

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Sancuso (Granisetron Transdermal System) safely and effectively. See full prescribing information for Sancuso.

Sancuso (Granisetron Transdermal System)
Initial U.S. Approval: September 2008

INDICATIONS AND USAGE

Sancuso is a serotonin subtype 3 (5-HT₃) receptor antagonist indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days. (1)

DOSAGE AND ADMINISTRATION

Apply a single transdermal system (patch) to the upper outer arm a minimum of 24 hours before chemotherapy. The patch may be applied up to a maximum of 48 hours before chemotherapy as appropriate. Remove the patch a minimum of 24 hours after completion of chemotherapy. The patch can be worn for up to 7 days depending on the duration of the chemotherapy regimen. (2)

DOSAGE FORMS AND STRENGTHS

52 cm² patch containing 34.3 mg of granisetron delivering 3.1 mg per 24 hours (3)

CONTRAINDICATIONS

Known hypersensitivity to granisetron or to any of the components of the patch (4)

WARNINGS AND PRECAUTIONS

- Granisetron may mask a progressive ileus and/or gastric distention caused by the underlying condition. (5.1)

- Mild application site reactions have occurred; remove patch if severe reactions or a generalized skin reaction occur. (5.2)
- Avoid direct exposure of application site to natural or artificial sunlight by covering with clothing while wearing the patch and for 10 days after removing it. (5.3)

ADVERSE REACTIONS

The most common adverse reaction is constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ProStrakan Inc. at 1-800-SANCUSO and www.Sancuso.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- No clinically relevant drug interactions have been reported in clinical studies with Sancuso. (7)

USE IN SPECIFIC POPULATIONS

- Use during pregnancy only if clearly needed. (8.1)
- Use caution when administering to nursing women. (8.3)
- Safety and effectiveness in pediatric patients have not been established. (8.4)
- Clinical studies of Sancuso did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE	6.2 Granisetron Experience	12.2 Pharmacodynamics
2 DOSAGE AND ADMINISTRATION	7 DRUG INTERACTIONS	12.3 Pharmacokinetics
2.1 Adults	8 USE IN SPECIFIC POPULATIONS	13 NONCLINICAL TOXICOLOGY
3 DOSAGE FORMS AND STRENGTHS	8.1 Pregnancy	13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
4 CONTRAINDICATIONS	8.3 Nursing Mothers	13.2 Phototoxicity
5 WARNINGS AND PRECAUTIONS	8.4 Pediatric Use	14 CLINICAL STUDIES
5.1 Gastrointestinal	8.5 Geriatric Use	16 HOW SUPPLIED/STORAGE AND HANDLING
5.2 Skin Reactions	8.6 Renal Failure or Hepatically-Impaired Patients	17 PATIENT COUNSELING INFORMATION
5.3 Exposure to Sunlight	10 OVERDOSAGE	*Sections or subsections omitted from the full prescribing information are not listed.
6 ADVERSE REACTIONS	11 DESCRIPTION	
6.1 Clinical Trials Experience	12 CLINICAL PHARMACOLOGY	
	12.1 Mechanism of Action	

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sancuso® (Granisetron Transdermal System) is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.

2 DOSAGE AND ADMINISTRATION

The transdermal system (patch) should be applied to clean, dry, intact healthy skin on the upper outer arm. Sancuso should not be placed on skin that is red, irritated or damaged.

Each patch is packed in a pouch and should be applied directly after the pouch has been opened.

The patch should not be cut into pieces.

2.1 Adults

Apply a single patch to the upper outer arm a minimum of 24 hours before chemotherapy. The patch may be applied up to a maximum of 48 hours before chemotherapy as appropriate. Remove the patch a minimum of 24 hours after completion of chemotherapy. The patch can be worn for up to 7 days depending on the duration of the chemotherapy regimen.

3 DOSAGE FORMS AND STRENGTHS

Sancuso is a 52 cm² patch containing 34.3 mg of granisetron. The patch releases 3.1 mg of granisetron per 24 hours for up to 7 days.

4 CONTRAINDICATIONS

Sancuso is contraindicated in patients with known hypersensitivity to granisetron or to any of the components of the patch.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal

The use of granisetron in patients may mask a progressive ileus and/or gastric distention caused by the underlying condition.

5.2 Skin Reactions

In clinical trials with Sancuso, application site reactions were reported which were generally mild in intensity and did not lead to discontinuation of use. The incidence of reactions was comparable with placebo.

If severe reactions, or a generalized skin reaction occur (e.g. allergic rash, including erythematous, macular, papular rash or pruritus), the patch must be removed.

5.3 Exposure to Sunlight

Granisetron may be affected by direct natural or artificial sunlight. Patients must be advised to cover the patch application site, e.g. with clothing, if there is a risk of exposure to sunlight throughout the period of wear and for 10 days following its removal because of a potential skin reaction (see Section 13.2).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of Sancuso was evaluated in a total of 404 patients undergoing chemotherapy who participated in two double-blind, comparator studies with patch treatment durations of up to 7 days. The control groups included a total of 406 patients who received a daily dose of 2 mg oral granisetron, for 1 to 5 days.

Adverse reactions considered by the investigators as drug-related occurred in 8.7% (35/404) of patients receiving Sancuso and 7.1% (29/406) of patients receiving oral granisetron. The most common adverse reaction was constipation that occurred in 5.4% of patients in the Sancuso group and 3.0% of patients in the oral granisetron group.

Table 1 lists the treatment emergent adverse reactions that occurred in at least 3% of patients treated with Sancuso or oral granisetron.

Table 1: Incidence of Adverse Reactions in Double-Blind, Active Comparator Controlled Studies in Cancer Patients Receiving Chemotherapy (Events ≥ 3% in either group)

Body System Preferred Term	Sancuso TDS N=404 (%)	Oral granisetron N=406 (%)
Gastrointestinal disorders		
Constipation	5.4	3.0
Nervous system disorders		
Headache	0.7	3.0

5-HT₃ receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. Three ECGs were performed on 588 randomized patients in the Phase 3 study: at baseline before treatment, the first day of chemotherapy, and 5 to 7 days after starting chemotherapy. QTcF prolongation greater than 450 milliseconds was seen in a total of 11 (1.9%) patients after receiving granisetron, 8 (2.7%) on oral granisetron and 3 (1.1%) on the patch. No new QTcF prolongation greater than 480 milliseconds was observed in any patient in this study. No arrhythmias were detected in this study.

6.2 Granisetron 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.

Adverse events reported in clinical trials with other formulations of granisetron include the following:

Gastrointestinal: abdominal pain, diarrhea, constipation, elevation of ALT and AST levels, nausea and vomiting

Cardiovascular: Hypertension, hypotension, angina pectoris, atrial fibrillation and syncope have been observed rarely

Central Nervous System: dizziness, insomnia, headache, anxiety, somnolence and asthenia

Hypersensitivity: rare cases of hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, shortness of breath, hypotension, urticaria) have been reported

Other: fever; events often associated with chemotherapy have also been reported: leucopenia, decreased appetite, anemia, alopecia, thrombocytopenia.

7 DRUG INTERACTIONS

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system *in vitro*. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs. However, in humans, granisetron hydrochloride injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Granisetron hydrochloride injection also does not appear to interact with emetogenic cancer therapies. In agreement with these data, no clinically relevant drug interactions have been reported in clinical studies with Sancuso.

Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP1A1 and CYP3A4), inducers or inhibitors of these enzymes may change the clearance and hence, the half-life of granisetron. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by granisetron hydrochloride *in vitro*. *In vivo* human microsomal studies, ketoconazole inhibited ring oxidation of granisetron hydrochloride. However, the clinical significance of *in vivo* pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous granisetron hydrochloride. The clinical significance of this change is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies with granisetron hydrochloride have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m²/day, about 24 times the recommended human dose delivered by the Sancuso patch, based on body surface area) and oral doses up to 125 mg/kg/day (750 mg/m²/day, about 326 times the recommended human dose with Sancuso based on body surface area). Reproduction studies have been performed in pregnant rabbits at intravenous doses up to 3 mg/kg/day (36 mg/m²/day, about 16 times the human dose with Sancuso based on body surface area) and at oral doses up to 32 mg/kg/day (384 mg/m²/day, about 167 times the human dose with Sancuso based on body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Sancuso should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sancuso is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Sancuso in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

Clinical studies of Sancuso did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, cautious treatment selection for an elderly patient is prudent because of the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Failure or Hepatically-Impaired Patients

Although no studies have been performed to investigate the pharmacokinetics of Sancuso in patients with renal or hepatic impairment, pharmacokinetic information is available for intravenous granisetron (see CLINICAL PHARMACOLOGY: Pharmacokinetics 12.3).

10 OVERDOSAGE

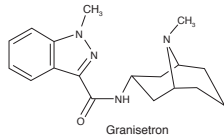
There is no specific antidote for granisetron overdosage. In the case of overdosage, symptomatic treatment should be given.

Overdosage of up to 38.5 mg of granisetron hydrochloride, as a single intravenous injection, has been reported without symptoms or only the occurrence of a slight headache.

In clinical trials there were no reported cases of overdosage with Sancuso.

11 DESCRIPTION

Sancuso contains granisetron, which is an anti-nauseant and antiemetic agent. Chemically it 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 $C_{20}H_{25}N_3O$, while its chemical structure is:



Granisetron is a white to off-white solid that is insoluble in water. Sancuso is a thin, translucent, matrix-type transdermal patch that is rectangular-shaped with rounded corners, consisting of a backing, the drug matrix and a release liner.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Granisetron is a selective 5-hydroxytryptamine₂ (5-HT₂) 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-D₁; or for histamine-H₁; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT₂ 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-HT₂ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT₂ 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

In human studies, transdermal granisetron has had no clinically significant effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in studies using granisetron.

The effect on oro-cecal transit time following application of Sancuso has not been studied. Granisetron hydrochloride injection exhibited no effect on oro-cecal transit time in healthy subjects given a single intravenous infusion of 50 mcg/kg or 200 mcg/kg. Single and multiple oral doses of granisetron hydrochloride slowed colonic transit in healthy subjects.

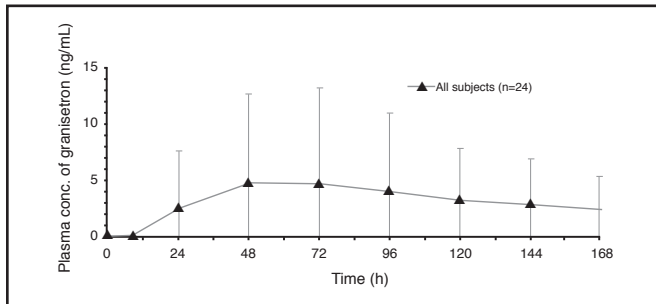
12.3 Pharmacokinetics

Absorption

Granisetron crosses intact skin into the systemic circulation by a passive diffusion process.

Following a 7-day application of Sancuso in 24 healthy subjects, high inter-subject variability in systemic exposure was observed. Maximal concentration was reached at approximately 48 hours (range: 24-168 hours) following patch application. Mean C_{max} was 5.0 ng/mL (CV: 170%) and mean AUC_{0-168h} was 527 ng-hr/mL (CV: 173%).

Mean Plasma Concentration of Granisetron (mean ± SD)



Based on the measure of residual content of the patch after removal, approximately 66% (SD: ± 10.9) of granisetron is delivered following patch application for 7 days.

Distribution

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

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. *In vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT₂ receptor antagonist activity.

Elimination

Clearance is predominantly by hepatic metabolism. Based on a study with intravenous injection, approximately 12% of the dose is excreted unchanged in the urine of healthy subjects in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine, and 34% in the feces.

Subpopulations

Gender

There is evidence to suggest that female subjects had higher granisetron concentrations than males following patch application. However, no statistically significant difference in clinical efficacy outcome was observed between genders.

Pediatrics

No studies have been performed to investigate the pharmacokinetics of Sancuso in pediatrics.

Elderly and Renal or Hepatic Impairment

Although no studies have been performed to investigate the pharmacokinetics of Sancuso in elderly subjects, and in patients with renal or hepatic impairment, the following pharmacokinetic information is available for intravenous granisetron.

In the elderly, and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron were determined following a single 40 mcg/kg intravenous dose of granisetron hydrochloride.

Elderly

In elderly volunteers (mean age 71 years) pharmacokinetic parameters following a single 40 mcg/kg intravenous dose of granisetron hydrochloride, lower clearance and longer half-life were observed compared to younger healthy volunteers.

Renal Failure Patients

Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of granisetron hydrochloride.

Hepatically-Impaired Patients

In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance following a single 40 mcg/kg intravenous dose of granisetron hydrochloride was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters of granisetron and the good tolerance of doses well above the recommended dose, dose adjustment in patients with hepatic functional impairment is not necessary.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m²/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m²/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m² body surface area), these doses represent about 2.6, 13 and 65 times the recommended clinical dose (3.1 mg/day, 2.3 mg/m²/day, delivered by the Sancuso patch, on a body surface area basis). There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m²/day, about 13 times the recommended human dose with Sancuso, on a body surface area basis) and above, and in females treated with 25 mg/kg/day (150 mg/m²/day, about 65 times the recommended human dose with Sancuso, on a body surface area basis). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m²/day, about 2.6 times the recommended human dose with Sancuso, on a body surface area basis) in males and 5 mg/kg/day (30 mg/m²/day, about 13 times the recommended human dose with Sancuso, on a body surface area basis) in females.

In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m²/day, about 261 times the recommended human dose with Sancuso, on a body surface area basis) 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, Sancuso should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

Granisetron 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 UDS assays. It, however, 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.

Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m²/day, about 16 times the recommended human dose of Sancuso, on a body surface area basis), and oral doses up to 100 mg/kg/day (600 mg/m²/day, about 261 times the recommended human dose of Sancuso, on a body surface area basis) was found to have no effect on fertility and reproductive performance of male and female rats.

13.2 Phototoxicity

When tested for potential photogenotoxicity *in vitro* in a Chinese hamster ovary (CHO) cell line, at 200 and 300 mcg/ml, granisetron increased the percentage of cells with chromosomal aberration following photoirradiation.

Granisetron was not phototoxic when tested *in vitro* in a mouse fibroblast cell line. When tested *in vivo* in guinea-pigs, Sancuso patches did not show any potential for photoirritation or photosensitivity. No phototoxicity studies have been performed in humans.

14 CLINICAL STUDIES

The effectiveness of Sancuso in the prevention of chemotherapy-induced nausea and vomiting (CINV) was evaluated in a Phase 3 randomized, parallel group, double-blind, double-dummy study conducted in the U.S. and abroad. The study compared the efficacy, tolerability and safety of Sancuso with that of 2 mg oral granisetron once daily in the prevention of nausea and vomiting in a total of 641 patients receiving multi-day chemotherapy.

The population randomized into the trial included 48% males and 52% females aged 16 to 86 years receiving moderately (ME) or highly emetogenic (HE) multi-day chemotherapy. Seventy-eight (78%) of patients were White, 12% Asian, 10% Hispanic/Latino and 0% Black.

The granisetron patch was applied 24 to 48 hours before the first dose of chemotherapy, and kept in place for 7 days. Oral granisetron was administered daily for the duration of the chemotherapy regimen, one hour before each dose of chemotherapy. Efficacy was assessed from the first administration until 24 hours after the start of the last day's administration of the chemotherapy regimen.

The primary endpoint of the trial was the proportion of patients achieving no vomiting and/or retching, no more than mild nausea and no rescue medication from the first administration until 24 hours after the start of the last day's administration of multi-day chemotherapy. Using this definition, the effect of Sancuso was established in 60.2% of patients in the Sancuso arm and 64.8% of patients receiving oral granisetron (difference -4.89%; 95% confidence interval -12.91% to +3.13%).

An assessment of patch adhesion in 621 patients receiving either active or placebo patches showed that less than 1% of patches became detached over the course of the 7 day period of patch application.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sancuso (Granisetron Transdermal System) is supplied as a 52 cm² patch containing 34.3 mg of granisetron. Each patch is printed on one side with the words "Granisetron 3.1 mg/24 hours". Each patch is packaged in a separate sealed foil-lined plastic pouch.

Sancuso is available in packages of 1 (NDC 42747-726-01) patch.

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

Sancuso should be stored in the original packaging.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (17.4)

17.1 Gastrointestinal

Because the use of granisetron may mask a progressive ileus and/or gastric distention caused by the underlying condition, patients should be instructed to tell their physician if they have pain or swelling in their abdomen.

17.2 Skin Reactions

Patients should be instructed to remove the patch if they have a severe skin reaction, or a generalized skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus).

When patients remove the patch, they should be instructed to peel it off gently.

17.3 Exposure to Sunlight

Granisetron may be degraded by direct sunlight or exposure to sunlamps. In addition, an *in vitro* study using Chinese hamster ovary cells suggests that granisetron has the potential for photogenotoxicity (see Section 13.2).

Patients must be advised to cover the patch application site, e.g. with clothing, if there is a risk of exposure to sunlight or sunlamps throughout the period of wear and for 10 days following its removal.

17.4 FDA-Approved Patient Labeling

Rx Only

Manufactured by:

Aveva Drug Delivery Systems Inc.,
Miramar
FL 33025

ProStrakan

Manufactured for:

ProStrakan Inc.,
Bedminster
NJ 07921

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