZAN dissolves.
- **Do not** take with liquids.
- **Do not** chew, spit, or talk while SYMPAZAN dissolves.



- **Wash your hands after taking SYMPAZAN.**
- **Throw away the empty foil pouch in the regular trash.**

Manufactured by:

Aquestive Therapeutics

Warren, NJ 07059

For more information or support about SYMPAZAN: Call 1-833-AQUESTV (1-833-278-3788).

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Revision Date: 11/2018