ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SANCUSO 3.1 mg/24 hours transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 52 cm^2 transdermal patch contains 34.3 mg of granisetron releasing 3.1 mg of granisetron per 24 hours.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, translucent, matrix-type, rectangular-shaped transdermal patch with rounded corners.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SANCUSO transdermal patch is indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5 consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult (see section 5.1).

4.2 Posology and method of administration

Posology
Adults
Apply a single transdermal patch 24 to 48 hours before chemotherapy, as appropriate.

Due to a gradual increase in plasma levels of granisetron following application of the transdermal patch, a slower onset of efficacy compared to 2 mg oral granisetron may be observed at the start of chemotherapy; the patch should be applied 24-48 hours before chemotherapy.

The transdermal patch should be removed a minimum of 24 hours after completion of chemotherapy. The transdermal patch can be worn for up to 7 days depending on the duration of the chemotherapy regimen.

Following routine haematological monitoring, the transdermal patch should only be applied to patients whose chemotherapy treatment is unlikely to be delayed in order to reduce the possibility of unnecessary exposure to granisetron.

Use of concomitant corticosteroids
The Multinational Association of Supportive Care in Cancer (MASCC) guidelines recommend the administration of dexamethasone with $5HT_3$ antagonist prior to chemotherapy. In the pivotal SANCUSO study, the concomitant use of corticosteroids, e.g. dexamethasone, was permitted provided it was part of the chemotherapy regimen. Any increase in corticosteroid use during the study was reported as rescue treatment.

Special populations
Elderly
Dosing as for adults (see sections 4.4 and 5.2).

Renal or hepatic impairment
No dose adjustment is necessary. Dosing as for adults (see sections 4.4 and 5.2). Although no evidence of an increased incidence of adverse reactions have been observed in patients with renal or hepatic impairment receiving granisetron orally and intravenously, based on granisetron pharmacokinetics, a degree of caution must be exercised in this population.

Paediatric population
The safety and efficacy of SANCUSO in children aged 0 to 18 years have not yet been established. No data are available.

Method of administration
The transdermal patch should be applied to clean, dry, intact healthy skin on the outer part of the upper arm. If it is not possible to apply the transdermal patch to the arm, it can be applied to the abdomen.

The transdermal patch should not be placed on skin that is red, irritated or damaged.

Each transdermal patch is packed in a sachet and should be applied directly after the sachet has been opened. The release liner is removed prior to application.

The transdermal patch should not be cut into pieces.

In the event of a transdermal patch becoming completely or partially detached, the original transdermal patch should be reattached in the same position using medical tape (if necessary). If reattachment is not possible or the transdermal patch is damaged, a new transdermal patch should be applied in the same position as the original transdermal patch. If this is not possible, a new transdermal patch should be applied on the opposite arm. The newly applied transdermal patch should be removed in line with the timing recommended above.

4.3 Contraindications

Hypersensitivity to the active substance, to other 5-HT_3 receptor antagonists or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Gastrointestinal disorders
Granisetron may mask a progressive ileus and/or gastric distension caused by an underlying condition. Patients with signs of sub-acute intestinal obstruction should be monitored following its administration, as granisetron may reduce lower bowel motility.

Cardiac disorders
5-HT_3 receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. This may potentially have clinical significance in patients with pre-existing arrhythmias or cardiac conduction disorders and/or treated with antiarrhythmics or beta blockers. No clinically relevant effects have been observed in clinical studies with SANCUSO.

Exposure to sunlight
Granisetron may be affected by direct natural or artificial sunlight, see section 5.3 for further information. Patients must cover the transdermal 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.

Showering or washing
Showering or washing normally can be continued while wearing SANCUSO. Activities such as swimming, strenuous exercise or using a sauna should be avoided.

External heat
External heat (for example hot water bottles or heat pads) should be avoided on the area of the transdermal patch.

Special populations
No dose adjustments are necessary for the elderly or patients with renal or hepatic impairment. Although no evidence of an increased incidence of adverse reactions have been observed in patients with renal or hepatic impairment receiving granisetron orally and intravenously, based on granisetron pharmacokinetics, a degree of caution must be exercised in this population.

Serotonin syndrome
There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone, but mostly in combination with other serotonergic medicinal products (including selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs). There have also been reports of possible drug-drug interactions between buprenorphine/Opioids and serotonergic medicinal products leading to serotonin syndrome. Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

Skin Reactions
In clinical studies with granisetron transdermal patch, application site reactions generally mild in intensity were reported and did not lead to discontinuation of use. If severe reactions, or a generalised skin reaction occur (e.g. allergic rash, including erythematous, macular, papular rash or pruritus), the transdermal patch must be removed.

Potential for drug abuse and dependence
Granisetron has no known potential for abuse and dependence.

4.5 Interaction with other medicinal products and other forms of interaction

For serotonergic medicinal products (e.g. SSRIs and SNRIs, buprenorphine, opiods or other serotonergic medicinal products), there have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicinal products (including SSRIs and SNRIs).

Co-administration of intravenous 5-HT3 receptor antagonists with oral paracetamol in human subjects has been reported to result in a block in the analgesic effect via a pharmacodynamic mechanism.

As granisetron is metabolised by hepatic cytochrome P450 active substance-metabolising enzymes (CYP1A1 and CYP3A4), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron.

In human subjects, hepatic enzyme induction by phenobarbital has led to an increase in total plasma clearance (approximately 25%) following intravenous administration of granisetron.

In vitro studies have shown that ketoconazole may inhibit the metabolism of granisetron via the cytochrome P450 3A isoenzyme family. The clinical significance of this is unknown.

In vitro studies using human microsomes indicate that granisetron neither stimulates nor inhibits the

cytochrome P450 enzyme system.

In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine).

No clinically relevant interactions between SANCUSO and emetogenic cancer chemotherapies have been seen. Furthermore, no interaction has been observed between granisetron and emetogenic cancer therapies. In agreement with these data, no clinically relevant interactions have been reported in clinical studies with SANCUSO. In clinical interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of granisetron.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data (less than 300 pregnancy outcomes) from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of SANCUSO during pregnancy.

Breast-feeding
It is unknown whether granisetron or its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with SANCUSO.

Fertility
There are no data on the effect of granisetron on human fertility.

4.7 Effects on ability to drive and use machines

The effect of SANCUSO on the ability to drive or operate machinery has not been studied.

4.8 Undesirable effects

Summary of the safety profile
The safety profile of SANCUSO is derived from controlled clinical trials and from post-marketing experience. The most commonly reported adverse reaction in clinical studies was constipation, occurring in approximately 8.7% of patients. The majority of adverse reactions were mild or moderate in severity.

Tabulated list of adverse reactions
Adverse reactions from clinical studies and spontaneous reports with SANCUSO are listed in the table below.

Within the system organ class, the adverse reactions are listed by frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Adverse reactions are presented in order of decreasing seriousness within each frequency grouping.

Table 1: Adverse reactions reported for SANCUSO

System Organ Class	Adverse reaction	Frequency
Immune system disorder	Hypersensitivity reactions	Not known
Metabolism and nutrition disorders	Decreased appetite	Uncommon
Nervous system disorders	Headache	Uncommon
	Dystonia	Rare
	Dyskinesia	Rare
	Serotonin syndrome	Unknown
Ear and labyrinth disorders	Vertigo	Uncommon
Vascular disorders	Flushing	Uncommon
Gastrointestinal disorders	Constipation	Common
	Dry mouth, nausea, retching	Uncommon
Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon
General disorders and administration site conditions	Generalised oedema Application site irritation* Application site reactions**	Uncommon Uncommon Unknown

* Application site irritation includes: Application site pruritus and Skin irritation (Spontaneous reports)
**Application site reactions includes: Application site erythema, Application site rash, Application site pain, Application site hypersensitivity, Application site vesicles, Application site burn, Application site urticaria and Application site discolouration.

Description of selected adverse reactions
Patients who are being treated with moderately or highly emetogenic chemotherapy may still experience vomiting despite treatment with antiemetic therapy, including SANCUSO.

Serotonin Syndrome
There have been reports of serotonin syndrome with the use of 5-HT3 antagonists either alone, but mostly in combination with other serotonergic medicinal products (including Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Noradrenaline (norepinephrine) Reuptake Inhibitors (SNRIs)). There have also been reports of possible drug-drug interactions between buprenorphine/Opioids and serotonergic medicinal products leading to serotonin syndrome (see section 4.5). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

Class effects
Class effects for granisetron seen with other formulations (oral and intravenous) include the following:

- Hypersensitivity reactions, e.g. anaphylaxis, urticaria
- Insomnia
- Headache
- Extrapyramidal reactions
- Somnolence
- Dizziness
- QT prolongation
- Constipation
- Diarrhoea
- Elevated hepatic transaminases
- Rash
- Asthenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for granisetron. In the event of overdose, the transdermal patch should be removed. Symptomatic treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists, ATC code: A04AA02.

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine ($5HT_3$ receptors). Pharmacological studies have demonstrated that granisetron is effective against nausea and vomiting as a result of cytostatic therapy. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types, including $5HT_1$, $5HT_2$, $5HT_4$ and dopamine D_2 binding sites.

A pivotal, randomised, double-blind, double-dummy, multinational Phase III 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 study was designed to show non-inferiority of SANCUSO to oral granisetron.

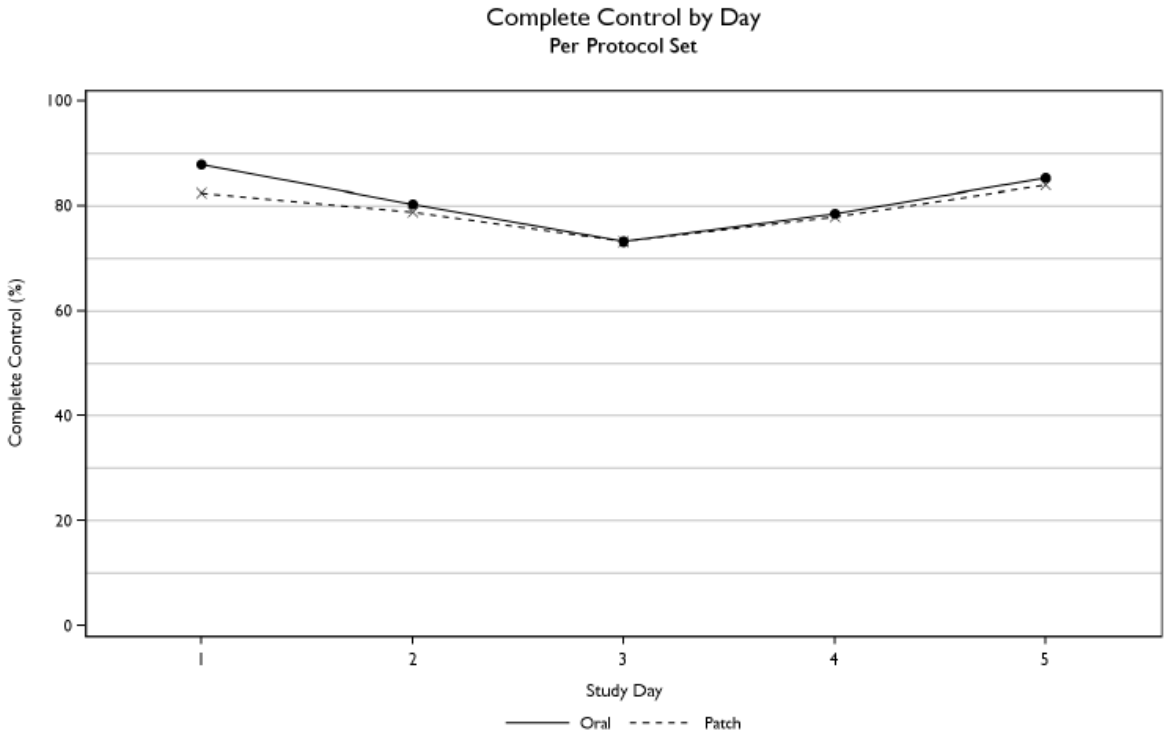
The population randomised into the trial included 48% males and 52% females aged 16 to 86 years receiving moderately emetogenic (ME) or highly emetogenic (HE) multi-day chemotherapy. 78% of patients were white, with 12% Asian and 10% Hispanic/Latino.

The granisetron transdermal patch was applied 24 to 48 hours prior to 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 prior to each dose of chemotherapy. Anti-emetic activity was assessed from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen.

Non-inferiority of SANCUSO versus oral granisetron was confirmed, with complete control (CC) achieved in 60.2% of patients in the SANCUSO arm and 64.8% of patients receiving oral granisetron in the per protocol set (difference -4.89%; 95% confidence interval –12.91% to +3.13%; n=284 transdermal patch, n=298 oral). CC was defined as no vomiting and/or retching, no more than mild nausea and no rescue medicine from the first administration until 24 hours after the start of the last day's administration of multi-day chemotherapy.

Due to the gradual increase in plasma levels of granisetron following application of the transdermal patch, initial plasma levels at the start of chemotherapy may be lower than 2 mg oral granisetron and a slower onset of efficacy may therefore be observed. Consequently, SANCUSO is indicated for use in patients where oral anti-emetic administration is complicated by factors making swallowing difficult.

Complete control by day is illustrated below.



In clinical trials with SANCUSO, there were no treatment-related effects on heart rate or blood pressure. Assessment of serial ECGs in patients showed no QT prolongation and no change in ECG morphology. The effect of SANCUSO on QTc interval was specifically evaluated in a blinded, randomised, parallel, placebo and positive (moxifloxacin) controlled thorough QTc trial with SANCUSO in 240 adult male and female subjects. No significant effect on QTc prolongation was observed for SANCUSO.

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

There is no clinical trial experience with SANCUSO and patients on chemotherapy for less than 3 consecutive days, or over multiple cycles of chemotherapy, or with -high dose chemotherapy prior to -stem cell transplantation.

5.2 Pharmacokinetic properties

Absorption

Granisetron crosses intact skin into the systemic circulation by a passive diffusion process. Following SANCUSO application, granisetron is absorbed slowly, with maximal concentrations reached between 24 and 48 hours.

Based on the measure of residual content of the transdermal patch after removal, approximately 65% of granisetron is delivered resulting in an average daily dose of 3.1 mg per day.

Concurrent administration of a single intravenous bolus of 0.01 mg/kg (maximum 1 mg) granisetron at the same time a SANCUSO transdermal patch was applied was investigated in healthy subjects. An initial peak in plasma concentrations of granisetron, attributable to the intravenous dose, was reached at 10 minutes post-administration. The known pharmacokinetic profile of the transdermal patch over the period of wear (7 days) was not affected.

Following consecutive application of two SANCUSO transdermal patches in healthy subjects, each for seven days, granisetron levels were maintained over the study period with evidence of minimal accumulation.

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 was applied over the transdermal patch for 4 hours each day over the 5 day period of wear. While application of the heat pad was associated with a minor and transient increase in the transdermal patch flux during the period of heat pad application, no overall increase in granisetron exposure was observed when compared to a control group.

In a pharmacokinetic study in healthy volunteers, where SANCUSO was applied for a period of 7 days, mean total exposure ($AUC_{0\text{-infinity}}$) was 416 ng h/ml (range 55 – 1192 ng h/ml), with a between subject variability of 89%. Mean C_{max} was 3.9 ng/ml (range 0.7 – 9.5 ng/ml), with a between subject variability of 77%. This variability is similar to the known high variability in granisetron pharmacokinetics after oral or intravenous administration.

Distribution
Granisetron is distributed with a mean volume of distribution of approximately 3 l/kg. Plasma protein binding is approximately 65%. Granisetron distributes freely between plasma and red blood cells.

Biotransformation
No differences in the metabolic profiles of granisetron were observed between the oral and transdermal uses.

Granisetron is mainly metabolised to 7-hydroxygranisetron and 9'N-desmethylgranisetron. *In vitro* studies using human liver microsomes indicate that CYP1A1 is the major enzyme responsible for the 7-hydroxylation of granisetron, whereas CYP3A4 contributes to 9'desmethylation.

Elimination
Granisetron is cleared primarily by hepatic metabolism. After intravenous dosing, the mean plasma clearance ranged from 33.4 to 75.7 l/h in healthy subjects and from 14.7 to 33.6 l/h in patients with wide inter-subject variability. The mean plasma half-life in healthy subjects is 4-6 hours and in patients is 9-12 hours. After transdermal patch application, the apparent granisetron plasma half-life in healthy subjects was prolonged to approximately 36 hours due to the slow absorption rate of granisetron through the skin.

In clinical studies conducted with SANCUSO, clearance in cancer patients was shown to be approximately half that of healthy subjects.

After 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, with 49% in the urine and 34% in the faeces.

Pharmacokinetics in special populations
The effects of gender on the pharmacokinetics of SANCUSO have not been specifically studied. No consistent gender effects on pharmacokinetics were observed in clinical studies with SANCUSO, with a large inter-individual variability reported in both sexes. Population PK modelling has confirmed the absence of a gender effect on the pharmacokinetics of SANCUSO.

Elderly
In a clinical study no differences were seen in the plasma pharmacokinetics of SANCUSO in male and female elderly subjects (≥ 65 years) compared with younger subjects (aged 18-45 years inclusive).

Renal or hepatic impairment
No clinical studies have been performed specifically to investigate the pharmacokinetics of SANCUSO in patients with renal or hepatic impairment. No clear relationship between renal function (as measured by creatinine clearance) and granisetron clearance was identified in population PK modelling. In patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron were determined following a single 40 μg/kg intravenous dose of granisetron hydrochloride.

Hepatic impairment
In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters of granisetron and the good tolerance well above the recommended dose, dose adjustment in patients with functional hepatic impairment is not necessary.

Renal impairment
No correlation between creatinine clearance and total clearance was observed in cancer patients, indicating no influence of renal impairment on the pharmacokinetics of granisetron.

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

Paediatric population
There are limited data available in patients <18 years of age. No studies have been performed to investigate the pharmacokinetics of SANCUSO in paediatric patients <13 years of age.

5.3 Preclinical safety data

Preclinical data did not reveal any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies showed no special hazard for humans when used at the recommended dose. However, when administered in higher doses and over a prolonged period of time, the risk of carcinogenicity cannot be ruled out but with the short application period recommended for the transdermal delivery system, a carcinogenic risk for humans is not expected.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. These studies did not reveal any evidence of impaired fertility or harm to the foetus due to granisetron.

Fertility was unaffected following granisetron treatment in rats.

SANCUSO transdermal patches did not show any potential for photoirritation or photosensitivity when tested *in vivo* in guinea-pigs. Granisetron was not phototoxic when tested *in vitro* in a mouse fibroblast cell line. When tested for potential photogenotoxicity *in vitro* in a Chinese hamster ovary (CHO) cell line, granisetron increased the percentage of cells with chromosome damage following photoirradiation. Although, the clinical relevance of this finding is not completely clear, patients should be advised to cover the transdermal patch application site if there is a risk of exposure to sunlight throughout the period of wear and for 10 days following its removal (see section 4.4).

When tested for skin sensitising potential in guinea pigs, SANCUSO showed a low potential for irritancy.

A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which could affect cardiac depolarisation and repolarisation and therefore PR, QRS, and QT intervals. These data help to clarify the mechanisms by which some of the

ECG changes (particularly QT and QRS prolongation) associated with this class of substance can occur. However, no clinically relevant effects on ECG have been observed in clinical studies with SANCUSO, including a through QT study in 240 healthy subjects (section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer
Polyester

Matrix layer
Acrylate-vinylacetate copolymer

Release liner
Siliconised polyester

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Each transdermal patch is packaged in a heat-sealed sachet composed of polyester-coated paper/aluminium/LLDPE.

Each carton contains 1 transdermal patch.

6.6 Special precautions for disposal

The transdermal patch will still contain active substance following use. After removal, the used transdermal patch should be folded firmly in half, adhesive side inwards and then discarded out of the reach of children.

7. MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands
Tel: +31 (0) 237200822

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/766/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2012
Date of latest renewal: 9 January 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
PHARBIL Waltrop GmbH (a subsidiary of NextPharma)
Im Wirrigen 25
45731 Waltrop
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency:
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as a result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

SANCUSO 3.1 mg/24 hours transdermal patch
granisetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 52 cm^2 transdermal patch contains 34.3 mg of granisetron, releasing 3.1 mg of granisetron per 24 hours.

3. LIST OF EXCIPIENTS

Other ingredients: acrylate-vinylacetate copolymer, polyester, siliconised polyester.

4. PHARMACEUTICAL FORM AND CONTENTS

1 transdermal patch

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V., Bloemlaan 2, 2132NP Hoofddorp, The Netherlands

12. MARKETING AUTHORISATION NUMBERS

EU/1/12/766/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sancuso

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SANCUSO 3.1 mg/24 h transdermal patch
granisetron
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

Store in the original package in order to protect from light.
Keep out of the sight and reach of children.

Kyowa Kirin

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

SANCUSO 3.1 mg/24 hours transdermal patch
granisetron

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SANCUSO is and what it is used for

The active substance in SANCUSO is granisetron, which belongs to a group of medicines called antiemetics and antinauseants.

SANCUSO is a transdermal (skin) patch used to prevent nausea (feeling sick) and vomiting (being sick) in adults receiving chemotherapy treatments (medicines to treat cancer) lasting 3 to 5 days and who have difficulty swallowing tablets (for example due to soreness, dryness or inflammation of the mouth or throat).

You must talk to a doctor if you do not feel better or if you feel worse after the first day of chemotherapy.

2. What you need to know before you use SANCUSO

Do not use SANCUSO:
- if you are allergic to granisetron or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to any other anti-sickness medicines whose name ends in “setron” e.g. ondansetron.

Warnings and precautions
Tell your doctor or nurse before using this treatment if any of the following applies to you:

- if you have been told you have a heart disorder or disease
- if you have pain in your stomach or your stomach is swollen
- if you have problems with your kidneys or liver.

This medicine may not work as well and/or may affect your skin if exposed to direct sunlight or the light from sunlamps or tanning beds. It is important to do the following:
- while you wear the transdermal patch, keep it covered with clothing if you will be in sunlight or near a sunlamp, including tanning beds
- keep the skin where this medicine was applied covered for another 10 days after the transdermal patch is taken off to protect from exposure to direct sunlight.

It is not known how activities such as swimming, strenuous exercise or using a sauna or whirlpool, may affect this medicine. Avoid these activities while wearing this transdermal patch. You can continue to shower and wash normally while wearing the transdermal patch.

External heat, for example from hot water bottles or heat pads, should be avoided on the area of the transdermal patch.

Children and adolescents
This medicine should not be used by children or adolescents under 18 years.

Other medicines and SANCUSO
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. SANCUSO can affect the way some medicines work. Also, some other medicines can affect the way SANCUSO works. In particular, tell your doctor or nurse if you are taking the following medicines:
- Paracetamol, used to treat pain.
- Phenobarbital, used to treat epilepsy.
- Ketoconazole, used to treat fungal infections.
- SSRIs (selective serotonin reuptake inhibitors) used to treat depression and/or anxiety including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram.
- SNRIs (serotonin noradrenaline reuptake inhibitors) used to treat depression and/or anxiety including venlafaxine, duloxetine.
- Buprenorphine, Opioids or other serotonergic medicines.

Pregnancy and breast-feeding
Do not use this medicine if you are pregnant unless your doctor has specifically recommended it.

Stop breast-feeding while wearing the patch.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
SANCUSO has no or negligible effect on your ability to drive or use any machines.

3. How to use SANCUSO

Always use this medicine exactly as your doctor has told you. Check with your doctor or nurse if you are not sure.

The recommended dose is one single transdermal patch. The medicine in the transdermal patch passes gradually through your skin into your body and, therefore, the patch is applied 1 to 2 days (24 to 48 hours) before the start of chemotherapy treatment.

This medicine is for transdermal use. This medicine delivers the active substance slowly and constantly through your skin and into your blood stream for the duration that you are wearing the transdermal patch.

Things to remember when using the transdermal patch

- Do not keep or store the transdermal patch outside the sealed sachet.
- Do not cut the transdermal patch into smaller pieces.
- Use only one transdermal patch at a time.
- When you remove the transdermal patch, check your skin and tell your doctor if you notice a serious skin reaction (if your skin is very red, itchy or you notice any blisters).
- The transdermal patch may be affected by direct sunlight or exposure to sunlamps. While you are wearing the transdermal patch you must keep it covered, e.g. under clothing, if there is a risk of exposure to sunlight or sunlamps. Continue to keep the application site covered for a further 10 days after removing the transdermal patch.
- Contact with water during bathing or showering will not change the way SANCUSO works.
- However, the transdermal patch may become partially unstuck. Try to avoid wearing the transdermal patch in water for long periods of time.
- There is no information on the effect on the transdermal patch of activities such as strenuous exercise or the use of sauna or whirlpools; therefore, you should avoid these activities while wearing this transdermal patch.
- You should avoid external heat (for example hot water bottles or heat pads) on the area of the transdermal patch.

When to apply and remove the transdermal patch

Do not remove the transdermal patch from the sachet until you are ready to use it. Apply a transdermal patch at least 1 day (24 hours) before you are scheduled to have chemotherapy treatment. The transdermal patch may be applied up to a maximum of 2 days (48 hours) before chemotherapy. Wear the transdermal patch all the time during your chemotherapy. The transdermal patch can be worn for up to 7 days depending on the duration of your chemotherapy treatment. Remove the transdermal patch at least 1 day (24 hours) after completing your chemotherapy.

Where to apply the transdermal patch

Put the transdermal patch on a clean, dry, healthy area of skin on the outside part of your upper arm. If your arms are not suitable areas to apply the transdermal patch your doctor may ask you to put it on your abdomen. The area you choose should not be oily, recently shaved or have any skin problems such as being injured (cut or scraped) or irritated (redness or a rash). Do not put SANCUSO on areas that have been treated with creams, oils, lotions, powders or other skin products that could keep the transdermal patch from sticking well to your skin.

How to apply the transdermal patch

1. Remove a sachet from the box and tear it open using the slit provided. Each sachet contains one transdermal patch stuck onto a rigid plastic film.
2. Take the transdermal patch out of the sachet.

3. The sticky side of the transdermal patch is covered by a two-piece rigid plastic film. Bend the transdermal patch in the middle and remove one half of the rigid plastic film. Be careful not to stick the transdermal patch to itself and avoid touching the sticky side of the transdermal patch.
4. While holding the remaining half of the rigid plastic film, apply the transdermal patch to the skin on the outside part of your upper arm.

5. Remove the second half of the rigid plastic film and press the whole transdermal patch firmly in place with your fingers and smooth down. Press firmly making sure there is good contact with the skin, especially around the edges.
6. Wash your hands after applying the transdermal patch.
7. Keep the transdermal patch in place for the whole time you are having chemotherapy.
8. Do not re-use the transdermal patch after removal, see below for instructions on transdermal patch removal and disposal (see section 5).

After removing the transdermal patch
1. The used transdermal patch will still contain some granisetron and should be disposed of immediately as described in section 5.
2. After removing the transdermal patch you may find some sticky material is left on your skin. Gently wash the area with soap and water to remove it. Alcohol or other dissolving liquids such as nail polish remover may cause skin irritation and should not be used.
3. Wash your hands.
4. You may see mild redness on the skin where the transdermal patch is removed. This redness should go away over time. If it does not, tell your doctor.

If the transdermal patch becomes unstuck
If the transdermal patch starts to become unstuck, the same transdermal patch may be secured to the same area of skin. If required, use surgical bandages or medical adhesive tape to keep the transdermal patch in place. If the transdermal patch is lost or becomes damaged go back to your doctor.

If you use more SANCUSO than you should
If you use more SANCUSO than you should, simply remove the extra patch(es) and contact your doctor.

If you forget to use SANCUSO
It is important to use this medicinal product as instructed by your doctor to prevent you feeling sick or being sick following your chemotherapy. If you have forgotten to apply your transdermal patch at the right time, apply it as soon as you remember, and tell your doctor as soon as possible before your chemotherapy treatment.

If you stop using SANCUSO
It is important to use this medicine during the whole length of your chemotherapy (up to 7 days) to prevent you feeling sick or being sick following your chemotherapy. Talk to your doctor if you want to remove the patch before the end of your chemotherapy treatment course (up to 7 days).

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you are being treated with chemotherapy that is moderately or highly capable of making you feel sick, you may still be sick despite treatment with anti-sickness medicine, including this medicine.

Tell your doctor immediately if you develop constipation or if your stomach becomes painful or swollen. Constipation is a common side effect and may affect up to 1 in 10 people.

Remove the transdermal patch and tell your doctor if you notice:
- signs and symptoms of a condition called Serotonin Syndrome, which can be serious and in some cases life threatening. These may include changes in blood pressure (which could make you feel dizzy or have a headache), fast heartbeat, blurred vision (which may be due to dilation of the pupil of the eye), sweating, increased bowel movements/noises, shivering, tremor, muscle twitching or jerking, and overactive reflexes. You may also have a high or

very high temperature (fever), feel agitated or confused, have stiff muscles, and notice that you are talking faster. How many people will get Serotonin Syndrome is not known (cannot be estimated from available data)

- a serious skin reaction (if your skin is very red, itchy or you notice any blisters). Skin reactions at the site of application, such as irritation, itching or redness are uncommon and may affect up to 1 in 100 people.

Other possible side effects:
Uncommon side effects are:
- headache, a feeling of "spinning" even when you are standing still (vertigo)
- decreased appetite, weight loss
- flushing (or redness)
- feeling sick (nausea), retching, dry mouth
- pain in your joints
- swelling due to water retention (oedema)
- changes in liver function tests (if you are having blood tests, tell the doctor or nurse that you have been given SANCUSO).

Rare side effects (may affect up to 1 in 1,000 people) are:
- abnormal muscle movements (such as shaking, muscle rigidity and muscle contractions).

Side effects with a frequency not known (cannot be estimated from available data):
- allergic skin reactions. The signs may include red, raised itchy bumps

Other possible side effects associated with granisetron products (frequency not known):
- Allergic reactions including urticaria (itchy, red, raised skin rash) and anaphalaxis (a serious allergic reaction which may include sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching)
- Difficulty sleeping/disturbed sleep
- Excessive sleepiness
- Prolonged QT interval in the ECG (changes to the heart rate trace (ECG) indicating a heart rhythm disorder)
- Constipation
- Diarrhoea
- Lack of energy/weakness /Loss of strength

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SANCUSO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and the sachet after 'EXP'. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Used transdermal patches still contain active ingredients, which may be harmful to others. Fold the used transdermal patch in half with the sticky side inwards and dispose of it safely, out of the reach of children. Do not throw away any medicines via wastewater or household waste.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help

protect the environment.

6. Contents of the pack and other information

What SANCUSO contains
- The active substance is granisetron. Each 52 cm^2 transdermal patch contains 34.3 mg of granisetron, releasing 3.1 mg of granisetron in 24 hours.
- The other ingredients are:
- Transdermal patch adhesive: acrylate-vinylacetate copolymer
- Backing layer: polyester
- Rigid plastic film: siliconised polyester

What SANCUSO looks like and contents of the pack
SANCUSO is a thin, clear, rectangular-shaped transdermal patch with rounded corners, stuck onto a rigid plastic film. The transdermal patch is contained in a sachet. Each carton contains one transdermal patch.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands
Tel: +31 (0) 237200822

Manufacturer
Pharbil Waltrop GmbH (a subsidiary of NextPharma)
Im Wirrigen 25
45731 Waltrop
Germany

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu