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

SANCUSO (granisetron transdermal system) Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE----------
SANCUSO is a serotonin-3 (5-HT_3) receptor antagonist indicated for the prevention of nausea and vomiting in adults receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days. (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage is a single transdermal system applied to the upper outer arm a minimum of 24 hours, up to a maximum of 48 hours, before chemotherapy. The transdermal system should be worn at minimum, 24 hours after chemotherapy is finished. The transdermal system can be worn for up to 7 days. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Transdermal System: 3.1 mg per 24 hours. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to granisetron or to any of the components of the transdermal system (4)

----------WARNINGS AND PRECAUTIONS----------
- Progressive Ileus and Gastric Distention: Granisetron may mask a progressive ileus and/or gastric distention; consider before use in patients with abdominal surgery. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. (5.1)
- Serotonin Syndrome: Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue SANCUSO and initiate supportive treatment. If concomitant use of SANCUSO with other serotonergic drugs is clinically warranted, patients should be aware of a potential increased risk of serotonin syndrome. (5.2, 7.1)
- Skin Reactions: Mild application site reactions have occurred; remove SANCUSO transdermal system if severe reactions or a generalized skin reaction occur. (5.3)
- Increased Drug Exposure with Use of External Heat Sources: Avoid exposing SANCUSO transdermal system and surrounding area to direct external heat sources, such as heating pads (5.4).
- Phototoxicity with Ultraviolet Light Exposure: Avoid direct exposure of application site to natural or artificial sunlight, including sunlamps, by covering with clothing throughout the period of wear and for 10 days after removal. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reaction (≥ 3%) is constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals Inc. at 1-877-484-2700 (X 225) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 07/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SANCUSO® is indicated for the prevention of nausea and vomiting in adults receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is a single transdermal system applied to the upper outer arm a minimum of 24 hours, up to a maximum of 48 hours, before chemotherapy. The transdermal system should be worn at minimum, 24 hours after chemotherapy is finished. The transdermal system can be worn for up to 7 days.

Application and Removal Instructions

- Each transdermal system releases 3.1 mg of granisetron per 24 hours for up to 7 days.
- Each transdermal system is packed in a pouch and should be applied directly after the pouch has been opened.
- Only wear one transdermal system at any time.
- **Do not cut the transdermal system.**
- Open the pouch and apply the transdermal system to clean, dry, nearly hairless, intact healthy skin on the upper outer arm.
- Do not place SANCUSO transdermal system on skin that is red, irritated, or damaged.
- Do not apply a heat pad or heat lamp over or in vicinity of the transdermal system and avoid extended exposure to heat *[see Warnings and Precautions (5.4)]*.
- Cover the application site of the transdermal system with clothing, if there is a risk of exposure to direct natural or artificial sunlight throughout the period of wear and for 10 days following its removal *[see Warnings and Precautions (5.5)]*.
- After the transdermal system is applied, wash hands thoroughly.
- Remove the transdermal system by peeling off gently from the skin.
- Upon removal, fold the transdermal system in half with the sticky side together, and discard in the household trash in a manner that prevents accidental contact or ingestion by children, pets or others.
- SANCUSO contains granisetron. Do not use other granisetron-containing products with SANCUSO.

3 DOSAGE FORMS AND STRENGTHS

Transdermal System: a 52 cm^2 thin, translucent, rectangular-shaped transdermal system with rounded corners imprinted on one side with "Granisetron 3.1 mg/24 hours". The transdermal system 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 transdermal system *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Progressive Ileus and Gastric Distention

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

5.2 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 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-HT_3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 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 SANCUSO and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue SANCUSO and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if SANCUSO is used concomitantly with other serotonergic drugs. *[see Drug Interactions (7)]*.

5.3 Skin Reactions

In clinical trials with SANCUSO, application site reactions were reported that 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), remove the SANCUSO transdermal system.

5.4 Increased Drug Exposure with Use of External Heat Sources

Prolonged exposure to heat results in increasing plasma concentrations of granisetron during the period of heat exposure *[see Clinical Pharmacology (12.3)]*. Do not apply a heat pad or heat lamp over or in the vicinity of the SANCUSO transdermal system and avoid extended exposure to heat *[see Dosage and Administration (2)]*.

5.5 Phototoxicity with Ultraviolet Light Exposure

Granisetron may be affected by direct natural or artificial sunlight, including sunlamps. An *in vitro* study using Chinese hamster ovary cells suggests that granisetron has the potential for photogenotoxicity *[see Nonclinical Toxicology (13.3)]*. To avoid a potential skin reaction, advise patients to cover the application site of the transdermal system with clothing if there is a risk of exposure to direct natural or artificial sunlight throughout the period of wear and for 10 days following its removal.

6 ADVERSE REACTIONS

The following are serious or otherwise clinically significant adverse reactions reported in other sections of labeling:

- Progressive ileus and gastric distention *[see Warnings and Precautions (5.1)]*
- Serotonin syndrome *[see Warnings and Precautions (5.2)]*
- Skin reactions *[see Warnings and Precautions (5.3)]*
- Increased drug exposure with use of external heat sources *[see Warnings and Precautions (5.4)]*
- Phototoxicity with ultraviolet light exposure *[se Warnings and Precautions (5.5)]*

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 clinical practice.

The safety of SANCUSO was evaluated in a total of 404 patients undergoing chemotherapy who participated in two double-blind, comparator studies with transdermal system 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 occurred in 9% (35/404) of patients receiving SANCUSO and 7% (29/406) of patients receiving oral granisetron. The most common adverse reaction was constipation that occurred in 5% of patients in the SANCUSO group and 3% of patients in the oral granisetron group.

Table 1 lists the 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 (≥ 3% in either group)

Body System **Preferred Term**	**SANCUSO Transdermal System N=404 (%)**	**Oral granisetron N=406 (%)**
Gastrointestinal disorders		
Constipation	5	3
Nervous system disorders		
Headache	1	3

5-HT_3 receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. Three ECGs were performed on 588 patients in a randomized, parallel group, double-blind, double-dummy 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 transdermal system. No new QTcF prolongation greater than 480 milliseconds was observed in any patient in this study. No arrhythmias were detected in this study.

Adverse reactions 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of SANCUSO. Because these reactions 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.

General Disorders and Administration Site Conditions: Application site reactions (pain, pruritus, erythema, rash, irritation, vesicles, burn, discoloration, urticaria) *[see Warnings and Precautions (5.3)]*; transdermal system non-adhesion.

Cardiac Disorders: 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-HT_3 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 SANCUSO and initiate supportive treatment *[see Warnings and Precautions (5.4)]*.

7.2 Concomitant Use Medications

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available published data and postmarketing reports with granisetron use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In a published *ex vivo* human placental perfusion model, no transplacental passage of granisetron was detected at a concentration (5 ng/mL) that mimics the plasma concentration achieved following transdermal application of SANCUSO. 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 24 times and 16 times, respectively, the maximum recommended human dose delivered by the SANCUSO transdermal system, based on body surface area *(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 risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits administered granisetron hydrochloride at intravenous doses up to 24 times and 16 times, respectively, the maximum recommended human dose delivered by the SANCUSO transdermal system, based on body surface area (*see Data*).

Data

Animal Data

Reproduction studies with granisetron hydrochloride have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m^2/day, about 24 times the recommended human dose delivered by the SANCUSO transdermal system, based on body surface area) and oral doses up to 125 mg/kg/day (750 mg/m^2/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/m^2/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/m^2/day, about 167 times the human dose with SANCUSO based on body surface area). These studies did not reveal any harm to the fetus due to granisetron.

8.2 Lactation

Risk Summary

There are no data on the presence of granisetron in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SANCUSO and any potential adverse effects on the breastfed child from SANCUSO or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of SANCUSO have not been established in pediatric patients.

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 Impairment or Hepatic Impairment

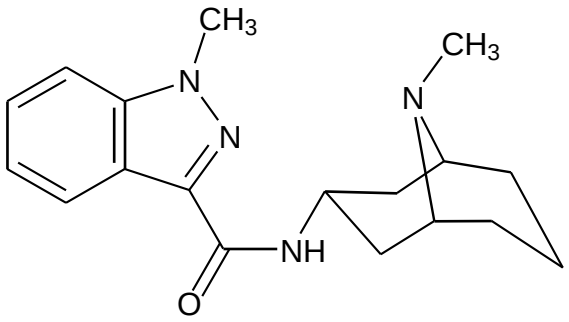
Although no studies have been performed to investigate the pharmacokinetics of SANCUSO in patients with renal or hepatic impairment, pharmacokinetic information is available for intravenous granisetron *[see Clinical Pharmacology (12.3)]*. No dosage adjustment is recommended for renal or hepatic impairment.

10 OVERDOSAGE

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

11 DESCRIPTION

SANCUSO contains granisetron, which is a serotonin-3 (5-HT_3) receptor antagonist. 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 $C_{18}H_{24}N_4O$, while its chemical structure is:



Granisetron

Granisetron is a white to off-white solid that is insoluble in water. The inactive ingredients are acrylate-vinylacetate copolymer, polyester, titanium dioxide, polyamide resin and polyethylene wax. SANCUSO is a 52 cm^2 thin, translucent, matrix-type transdermal system that is rectangular- shaped with rounded corners, consisting of a backing (polyester), the drug matrix (acrylate- vinylacetate copolymer) and a release liner (siliconized polyester).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1, 5-HT_{1A}, 5-$HT_{1B/C}$, 5-HT_2; for alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D_2; or for histamine-H_1; benzodiazepine; picrotoxin or opioid receptors.

Serotonin receptors of the 5-HT_3 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-HT_3 receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT_3 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

The effect of granisetron on QTc prolongation was evaluated in a randomized, single-blind, positive (moxifloxacin 400 mg) - and placebo controlled parallel study in healthy subjects. A total of 120 subjects were administered SANCUSO transdermal system (n=60) or intravenous granisetron (10 mcg/kg over 30 seconds; n=60). In a study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo adjusted, baseline corrected QTc based on Fridericia correction method (QTcF) for SANCUSO was below 10 ms. This study suggests that SANCUSO does not have significant effects on QT prolongation.

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.

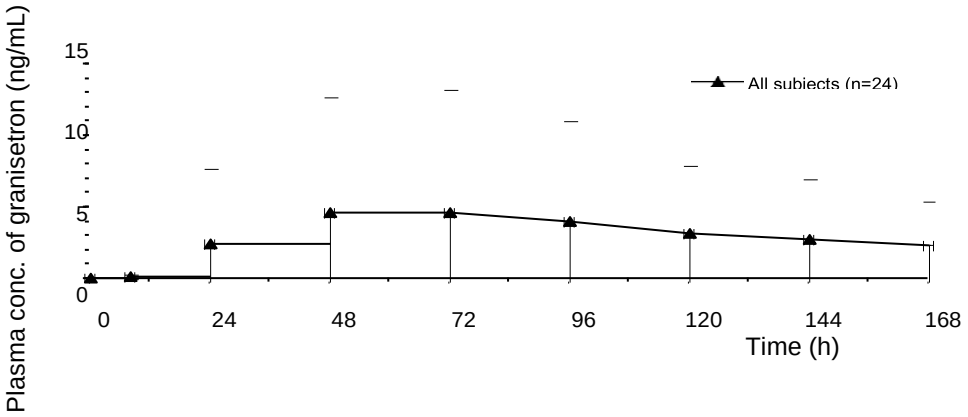
12.3 Pharmacokinetics

Absorption

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

Following a 7-day application of SANCUSO transdermal system 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 application. Mean C_{max} was 5 ng/mL (CV: 170%) and mean $AUC_{0\text{-}168hr}$ was 527 ng-hr/mL (CV: 173%).

Mean Plasma Concentration of Granisetron (mean ± SD)



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

Following consecutive application of two SANCUSO transdermal systems, each for seven days, granisetron plasma concentrations were maintained over the study period with evidence of minimal accumulation. The mean plasma concentration at 24 hours after the second transdermal system application was 1.5-fold higher due to residual granisetron from the first transdermal system. As the plasma concentration increased after the second transdermal system application, the difference decreased and the mean plasma concentration at 48 hours was 1.3-fold higher after application of the second transdermal system compared to that after application of the first transdermal system.

In a study designed to assess the effect of heat on the transdermal delivery of granisetron from SANCUSO in healthy subjects, a heat pad generating an average temperature of 42°C (107.6°F) was applied over the transdermal system for 4 hours each day over the 5 day period of wear. The application of the heat pad was associated with an increase in plasma granisetron concentrations during the period of heat pad application. The elevated plasma concentration declined after removal of the heat pad. Mean C_{max} with intermittent heat exposure was 6% higher than without heat. Mean partial AUCs over 6 hours with 4 hour of heat application (AUC_{0-6}, AUC_{24-30}, and AUC_{48-54}) were 4.9, 1.4, and 1.1 fold higher, respectively, with heat pad than without heat pad *[see Dosage and Administration (2), Warnings and Precautions (5.4)]*.

Distribution

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

Elimination

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-HT_3 receptor antagonist activity.

Excretion
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.

Use in Specific Populations

Geriatric Patients
Following application of SANCUSO transdermal system in healthy subjects, mean AUC_{0-z}, C_{max}, and C_{avg} were 17%, 15%, and 16% higher, respectively in male and female elderly subjects (≥ 65 years) compared to younger subjects (aged 18-45 years inclusive). These pharmacokinetic parameters were largely overlapped between the two age groups with high variability (CV: >50%).

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

Male and Female Patients
There is evidence to suggest that female subjects had higher granisetron concentrations than males following transdermal system application. However, no statistically significant difference in clinical efficacy outcome was observed between males and females.

Racial or Ethnic Groups
The pharmacokinetic profile of granisetron from SANCUSO was assessed in healthy Japanese males. Following the application of a single 6-day SANCUSO 52 cm^2 transdermal system, in healthy male Japanese subjects, mean C_{max}, $AUC_{(0-144)}$, and $AUC_{(0-\infty)}$ values were 5.02 ng/mL (CV: 66%), 492 ng.hr/mL (CV: 72%), and 562 ng.hr/mL (CV: 60%), respectively, and a median t_{max} value was 48 hours.

Patients with Renal Impairment
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.

Patients with Hepatic Impairment
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.

Body Mass Index
In a clinical study designed to assess granisetron exposure from SANCUSO in subjects with differing levels of body fat, using body mass index (BMI) as a surrogate measure for subcutaneous fat, no significant differences were seen in the plasma pharmacokinetics of SANCUSO in male and female subjects with low BMI [<19.5 kg/m^2 (males), <18.5 kg/m^2 (females)] and high BMI (30.0 to 39.9 kg/m^2 inclusive) compared to a control group (BMI 20.0 to 24.9 kg/m^2 inclusive).

Drug Interaction Studies

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 *in vitro* 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent about 2.6, 13, and 65 times the recommended clinical dose (3.1 mg/day, 2.3 mg/m^2/day, delivered by the SANCUSO transdermal system, 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/m^2/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/m^2/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/m^2/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/m^2/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/m^2/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 (1), Dosage and Administration (2)]*.

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/m^2/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/m^2/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.

13.3 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 *[see Warnings and Precautions (5.5)]*.

Granisetron was not phototoxic when tested *in vitro* in a mouse fibroblast cell line. When tested *in vivo* in guinea-pigs, SANCUSO transdermal system 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 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 transdermal system 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 emetogenic (ME) or highly emetogenic (HE) multi-day chemotherapy. Seventy-eight (78%) of patients were White, 12% Asian, 10% Hispanic/Latino and 0% Black.

SANCUSO 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, 1hour 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 transdermal system adhesion in 621 patients receiving either active or placebo transdermal system showed that less than 1% of transdermal systems became detached over the course of the 7 day period of transdermal system application.

16 HOW SUPPLIED/STORAGE AND HANDLING

SANCUSO (granisetron transdermal system) is a 52 cm^2 thin, translucent, rectangular-shaped transdermal system with rounded corners imprinted on one side with "Granisetron 3.1 mg/24 hours". The transdermal system releases 3.1 mg of granisetron per 24 hours for up to 7 days.

Each SANCUSO transdermal system is packaged in a separate sealed foil-lined plastic pouch supplied in packages of 1 (NDC 66220-637-31) transdermal system.

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

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Progressive Ileus and Gastric Distention
Advise the patient to report new or worsening constipation to their healthcare provider and seek immediate medical care if symptoms of an ileus (pain or swelling in their abdomen) occur *[see Warnings and Precautions (5.1)]*.

Serotonin Syndrome
Advise the patient of the possibility of serotonin syndrome with concomitant use of SANCUSO 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 (5.2)]*.

Skin Reactions

Instruct the patient remove the transdermal system if they have a severe skin reaction, or a generalized skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) *[see Warnings and Precautions (5.3)]*.

Increased Drug Exposure with Use of External Heat Sources

Advise the patient to avoid prolonged exposure to heat and not to apply a heat pad or heat lamp over or near the SANCUSO transdermal system and avoid extended exposure to heat *[see Warnings and Precautions (5.4)]*.

Phototoxicity with Ultraviolet Light Exposure

Advise the patient to avoid direct sunlight or exposure to sunlamps and to cover the application site of the transdermal system 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 *[see Warnings and Precautions (5.5)]*.

Application and Removal Instructions
Instruct the patient on how to apply and remove the transdermal system:

- Only wear one transdermal system at any time.
- Do not cut the transdermal system.
- Apply the transdermal system to clean, dry, nearly hairless, intact healthy skin on the upper outer arm.
- After the transdermal system is applied, wash hands thoroughly.
- Remove the transdermal system by peeling off gently from the skin.
- Upon removal, fold the used transdermal system in half with the sticky side together, and discard in household trash in a manner that prevents accidental contact or ingestion by children, pets or others.
- SANCUSO contains granisetron. Do not use other granisetron-containing products with

SANCUSO
[see Dosage and Administration (2)].

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