

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUSTOL® safely and effectively. See full prescribing information for SUSTOL.

SUSTOL® (granisetron) extended-release injection, for subcutaneous use
Initial U.S. Approval: 1993

INDICATIONS AND USAGE

SUSTOL is a serotonin-3 (5-HT₃) receptor antagonist indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens. (1)

DOSAGE AND ADMINISTRATION

Administration (2.1):

- For subcutaneous injection only.
- Intended for administration by a healthcare provider.
- Administer in skin of the back of the upper arm or in the skin of the abdomen at least 1 inch away from the umbilicus.
- Do not administer anywhere the skin is burned, hardened, inflamed, swollen, or otherwise compromised
- Due to the viscosity, administration requires a slow, sustained injection over 20 to 30 seconds.

Recommended Dosage (2.2):

- The recommended dosage in adults is 10 mg administered as a single subcutaneous injection at least 30 minutes before the start of emetogenic chemotherapy on Day 1.
- Do not administer SUSTOL more frequently than once every 7 days.
- Use of SUSTOL with successive emetogenic chemotherapy cycles for more than 6 months is not recommended.
- See full prescribing information for recommended dosage of concomitant dexamethasone.

Renal Impairment (2.3):

- In patients with moderate renal impairment (CL_{cr} 30-59 mL/min), administer SUSTOL not more frequently than once every 14 days.
- Avoid SUSTOL in patients with severe renal impairment (CL_{cr} < 30 mL/min).

DOSAGE FORMS AND STRENGTHS

Extended-Release Injection: 10 mg/0.4 mL in a single-dose, pre-filled syringe. (3)

CONTRAINDICATIONS

Hypersensitivity to granisetron, any of the components of SUSTOL, or to any of the other 5-HT₃ receptor antagonists. (4, 5.3)

WARNINGS AND PRECAUTIONS

- **Injection site reactions (ISRs), including infection, bleeding, pain, nodules, swelling and induration:** Monitor for ISRs following SUSTOL injection. Inform patients that some ISRs may occur 2 weeks or more after SUSTOL administration. In patients receiving antiplatelet agents or anticoagulants, consider the increased risk of bruising or severe hematoma prior to the use of SUSTOL. (5.1)
- **Gastrointestinal disorders:** Monitor for constipation and consider optimizing patients' current bowel regimens used for managing preexisting constipation. Also monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. Instruct patients to seek immediate medical care if signs and symptoms of ileus occur. (5.2)
- **Hypersensitivity reactions:** Serious reactions have been reported and may occur up to 7 days or longer following SUSTOL administration and may have an extended course. If a reaction occurs, administer appropriate treatment and monitor until signs and symptoms resolve. (5.3)
- **Serotonin syndrome:** Reported with 5-HT receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue SUSTOL and initiate supportive treatment. If concomitant use of SUSTOL with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome. (5.4, 7.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 3%) are injection site reactions, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, asthenia, and gastroesophageal reflux. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Heron Therapeutics, Inc. at 844-HERON11 (1-844-437-6611) and www.SUSTOL.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- For subcutaneous injection only.
- *SUSTOL is intended for administration by a health care provider.*
- SUSTOL is supplied as a refrigerated kit consisting of a single-dose, pre-filled, sterile syringe, a special thin walled 18 Ga 5/8" administration needle, two syringe warming pouches, and a Point Lok[®] needle protection device. *See the SUSTOL Instructions for Use included in the kit for complete administration instructions with illustrations.*
- *Do not substitute non-kit components for any of the components from the kit for administration.*

Preparation

1. At least 60 minutes prior to administration, remove the SUSTOL kit from refrigeration.
2. Unpack the kit to allow the SUSTOL syringe and *all other contents to warm to room temperature.*
3. Activate one of the syringe warming pouches, and wrap the SUSTOL syringe in the warming pouch for *5 to 6 minutes to warm SUSTOL to body temperature.*
4. Prior to administration, inspect the SUSTOL syringe visually for particulate matter and discoloration. Note that the syringe is amber colored glass. SUSTOL should not be administered if particulate matter or discoloration is observed, the tip cap is missing or has been tampered with, or if the Luer fitting is missing or dislodged.

Administration

1. Use standard aseptic technique when performing the injection.
2. Administer SUSTOL as a single subcutaneous injection in the skin of the back of the upper arm or in the skin of the abdomen at least one inch away from the umbilicus. Avoid injecting SUSTOL anywhere the skin is burned, hardened, inflamed, swollen, or otherwise compromised [*see Warnings and Precautions (5.1)*]. Topical anesthetic may be used at the injection site prior to administration of SUSTOL.
3. Due to the viscosity of SUSTOL, the time required for injection is greater than most medications administered subcutaneously. SUSTOL requires a slow, sustained injection which **may take up to 20 to 30 seconds**. Pressing the plunger harder will NOT expel SUSTOL faster.

2.2 Recommended Dosage

The recommended dosage of SUSTOL is 10 mg administered subcutaneously. Administer SUSTOL in combination with dexamethasone at least 30 minutes before the initiation of MEC or AC combination chemotherapy. Administer SUSTOL on Day 1 of chemotherapy and not more frequently than once every 7 days because of the extended-release properties of the formulation.

For patients receiving MEC, the recommended dexamethasone dosage is 8 mg intravenously on Day 1. For patients receiving AC combination chemotherapy regimens, the recommended dexamethasone dosage is 20 mg intravenously on Day 1, followed by 8 mg orally, twice a day, on Days 2, 3 and 4.

If SUSTOL is administered with an NK₁ receptor antagonist, see the prescribing information of the NK₁ receptor antagonist for the recommended dexamethasone dosage.

2.3 Dosage Adjustment in Renal Impairment

In patients with moderate renal impairment (creatinine clearance of 30 to 59 mL/min), administer SUSTOL on Day 1 of chemotherapy and not more frequently than once every 14 days. Avoid SUSTOL in patients with severe renal impairment (creatinine clearance of less than 30 mL/min) [see *Use in Specific Populations (8.6)*].

3 DOSAGE FORMS AND STRENGTHS

SUSTOL is supplied as a clear, colorless to slightly yellow, viscous liquid and is available as an:

- Extended-Release Injection: 10 mg/0.4 mL in a single-dose pre-filled syringe.

4 CONTRAINDICATIONS

SUSTOL is contraindicated in patients with hypersensitivity to granisetron, any of the components of SUSTOL, or to any of the other 5-HT₃ receptor antagonists [see *Warnings and Precautions (5.3)*, *Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Injection Site Reactions (ISRs)

Infections

Infections at the injection site occurred in 0.4% (7 of 1814) of patients with cancer and 0.2% (1 of 412) of healthy subjects in clinical trials. Infections had a median onset of 9 days (range 7 to 16 days) following SUSTOL administration. One patient who was neutropenic at the time of the infection was hospitalized. All patients with infection were treated with antibiotics and had complete resolution.

Bruising and/or hematomas

Bruising and/or hematomas at the injection site occurred in 426 of 1131 (38%) patients treated with SUSTOL 10 mg with a median time to onset of 2 days. Bruising and/or hematomas with a delayed onset (onset 5 or more days following SUSTOL administration) were reported in 175 (15%) patients. Severe bruising or hematoma (e.g., greater than 4 cm bruise or hematoma) occurred in 3% of patients. Patients receiving concomitant anticoagulant and antiplatelet medications were at greater risk for severe injection site bruising and hematomas.

Bleeding

Bleeding at the injection site occurred in 70 of 1814 (4%) patients treated with SUSTOL. One patient required emergency management. Bleeding for longer than 5 days was reported in 23 (1%) patients.

Pain and Tenderness

In a clinical trial that collected information about injection site pain and tenderness from patient diaries, pain with or without tenderness at the injection site was reported by 91 of 456 (20%) of patients treated with SUSTOL 10 mg, and an additional 50 of 456 (11%) of patients reported tenderness without pain. Pain and/or tenderness severe enough to require taking pain medication, interfere with patient activity level, or cause significant discomfort at rest was reported in 2% of patients. Among all patients who reported pain and/or tenderness with SUSTOL 10 mg in clinical trials, the median duration was 5 days, and pain lasting longer than 7 days occurred in 6% of patients.

Nodules

Nodules at the injection site occurred in 203 of 1131 (18%) of patients treated with SUSTOL 10 mg. Nodules persisted for a median of 15 days and 73 patients (6%) had nodules with durations longer than 21 days.

Management of ISRs

- Monitor patients for ISRs following SUSTOL injection. Some ISRs (infections, bruising, and hematoma) may occur up to 2 weeks or more after SUSTOL administration.
- In patients receiving antiplatelet agents or anticoagulants, consider the increased risk of bruising or severe hematoma prior to the use of SUSTOL.
- In patients with ongoing or unresolved ISRs, administer SUSTOL at a site away from areas affected by ISRs [*see Dosage and Administration (2.1)*].

5.2 **Gastrointestinal Disorders**

Constipation

In clinical trials, 224 of 1131 (20%) of patients treated with SUSTOL 10 mg reported constipation compared to 13% to 15% in the 5-HT₃ receptor antagonist control arms. Hospitalization due to constipation or fecal impaction was reported in 5 SUSTOL-treated patients (0.3%). Monitor patients for the development of constipation while receiving treatment with SUSTOL taking into consideration the extended-release properties of the SUSTOL polymer formulation over at least 5 to 7 days, particularly in patients receiving opioid medications. Consider optimizing bowel regimens in patients using SUSTOL.

Progressive Ileus and Gastric Distention

SUSTOL may mask a progressive ileus and/or gastric distention. This should be particularly considered before use of SUSTOL in patients who have had recent abdominal surgery. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction.

5.3 **Hypersensitivity Reactions**

Hypersensitivity reactions, including anaphylaxis, have been reported in granisetron-treated patients who have exhibited hypersensitivity to other 5-HT₃ receptor antagonists [*see Contraindications (4)*]. Avoid SUSTOL in patients who have had hypersensitivity reactions to other 5-HT₃ receptor antagonists [*see Contraindications (4)*].

Due to the extended-release properties of the SUSTOL polymer formulation, exposure to granisetron may continue for 5 to 7 days following administration. Hypersensitivity reactions may occur up to 7 days or longer following SUSTOL administration and may have an extended course. Inform patients of the signs and symptoms of

anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur. If hypersensitivity reactions occur, administer appropriate treatment and monitor patients until signs and symptoms resolve.

5.4 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT₃ receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT₃ receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT₃ receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of SUSTOL and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue SUSTOL and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if SUSTOL is used concomitantly with other serotonergic drugs [*see Drug Interactions (7.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Injection Site Reactions [*see Warnings and Precautions (5.1)*]
- Gastrointestinal Disorders [*see Warnings and Precautions (5.2)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.3)*]
- Serotonin Syndrome [*see Warnings and Precautions (5.4)*]

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.

SUSTOL

The safety of a 10 mg subcutaneous dose of SUSTOL was evaluated in two double-blind, randomized, active-controlled studies, in which 210 patients (23%) received MEC and 467 patients (51%) received AC combination chemotherapy. The data described below reflect exposure to a single 10 mg dose of SUSTOL in 924 patients whose mean age was 56 years (range 19 to 91 years); 76% of patients were female; 70% of patients were Caucasian, 16%, Asian, 10% Black, and 4% other races. Dexamethasone was co-administered with SUSTOL in Study 1 and Study 2 and an NK1 receptor antagonist was co-administered with SUSTOL in Study 2.

Table 1 lists the most common adverse reactions reported in at least 3% of patients following a single-dose of SUSTOL 10 mg in Study 1 and/or Study 2. Overall, injection site reactions (ISRs) were the most common group of

adverse reactions in SUSTOL-treated patients. Specific types of ISRs reported by SUSTOL-treated patients are shown in [Table 2](#).

Table 1. Adverse Reactions Occurring in at Least 3% of Patients Treated with SUSTOL 10 mg in Study 1 and/or Study 2

| Adverse Reaction | Study 1 | | Study 2 | |
|--|-------------------------------------|--|-------------------------------------|--|
| | SUSTOL 10 mg subcutaneous (N=468) % | Palonosetron hydrochloride 0.25 mg intravenous (N=463) % | SUSTOL 10 mg subcutaneous (N=456) % | Ondansetron 0.15 mg/kg intravenous (N=459) % |
| Injection Site Reactions, any ^a | 37 | 15 ^b | 62 | See footnote ^b |
| Constipation | 14 | 11 | 22 | 15 |
| Fatigue | 11 | 10 | 21 | 24 |
| Headache | 9 | 9 | 13 | 19 |
| Diarrhea | 8 | 7 | 9 | 8 |
| Abdominal Pain | 7 | 7 | 7 | 4 |
| Insomnia | 4 | 2 | 5 | 6 |
| Dyspepsia | 3 | 3 | 6 | 7 |
| Dizziness | 3 | 2 | 5 | 5 |
| Asthenia | 4 | 6 | 2 | 2 |
| Gastroesophageal Reflux | 1 | 1 | 5 | 4 |

^a Rates of individual injection site reactions (ISRs) are shown in [Table 2](#)

^b The placebo subcutaneous injection for Study 1 was normal saline and for Study 2 was a SUSTOL-matched control consisting of the SUSTOL polymer vehicle without active drug.

Injection Site Reactions (ISRs)

Injection site reactions occurred in 37% (175/468) in Study 1, Cycle 1 only, and 62% (281/456) in Study 2 of SUSTOL-treated patients. The ISR manifestations included pain, erythema, mass/nodule, swelling/induration, and bleeding. The incidence of individual ISRs is shown in

[Table 2](#). Patients may have experienced one or more types of injection site reactions; a total of 213 of 924 patients had three or more.

ISR reporting procedures included both investigator- and patient-reported outcomes in Study 2, while Study 1 used only investigator reporting.

Table 2. Injection Site Adverse Reactions Following a Single 10 mg SUSTOL Dose

| Injection Site Reaction | Study 1 Treatment Arm (Subcutaneous Injection) | | Study 2 ^{a,b} SUSTOL (N=456) % |
|------------------------------------|---|--------------------------------|--|
| | SUSTOL (N=468) % | Saline Control (N=463) % | |
| Total Subjects with at least 1 ISR | 37 | 15 | 62 |
| Pain | 3 | 1 | 20 |
| Tenderness | 4 | 1 | 27 |
| Bruising/Hematoma | 22 | 10 | 45 |
| Bleeding | 2 | 1 | 4 |
| Erythema/Redness | 11 | 3 | 17 |
| Swelling/Induration | 1 | 0 | 10 |
| Mass/Nodule | 11 | 1 | 18 |
| Infection at injection site | <1 | 0 | 1 |
| Other ^c | 2 | 1 | 1 |

^a Patient diary was used in Study 2 to collect ISR information daily.

^b The placebo subcutaneous injection for Study 2 was a SUSTOL-matched control consisting of the SUSTOL polymer vehicle without active drug. ISR data for this group are not shown.

^c Other includes injection site discoloration, vesicles, irritation, lipoma, paresthesia, pruritus, rash, reaction, scab, scar, and warmth.

Less common adverse reactions reported in less than 3% of SUSTOL-treated patients in clinical trials are syncope, elevation of serum transaminase levels, pancreatitis, atrial fibrillation, somnolence, flushing, and hypersensitivity reactions (e.g., anaphylaxis, urticaria).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of other formulations of granisetron. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

| System Organ Class | Adverse Reactions |
|-----------------------|--|
| <i>Cardiovascular</i> | bradycardia, chest pain, palpitations, sick sinus syndrome |

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue SUSTOL and initiate supportive treatment [see *Warnings and Precautions (5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of SUSTOL in pregnant women. Limited published data on granisetron use during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits administered granisetron hydrochloride during organogenesis at intravenous doses up to 61 times and 41 times respectively the maximum recommended human dose (MRHD) of SUSTOL 10 mg/week [*see Data*].

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

Data

Animal Data

Reproduction studies with granisetron hydrochloride have been performed in pregnant rats following administration during the period of organogenesis at intravenous doses up to 9 mg/kg/day (approximately 61 times the maximum recommended human dose (MRHD) of SUSTOL 10 mg/week, based on body surface area) and oral doses up to 125 mg/kg/day (approximately 851 times the MRHD of SUSTOL 10 mg/week, based on body surface area). Reproduction studies have been performed in pregnant rabbits in which granisetron hydrochloride was administered during the period of organogenesis at intravenous doses up to 3 mg/kg/day (approximately 41 times the MRHD of SUSTOL 10 mg/week, based on body surface area) and at oral doses up to 32 mg/kg/day (approximately 436 times the MRHD of SUSTOL 10 mg/week, based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to granisetron hydrochloride.

Reproduction studies with the polymer vehicle for SUSTOL have been performed in pregnant rats and rabbits following administration of the polymer vehicle during the period of organogenesis at subcutaneous doses up to 0.295 and 1.18 g per day, respectively, (approximately 45 and 36 times, respectively the amount of polymer vehicle present in the maximum recommended /weekly single human dose of SUSTOL, based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to the polymer vehicle. A pre and postnatal development study with the polymer vehicle for SUSTOL in rats showed no evidence of any adverse effects on pre and postnatal development at subcutaneous doses (administered on gestation days 7 through lactation day 20) up to 0.295 g per day (approximately 45 times the amount of polymer vehicle present in the maximum recommended /weekly single human dose of SUSTOL, based on body surface area).

8.2 Lactation

Risk Summary

There are no data on the presence of SUSTOL in human milk, the effects of SUSTOL on the breastfed infant, or the effects of SUSTOL on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of SUSTOL to an infant during lactation; therefore, the developmental and health benefits of breastfeeding

should be considered along with the mother's clinical need for SUSTOL and any potential adverse effects on the breastfed infant from SUSTOL or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SUSTOL in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

Of the 738 patients administered 10 mg of SUSTOL in the comparator controlled studies, 177 (24%) were 65 and over while 39 (5%) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

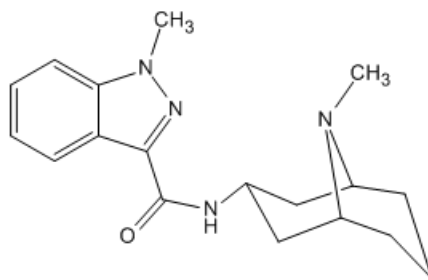
Breakdown products of the polymer vehicle in SUSTOL can be detected in urine of healthy subjects [see *Clinical Pharmacology (12.5)*]. There are no pharmacokinetic data regarding elimination of the polymer vehicle of SUSTOL in patients with renal impairment and the clinical significance of potential prolonged elimination is not known. Avoid SUSTOL in patients with severe renal impairment. In patients with moderate renal impairment, administer SUSTOL not more frequently than once every 14 days [see *Dosage and Administration (2.3)*].

10 OVERDOSAGE

There is no specific antidote for granisetron overdose. In the case of overdose, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride, as a single intravenous injection, has been reported without symptoms or with only the occurrence of headache.

11 DESCRIPTION

SUSTOL (granisetron) extended-release injection, contains granisetron, a serotonin-3 (5-HT₃) receptor antagonist. Granisetron is 1-methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide with a molecular weight of 312.4. Its empirical formula is C₁₈H₂₄N₄O, with the following chemical structure:



Granisetron is a white to off-white crystalline solid that is insoluble in water.

SUSTOL is a sterile, clear, colorless to slightly yellow, viscous liquid supplied in a single-dose, pre-filled syringe. Each syringe contains 10 mg granisetron incorporated in an extended-release polymer formulation; the inactive ingredients are triethylene glycol poly(orthoester) polymer, 392 mg and polyethylene glycol monomethyl ether, NF, 98 mg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Granisetron is a selective 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT₁, 5-HT_{1A}, 5-HT_{1B/C}, 5-HT₂; for alpha₁-, alpha₂-, or beta-adrenoreceptors; for dopamine-D₂; or for histamine-H₁; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT₃ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT₃ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT₃ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of SUSTOL on QTc prolongation was evaluated in a double-blind randomized, four-way crossover, placebo and positive (moxifloxacin) controlled study in 51 adult male and female healthy subjects. At 2-fold the recommended dosage of SUSTOL, there was no significant effect on the QTcF interval.

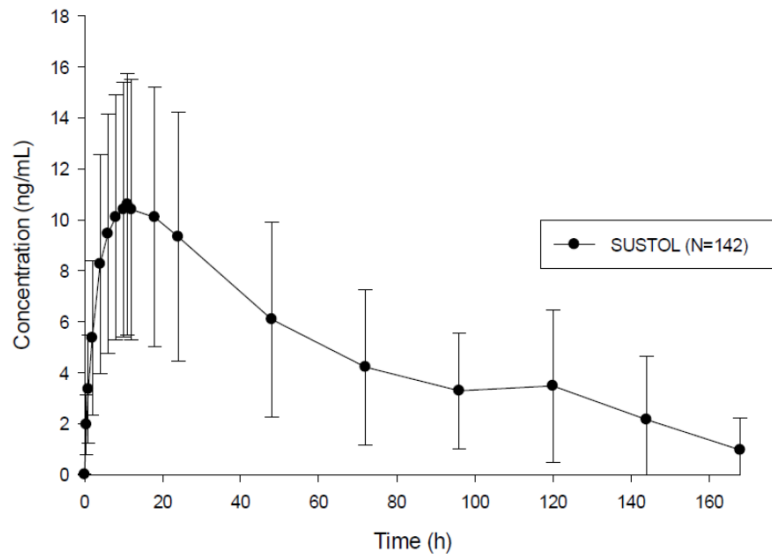
In 142 cancer patients, 24-hour Holter monitoring and 12-lead ECGs were evaluated. QTcF greater than 450 msec were seen in a total of 20 (19%) patients administered SUSTOL and 9 (31%) patients administered intravenous palonosetron hydrochloride. In the SUSTOL group, one patient had a QTcF interval greater than 500 msec and 4 patients had a change from baseline QTcF greater than 60 msec.

12.3 Pharmacokinetics

Absorption

SUSTOL is an extended-release injection formulation of granisetron using a polymer-based drug delivery system. Following a single-dose administration in healthy subjects, granisetron is released from the polymer over an extended period of time and remains detectable in plasma for 7 days post-dose (Figure 1). A mean concentration of 3.5 ng/mL (range 0 to 14 ng/mL) was observed at 5 days post-dose [*see Warnings and Precautions (5.3)*].

Figure 1. Plasma Concentrations of Granisetron Over 7 Days after a Single Subcutaneous Injection of SUSTOL in Healthy Subjects



The granisetron pharmacokinetic parameters following injection of SUSTOL were similar between the abdomen and upper arm injection sites as shown in Table 3.

Table 3. Granisetron Pharmacokinetic Parameters Following a Single 10 mg Subcutaneous Injection of SUSTOL in Healthy Subjects by Injection Site Location

| Parameter ^a | Injection Site Location | |
|----------------------------------|-------------------------|--------------------|
| | Abdomen N=113 | Upper Arm N=113 |
| C _{max} (ng/mL) | 9.8 ± 4.8 | 10.8 ± 4.6 |
| T _{max} (hours) [range] | 12 [1 to 144] | 11 [1 to 120] |
| AUC _{inf} ng.h/mL | 680 ± 362 | 720 ± 366 |

^a Values shown are mean ± SD, except for T_{max} where median [range] are shown.

In patients, peak plasma granisetron concentrations were delayed compared to healthy subjects with a median T_{max} of approximately 24 hours.

Distribution

Plasma protein binding of granisetron is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Metabolism

Published data suggests that granisetron is metabolized by CYP1A1 and CYP3A4. Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation.

Elimination

Metabolism: Following a single 10 mg subcutaneous injection of SUSTOL, the terminal elimination half-life of granisetron was approximately 24 hours and was comparable between healthy subjects and patients.

Granisetron clearance is predominantly by hepatic metabolism.

Excretion: Approximately 12% of a granisetron dose, following intravenous administration of granisetron hydrochloride, is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine and 34% in the feces.

Specific Populations

Age: Geriatric Population: In a pooled analysis of samples collected from 56 cancer patients in 3 clinical studies, the mean C_{max} and mean AUC_{0-inf} for granisetron following subcutaneous administration of a 10 mg dose of SUSTOL was 39% and 76% higher in patients 65 years of age and older than in patients less than 65 years of age. These pharmacokinetic differences are not considered clinically meaningful taking into consideration the small number of patients 65 years of age and older in the analysis ($n = 16$) and the high inter-patient variability.

Sex: In a pooled analysis of samples collected from 56 cancer patients in 3 clinical studies, the mean C_{max} and mean AUC_{0-inf} for granisetron following subcutaneous administration of a 10 mg dose of SUSTOL was 34% and 132% higher in males than in females. These pharmacokinetic differences are not considered meaningful taking into consideration the small number of males in the analysis ($n = 13$) and the high inter-patient variability.

Renal Impairment: The total clearance of granisetron was similar in patients with severe renal failure compared to patients with normal renal function following a single 40 mcg/kg intravenous dose of granisetron hydrochloride.

Breakdown products of the polymer vehicle in SUSTOL can be detected in urine of healthy subjects [see *Clinical Pharmacology (0)*]. There are no pharmacokinetic data regarding elimination of the polymer vehicle of SUSTOL in patients with renal impairment [see *Dosage and Administration (2.3)*, *Use in Specific Populations (8.6)*].

Hepatic Impairment: The total clearance of granisetron was approximately 50% lower in patients with hepatic impairment (neoplastic liver disease) compared to patients with normal hepatic function following a single 40 mcg/kg intravenous dose of granisetron hydrochloride. The high inter-subject variability in the pharmacokinetic parameters of granisetron in patients with hepatic impairment limits the interpretation of these findings.

Drug Interaction Studies

Effect of Other Drugs on Granisetron

Granisetron is metabolized by the hepatic cytochrome P-450 drug-metabolizing enzymes CYP1A1 and CYP3A4. Inducers or inhibitors of CYP1A1 and CYP3A4 enzymes may affect the clearance and half-life of granisetron. In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of granisetron. However, the potential for an *in vivo* pharmacokinetic interaction with ketoconazole is not known.

Phenobarbital: Administration of intravenous granisetron hydrochloride with phenobarbital, an enzyme inducer, resulted in a 25% increase in total plasma clearance of granisetron. The clinical significance of this interaction is not known.

Effect of Granisetron on Other Drugs

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system *in vitro*. In addition, the *in vitro* activity of the cytochrome P-450 subfamily 3A4, which is involved in the metabolism of some narcotic analgesics, is not modified by granisetron.

12.5 Polymer Breakdown Products

In a metabolic fate study conducted in healthy subjects, breakdown products of the triethylene glycol poly(orthoester) polymer vehicle of the SUSTOL formulation including triethylene glycol (TEG), pentaerythritol (PE), and the oxidative metabolite of TEG, triethylene glycol monocarboxylic acid (TEG acid) were detected in urine with incomplete recovery by the end of study period (10 days). Accumulation of these metabolites in plasma was not noted. The recovery of the polymer load was incomplete in this study and could be due to insufficient sampling and assay sensitivity issues preventing detection of additional metabolites [see *Dosage and Administration (2.3)*, *Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals with SUSTOL have not been performed to evaluate the carcinogenic potential of the polymer vehicle of SUSTOL. In a 24-month carcinogenicity study of granisetron hydrochloride, rats were treated orally with 1, 5 or 50 mg/kg/day. The 50 mg/kg/day dose was reduced to 25 mg/kg/day during week 59 due to toxicity. For a 60 kg person, the 1, 5, and 25 mg/kg/day doses represent approximately 7, 34 and 169 times, respectively, the maximum recommended human dose (MRHD) (10 mg granisetron/week, approximately 6.2 mg/m²/week) of SUSTOL 10 mg/week, based on body surface area. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in male rats treated with 5 mg/kg/day (approximately 34 times the MRHD of SUSTOL 10 mg/week, based on body surface area) and above, and in female rats treated with 25 mg/kg/day (approximately 169 times the MRHD of SUSTOL 10 mg/week, based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (approximately 7 times the MRHD of SUSTOL 10 mg/week, based on body surface area) in male rats and 5 mg/kg/day (approximately 34 times the MRHD of SUSTOL 10 mg/week, based on body surface area) in female rats.

In a 12-month oral toxicity study with granisetron hydrochloride, rats were treated at 100 mg/kg/day (approximately 677 times the MRHD of SUSTOL 10 mg/week, based on body surface area). This dose produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24 month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive. Because of the tumor findings in rat studies, SUSTOL should be prescribed only at the dose and for the indication recommended [see *Indications and Usage (1)*, *Dosage and Administration (2.2)*].

Granisetron hydrochloride was not mutagenic in an *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) assays. However, granisetron hydrochloride was positive in a mouse lymphoma assay with metabolic activation and produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Neither SUSTOL nor the polymer vehicle for SUSTOL was mutagenic in the Ames test, mouse lymphoma assay, and the *in vivo* rat bone marrow micronucleus test.

Granisetron hydrochloride at subcutaneous doses up to 6 mg/kg/day (approximately 40 times the MRHD of SUSTOL 10 mg/week, based on body surface area), and oral doses up to 100 mg/kg/day (approximately 677 times the MRHD of SUSTOL 10 mg/week, based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

The polymer vehicle for SUSTOL at subcutaneous doses up to 0.295 g per day (approximately 45 times the amount of polymer vehicle present in the maximum recommended /weekly single human dose of SUSTOL, based on body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

In a randomized, multicenter, double-blind, parallel group study, a single 10 mg subcutaneous dose of SUSTOL was compared to a single 0.25 mg intravenous dose of palonosetron hydrochloride in cancer patients administered moderately emetogenic (MEC) or anthracycline plus cyclophosphamide (AC) combination chemotherapy. SUSTOL or palonosetron hydrochloride was administered 30 minutes prior to chemotherapy on Day 1. Patients also received either 8 or 20 mg intravenous dexamethasone on Day 1 depending on chemotherapy regimen. Patients who received 20 mg of intravenous dexamethasone also received oral dexamethasone 8 mg twice daily on Days 2, 3, and 4.

In this study of 733 patients (371 in the SUSTOL 10 mg arm and 362 in the palonosetron arm), 79% of patients were female and 63% were Caucasian. The mean age was 57 years (range 22 to 91 years), 55% received MEC and 45% received AC combination chemotherapy regimens. The most common MEC regimens were carboplatin/paclitaxel (31%).

The primary endpoints were proportion of patients with complete response (CR) [defined as no emetic episodes (vomiting or retching) and no use of rescue medication] during the acute phase (0 to 24 hours) and the delayed phase (>24 to 120 hours) following the administration of chemotherapy in Cycle 1. The study design allowed for assessment of non-inferiority of SUSTOL to palonosetron hydrochloride in the acute and delayed phase of MEC and of AC combination chemotherapy.

Non-inferiority of SUSTOL to palonosetron hydrochloride was demonstrated in the acute and delayed phases of MEC and of AC combination chemotherapy [Table 4].

Table 4. Number and Percentage of Patients Who Achieved Complete Response with MEC or AC Combination Chemotherapy[‡]

Moderately Emetogenic Chemotherapy

| Complete Response | SUSTOL 10 mg subcutaneous N=200 n (%) | Palonosetron hydrochloride, 0.25 mg intravenous N=206 n (%) | Difference (95% CI[§]): SUSTOL minus Palonosetron |
|---------------------------------|--|--|---|
| Acute Phase (0 – 24 hours) | 166 (83) | 183 (89) | -6 (-13, 1) |
| Delayed Phase (>24 – 120 hours) | 137 (69) | 144 (70) | -1 (-10, 8) |

[‡] Complete response defined as no emetic episodes and no use of rescue medications.

[§] This study was designed to show non-inferiority in the acute phase or delayed phase for patients receiving moderately emetogenic chemotherapy. A lower bound greater than -15% demonstrates non-inferiority between SUSTOL and comparator.

AC Combination Chemotherapy

| Complete Response | SUSTOL 10 mg subcutaneous N=171 n (%) | Palonosetron hydrochloride, 0.25 mg intravenous N=156 n (%) | Difference (95% CI^{§§}): SUSTOL minus Palonosetron |
|---------------------------------|--|--|--|
| Acute Phase (0 – 24 hours) | 120 (70) | 99 (64) | 6 (-3, 17) |
| Delayed Phase (>24 – 120 hours) | 85 (50) | 74 (47) | 2 (-9, 13) |

^{§§} This study was designed to show non-inferiority in the acute phase and superiority in the delayed phase. A lower bound greater than -15% demonstrates non-inferiority between SUSTOL and comparator. Because a lower bound did not exceed 0%, superiority was not demonstrated between SUSTOL and comparator.

16 HOW SUPPLIED/STORAGE AND HANDLING

SUSTOL extended-release injection is supplied in cartons of six kits (NDC 47426-101-06); each kit contains:

- One sterile single-dose amber colored glass syringe which contains 10 mg granisetron/0.4 mL,
- One sterile 18 Ga 5/8” special thin walled administration needle,
- Two sodium acetate syringe warming pouches,
- One Point Lok needle protection device.

Storage

Store SUSTOL in the refrigerator at 2°C to 8°C (36°F to 46°F).

SUSTOL can be placed back in the refrigerator after being kept at room temperature. SUSTOL can remain at room temperature for up to a maximum of 7 days.

Protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

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

Administration

- SUSTOL is intended for subcutaneous injection by a health care provider.

Injection Site Reactions [see Warnings and Precautions (5.1)]

- Inform the patient that ISRs may occur and may include infections, bruising and/or hematomas, bleeding, pain and tenderness, and nodules.
- Inform the patient that some ISRs (infections, bruising, and hematoma) may occur up to 2 weeks or more after SUSTOL administration.
- Instruct the patient to seek immediate medical care for the following ISRs:
 - signs of infection at the injection site.
 - injection site bleeding that is severe or lasts for longer than one day.
- Advise the patient to tell their healthcare provider if they experience:
 - pain or tenderness severe enough to require treatment with pain medication or interfere with daily activity.
 - bruising and/or hematoma or a persistent nodule at the injection site.

Gastrointestinal

Advise the patient to report new or worsening constipation to their healthcare provider and seek immediate medical care if signs and symptoms of an ileus occur [Warnings and Precautions (5.2)].

Hypersensitivity reactions

Advise the patient that hypersensitivity reactions may occur up to 7 days or longer following SUSTOL administration. Inform the patient of the signs and symptoms of hypersensitivity reactions, and have them seek immediate medical care should signs and symptoms occur [see Warnings and Precautions (5.1, 5.3)].

Serotonin Syndrome

Advise the patient of the possibility of serotonin syndrome, especially with concomitant use of SUSTOL and another serotonergic agent such as medications to treat depression and migraines. Advise the patient to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms [see Warnings and Precautions (5.4)].

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MEDICATION GUIDE
SUSTOL® (sus'tol)
(granisetron)
extended-release injection, for subcutaneous use

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

SUSTOL can cause serious side effects, including:

- Injection site reactions. Some injection site reactions may be serious and require medical care. Injection site reactions may include infections, bruising, swelling that is caused by blood that collects under the skin (hematoma), bleeding, pain and tenderness, and small bumps (nodules) at the injection site. Infections, bruising, and hematomas can happen up to 2 weeks or more after receiving SUSTOL.

Tell your healthcare provider if you have:

- pain or tenderness that you need to take pain medicine for or if you have pain that interferes with your daily activity.
- bruising, hematoma, or a nodule at the injection site that does not go away. Your risk of severe bruising and hematomas at the injection site is increased if you take a blood thinner medicine (anticoagulant or antiplatelet medicine).

Get medical care right away if you have:

- signs of an infection at the injection site, including continued redness or warmth, or if you have a fever.
- bleeding at the injection site that is severe or lasts for longer than 24 hours.
- Stomach and intestinal problems. Problems having a bowel movement (constipation) that may be serious, can happen up to 7 days after treatment with SUSTOL. These problems may be more likely in people taking opioid pain medicines. SUSTOL can make it harder to identify certain stomach and bowel problems you may have. Tell your healthcare provider if you have constipation or your constipation worsens after you receive SUSTOL. Get medical care right away if you have pain or swelling in your stomach-area (abdomen).
- Serious allergic reactions. Serious allergic reactions have happened in people who receive SUSTOL and who have had allergic reactions to other medicines used to help prevent nausea and vomiting called 5-HT₃ receptor antagonists. Serious allergic reactions can happen up to 7 days or longer after treatment. Get emergency medical help right away if you have any signs or symptoms of a serious allergic reaction, including:
 - hives
 - swollen face
 - breathing trouble
 - chest pain

What is SUSTOL?

- SUSTOL is a prescription medicine called an "antiemetic."
- SUSTOL is used in adults to help prevent the nausea and vomiting that happens right away or later with certain anti-cancer medicines (chemotherapy).

It is not known if SUSTOL is safe and effective in children under 18 years of age.

Who should not receive SUSTOL?

Do not receive SUSTOL if you are allergic to:

- granisetron or any of the ingredients in SUSTOL. See the end of this Medication Guide for a complete list of ingredients in SUSTOL.
- any other 5-HT₃ receptor antagonist medicine used to help prevent nausea and vomiting.

What should I tell my healthcare provider before receiving SUSTOL?

Before receiving SUSTOL, tell your healthcare provider about all of your medical conditions, including if you:

- have constipation
- have had recent stomach-area (abdominal) surgery
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if SUSTOL will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SUSTOL passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you will receive SUSTOL.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using SUSTOL with certain other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive SUSTOL?

- SUSTOL will be given to you by an injection under your skin (subcutaneously) in the back of your upper arm or in your stomach-area (abdomen) on Day 1 of your chemotherapy cycle.
- SUSTOL will be given to you by a healthcare provider.
- SUSTOL is usually given about 30 minutes before you receive your anti-cancer medicine (chemotherapy).
- You should not receive SUSTOL more often than 1 time every 7 days.

What are the possible side effects of SUSTOL?

SUSTOL may cause serious side effects, including:

- See “What is the most important information I should know about SUSTOL?”
- Serotonin Syndrome. A possible life-threatening problem called serotonin syndrome can happen with medicines called 5-HT₃ receptor antagonists, including SUSTOL, especially when used with medicines used to treat depression and migraine headaches called serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and certain other medicines. Tell your healthcare provider or nurse right away if you have any of the following symptoms of serotonin syndrome:
 - agitation, seeing things that are not there (hallucinations), confusion, or coma
 - fast heartbeat or unusual and frequent changes in your blood pressure
 - dizziness, sweating, flushing, or fever
 - tremors, stiff muscles, muscle twitching, overactive reflexes, or loss of coordination
 - seizures
 - nausea, vomiting, or diarrhea

The most common side effects of SUSTOL include: injection site reactions, constipation, fatigue, headache, diarrhea, stomach-area (abdominal) pain, trouble sleeping or falling asleep, indigestion, dizziness, weakness, and heartburn.

These are not all the possible side effects of SUSTOL. Tell your healthcare provider if you have any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of SUSTOL

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

What are the ingredients in SUSTOL?

Active ingredient: granisetron

Inactive ingredients: triethylene glycol poly(orthoester) polymer and polyethylene glycol monomethyl ether

Manufactured by: Lifecore Biomedical, Chaska, MN 55318

Marketed by: Heron Therapeutics, Inc., Redwood City, CA 94063

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For more information, go to www.SUSTOL.com or call 1-844-437-6611.