Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Granisetron

Proprietary Product Name: Sancuso

Sponsor: Invida Australia Pty Ltd

**June 2011**

TGA Health Safety Regulation

## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | New Route of Administration and New Dosage Form |
| *Decision:* | Approved |
| *Date of Decision:* | 2 March 2011 |
| | |
| *Active ingredient(s):* | Granisetron |
| *Product Name(s):* | Sancuso |
| *Sponsor's Name and Address:* | Invida Australia Pty Ltd<br>Level 8/67 Albert Avenue<br>Chatswood NSW 2067 |
| *Dose form(s):* | Transdermal patch |
| *Strength(s):* | 3.1 mg/24 hours |
| *Container(s):* | Sachet |
| *Pack size(s):* | 1 sachet |
| *Approved Therapeutic use:* | The prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration. |
| *Route(s) of administration:* | Transdermal |
| *Dosage:* | One patch for up to 5 days |
| *ARTG Number (s)* | 165621 |

## Product Background

Granisetron is a 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist which is currently registered in Australia in injection and tablet formulations (Kytril, Roche Products). The approved indications for the registered products include the prevention of chemotherapy induced nausea and vomiting (CINV).

This AusPAR describes the evaluation of an application from a different sponsor, Invida Australia Pty Ltd, through its agent Commercial Eyes Pty Ltd, seeking approval of a transdermal patch presentation of granisetron. The proposed indication is:

*For the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.*

There are several 5-HT$_3$ receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron and tropisetron) registered in Australia, in various dosage forms including injection, tablets, capsules, syrup, suppositories and wafers. 5- HT$_3$ receptor antagonists block serotonin receptors and subsequently the neuronal cascade of events leading to nausea and vomiting is in effect blunted or blocked from further activation.[1] The proposed product is the first transdermal patch presentation for this class of drugs.

[1] EMA. EPAR for Aloxi (palanosetron). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000563/WC500024256.pdf

Sancuso is a thin translucent matrix type transdermal patch, which is rectangular with rounded corners consisting of backing of the drug matrix and a release liner. The patch is 52 $cm^2$ in size (approximately 8 x 6.7 cm) and contains a total of 34.3 mg of granisetron. It releases 3.1 mg of granisetron per 24 hours. The proposed dosage regimen is for the patch to be applied 24 – 48 hours before chemotherapy, and to remain in place until at least 24 hours after completion of chemotherapy. The maximum proposed duration of patch application is 7 days.

### Regulatory Status

A similar application was approved in the United States on 12 September 2008 for the same indication as proposed in Australia. A submission was made to the European Union (EU) on 12 July 2007. Following conclusion of the Decentralised Procedure (Procedure DK/H/1306/01/DC) and discussions with the European Commission the application was resubmitted via the Centralised Procedure. No application at this time has been made to Canada or New Zealand.

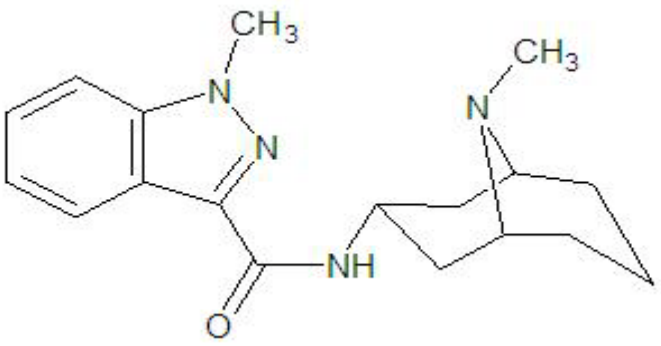
### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

### Drug Substance (active ingredient)

Granisetron is synthetic. It is achiral. The transdermal patch is formulated with granisetron base. The drug is dissolved during patch manufacture.




granisetron $C_{18}H_{24}N_4O$ MW 312.4

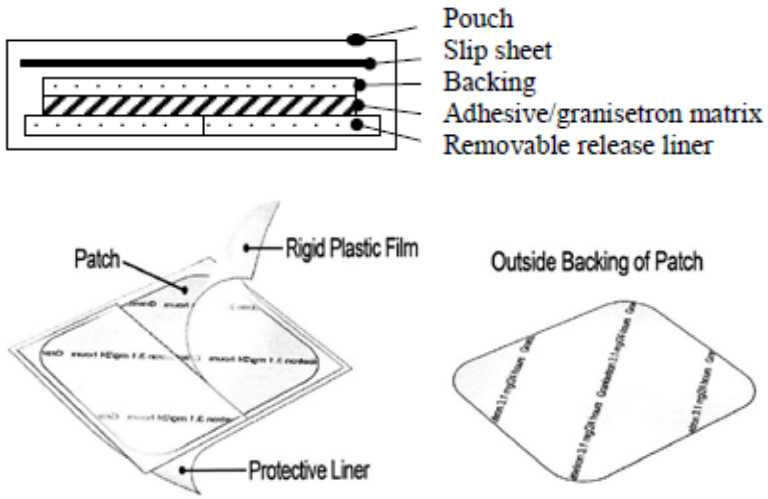
The free base was chosen (rather than the established hydrochloride salt) because it was anticipated to have higher skin permeability. Controls on the drug substance are based on official standards for the hydrochloride salt (total impurities not more than [NMT] 1.0%).

### Drug Product

Sancuso patches are a transdermal drug delivery system with granisetron incorporated in a self-adhesive polymer matrix. The patch is supplied in a sachet, with a thin protective 'slip sheet' over the printed, outer, backing sheet. The patch is applied by sequentially removing a two-section, rigid, 'release liner' from the drug side. This puts the drug/adhesive mixture in direct contact with the skin. The patch is rectangular with rounded corners; it is relatively large (80 x 67 mm = 52 $cm^2$). A cross-sectional diagram of

the system and its primary packaging is shown in Figure 1, together with overviews of the patch.

**Figure 1: Details of the proposed patch**




The layer in direct skin contact contains the drug (34.3 mg) and a proprietary acrylate-vinyl acetate adhesive. Residual acrylate monomer levels are acceptably controlled. The patches are made by dissolving granisetron in a solvent, mixing with an ethyl acetate solution of the adhesive, coating liner sheets, then drying to remove the solvents.

The patch formulation has not changed during the clinical studies, although the area of the patch used differs in some studies.

The nominal drug delivery (3.1 mg/24 hours) is based on the amount of unrecovered drug after 7 days in the clinical study 392MD/26/C.

There are routine batch controls on adhesion and peel force. The pharmacokinetic study 392MD/11/C reports two of 36 patches were lost (5%; on Day 4 and Day 5), and suggests that adhesion was affected because the study was conducted in summer (with higher perspiration).

Granisetron in the patch is degraded if exposed to sunlight when removed from the sachet (for example, in use).

***Characterisation of granisetron in adhesive***

The quality evaluator suggested that the physicochemistry of granisetron in the adhesive after drying was poorly characterised. The solubility of the drug in the adhesive was not disclosed in the original submission.

The sponsor stated that the solubility of granisetron base in the adhesive was estimated by calculation during product development. An AAPS Poster *Predicting Drug Solubility In Transdermal Adhesives* was provided (R6290: P. Foreman et al, National Starch and Chemical Company); this describes prediction of drug solubility in adhesives using computational approaches (with known values for polymer water absorption and drug octanol-water partition coefficient).

This, together with low levels of observed crystallisation, suggests granisetron is a supersaturated solution, a microdispersion or a solid solution in the adhesive. It is unclear whether the adhesive is susceptible to rheological transitions.

The sponsor argued that "the prolonged flux observed in the clinical studies is achieved by means of a dynamic process involving the solid solution continually feeding the supersaturated solution, thereby sustaining the concentration gradient between the patch and the skin over the treatment period. This is supported by the finding that, on average, residual drug remains in the patches after clinical treatment, which still provides sufficient drug to achieve supersaturation in the adhesive matrix (that is, well above the calculated solubility figure)."

***Crystallisation***

Granisetron is apparently dissolved in the adhesive matrix as a supersaturated solution, although this has not been rigorously characterised. Visible crystallisation of granisetron (about 1 mm long) has been observed in some patches on storage. There is a visual test for crystallisation of the drug in the patches. Some patches used in clinical trials would have contained crystallised drug, however, this was not characterised at the time.

It remains unclear whether there are pharmaceutically significant differences between batches or physicochemical changes on storage in granisetron in the patches. It is possible that subvisible changes might affect drug release. Some exploratory data on the *in vitro* flux of granisetron through a silicone membrane were provided and suggest that visible crystallisation might not significantly affect drug release. The sponsor argued that observed levels of visible crystallisation are low, consistent and without a significant trend on storage. It is likely that comparable levels have been present in patches used in clinical trials. "The low levels of crystals observed are considered insignificant to the performance of the product, particularly because residual drug is still present in the patch after treatment and the low level of crystal content would represent a very low proportion of this amount."

However solid drug does not drive diffusion and changes in crystal size or form could theoretically affect patch performance.

***In vitro Release***

*In vitro* drug release is routinely monitored for each batch with the patch taped (drug layer outwards) on a steel cylinder rotated in an appropriate medium at 32ºC. Limits are proposed for drug release at times up to 72 hours. This provides some test of product consistency (but obviously does not mimic the skin barrier which probably controls absorption *in vivo*). No direct investigation was made as to whether this routine *in vitro* test method is discriminatory (for example, able to detect batches with crystallised drug). All available batch data are very similar, although much wider limits are proposed and are unlikely to provide significant control on any future variability.

The sponsor argued that the test "is designed to provide a quality control tool with which to assess the reproducibility of finished product batch manufacture." The sponsor noted very consistent *in vitro* dissolution profiles have been seen, notwithstanding variations in sample crystallisation. The sponsor argues that the test method is discriminatory and has provided some laboratory evidence.

The sponsor argues that deriving an *in vitro/in vivo* correlation is not feasible (and has not been attempted) because 90% of the drug is released *in vitro* in about 2 days, whereas only about 50% is absorbed *in vivo* over 5 days. *In vivo* flux is also controlled by the rate of passage through the skin rather than release rate from the product.

The sponsor argued that, given that the *in vitro* dissolution profiles are very consistent, it is not feasible to obtain patches with distinct *in vitro* release profiles without radically changing the formulation. Thus it is not possible to produce appropriate slow, target and fast release batches for conducting an *in vitro*/*in vivo* correlation study.

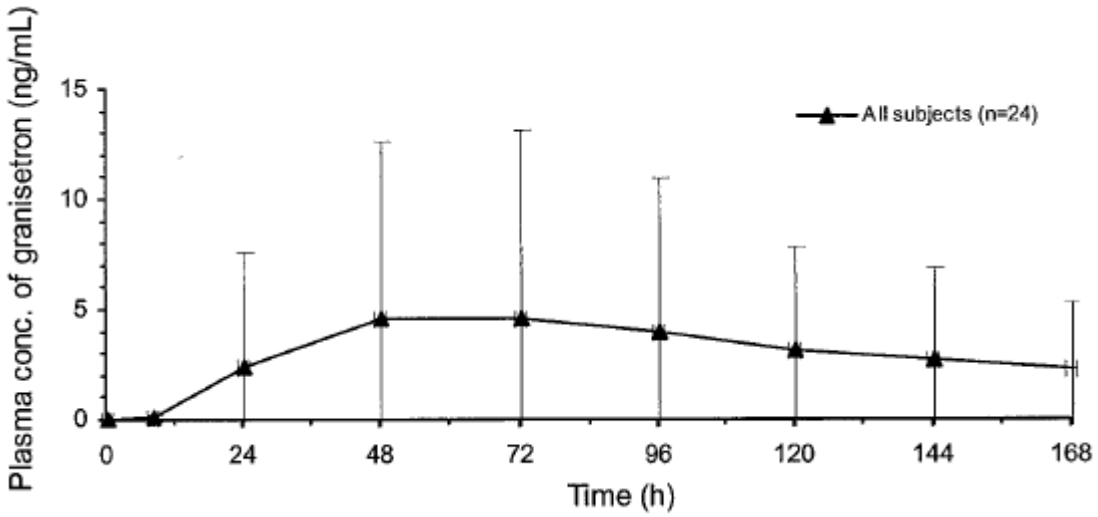
It was claimed that any variation in the finished product that would cause a difference in clinical performance would be noted during routine batch analysis.

## Bioavailability

Drug release was determined in most of the clinical studies by measuring residual granisetron in patches after removal from patients after 5 or 6 days. For the proposed 52 $cm^2$ patch, this allowed calculation of drug release by difference: mean 3.51 [standard deviation (SD) 0.90] mg/day and 3.68 [0.51] mg/day in two studies. The label claim of 3.1 mg/day is based on the mean drug release from patches in the 7-day study 392MD/26/C (Coefficient of variation [CV]: 16.6%).

The proposed PI shows a mean plasma graph (Figure 2) with a fairly steady increase up to about 48 hours, then declining concentrations up to 168 hours (7 days), albeit with significant intersubject variability:

**Figure 2: Mean plasma concentration of granisetron (mean ± SD)**

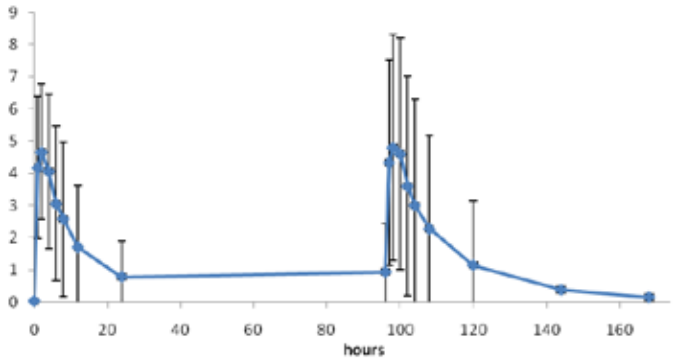



Drug absorption from three patch sizes [15 $cm^2$ = 9.9 mg; 33 $cm^2$ = 21.8 mg; 52 $cm^2$ = 34.3 mg] was measured in 12 subjects in crossover study 329MD/11/C. Granisetron release proportional to the area of the patch was claimed.

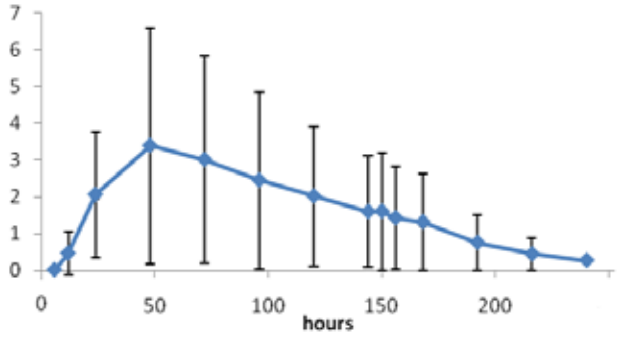
One pharmacokinetic study was evaluated by the quality evaluator. **Study 392MD/11/C** was a four way crossover comparison of three different patches applied to the upper arm and granisetron hydrochloride tablets in 12 healthy males. Two of the three patches were different sizes to the proposed formulation ('D' = 15 $cm^2$ ≡ 9.9 mg of granisetron total; 'C' 33 $cm^2$ ≡ 21.8 mg; 'B' 52 $cm^2$ ≡ 34.3 mg [proposed size]) applied for 6 days. Tablet doses ('A'; 2 mg) were taken daily for 5 days. Kevatril tablets were sourced from Roche, Germany. There was a 5 day washout between doses.

The plasma profiles on the first and fifth days with tablet dosing are variable – the area under the plasma concentration time curve (AUC) CV 96% and 120%. The results (Figure 3) suggest slight accumulation (possibly confounded by limited pharmacokinetic sampling), with steady state by about the second day.

**Figure 3: Plasma granisetron (ng/mL): mean ± SD (TGA Plot)**




2 mg tablets




52 cm$^2$ patches

The proposed 34.3 mg/52 cm$^2$ patches gave a mean area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) of 420 ng.h/mL (CV% 89) over 6 days; daily 2 mg Kevatril tablet dosing gave a final mean daily area under the plasma concentration time curve from time zero to 24 hours ($AUC_{0-24}$) of 62 ng.h/mL (CV% 110). Peak concentrations were lower with the patches as expected (patch: mean maximal plasma concentration [$C_{max}$] 3.85 ng/mL [SD 3.0]; 2 mg Kevatril tablet mean $C_{max}$ 5.25 ng/mL [SD 2.2] Day 1 and mean 5.5 ng/mL [SD 3.8] on Day 5).

There is some difficulty in usefully comparing variability in plasma profiles of patches and tablets. The sponsor argues that the variability after patch dosing (AUC CV 89%) is comparable to that seen with the tablets and also as reported for oral (1 mg: CV 82%) and even intravenous dosing (infusion: AUC CV 100% or 79%). In Study 392MD/11/C above, with tablet dosing AUC CV% was 96 and 120% on first and fifth days respectively.

## Advisory Committee Consideration

The application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 135th meeting.

The PSC queried the available batch analyses and noted that updated information will be presented to the PSC.

The Committee drew attention to the fact that some of the clinical and pharmacokinetic studies used Kevatril granisetron tablets (encapsulated in some studies). These appear to have been sourced overseas: no *in vitro* comparison was provided and it is not clear whether they would be bioequivalent to Australian Kytril tablets. The sponsor argued that the application does not rely on the demonstration of bioequivalence given other clinical data.

The PSC was unable to recommend approval for registration on pharmaceutic and biopharmaceutic grounds due to the deficiencies in the data provided in support of this application which make it difficult to fully characterise the drug product. In particular, the Committee raised concerns about the high degree of variability in bioavailability observed in Study 392MD/4/C and the absence of *in vitro in vivo* correlation (IVIVC) data.

The PSC asked to see responses to these issues: some of the response data are summarised above, and the detailed reports were presented to the PSC immediately prior to the ACPM meeting.

At that second PSC consideration at its 136th meeting, the PSC agreed that some of the issues of concern raised at its 135th meeting had been resolved.

The PSC noted that bioequivalence has not been established between the proposed formulation and the currently registered tablet formulation available for supply in

Australia. The Committee considered that this may be acceptable if safety and efficacy data were adequate.

The PSC noted new information comparing the pharmacokinetic variability of other granisetron dosage forms.

The Committee recommended that the pharmacokinetic variability observed with this product should be considered in the context of variability in the clinical efficacy and safety data.

The Committee agreed that the attention of the Delegate and the Advisory Committee on Prescription Medicines (ACPM) should be drawn to the high rate of patch loss, particularly in hot climates.

The PSC concluded that there should be no objection on pharmaceutic and biopharmaceutic grounds to the approval of this application provided all outstanding issues were addressed to the satisfaction of the TGA.

### Quality Summary and Conclusions

Constraint on the approved commercial batch scale was considered appropriate. The *in vitro* drug release test was not considered to provide good routine control. The PSC concluded that there should be no objection on pharmaceutic and biopharmaceutic grounds to the approval of this application provided all outstanding issues were addressed to the satisfaction of the TGA.

The pharmacokinetic variability was ultimately an issue for clinical judgement.

## III. Nonclinical Findings

### Introduction

Granisetron has been registered on the Australian Register of Therapeutic Goods (ARTG) as tablet and intravenous (IV) injection forms since 1997 and 2005, respectively. For both formulations, the maximum recommended human dose (MRHD) is 9 mg/day granisetron as base for adults. In this application, the sponsor sought registration of a granisetron base transdermal system (TDS) (34.3 mg/52 $cm^2$ patch) at the daily dose of 3.1 mg for adults. Therefore, systemic exposure to granisetron administered by the proposed TDS would be lower than that at the MRHD of the registered granisetron IV injection and tablet products. For this reason, this report mainly focuses on the assessment of local tolerance of granisetron TDS and safety of the adhesive contained in the proposed product.

The nonclinical data provided in relation to the TDS patch included four repeat dose toxicity studies, one skin sensitisation study and three phototoxicity studies. The systemic toxicity from sustained exposure to granisetron was also assessed in rat and dog studies by continuous IV infusion. All toxicity studies were conducted in compliance with Good Laboratory Practice (GLP). In the repeat dose toxicity studies, effects of granisetron were evaluated in rats and dogs following TD, IV or oral (PO) administration. The data provided were sufficiently comprehensive.

## Pharmacology

### *Primary pharmacodynamics and efficacy*

No new pharmacology data were submitted in the current application. In previously evaluated studies on granisetron, granisetron was shown to be highly selective for the 5-hydroxytryptamine-3 (5-$HT_3$) receptor and a specific 5-$HT_3$ antagonist. Among its metabolites, two metabolites (N1-desmethyl granisetron and 7-hydroxy granisetron) were also active. In animal studies, granisetron was shown to be a potent antiemetic in situations where the emetic response involved activation of 5-$HT_3$ receptors, as in the case of emesis induced by cytotoxic drugs and X-irradiation. Against cisplatin-induced emesis in animal models of emesis induced by chemotherapy, granisetron was equally effective by the PO, IV, intramuscular (IM) and subcutaneous (SC) routes. No nonclinical study was provided to investigate antiemetic or antinausea efficacy of granisetron following the application of TDS at the proposed dose.

### *Safety pharmacology*

No new data were provided for the current application. This is acceptable for a drug product with a lower dose and plasma concentration than the registered products for the same indication.

## Pharmacokinetics

Pharmacokinetics data on granisetron were not submitted in this application. However, toxicokinetic data were generated in repeat dose toxicity studies in rats and dogs. Absorption of granisetron from the TD patch was demonstrated in both species. Sustained systemic exposure was attained in both species following administration of the patch or continuous IV infusion. Although there were differences in plasma granisetron concentration between male and female animals in each study, $C_{max}$ and AUC in all studies were high relative to those observed in humans at the proposed clinical dose. Systemic exposures achieved in rats and dogs are compared with the clinical exposure below.

### *Relative exposure*

In a clinical study (392MD/26/C), mean $C_{max}$, average plasma concentration ($C_{avg}$) and the area under the plasma concentration time curve from time zero to 168 hours ($AUC_{0-168}$) values of granisetron were 5.0 ng/mL, 3.2 ng/mL and 530 ng·h/mL, respectively, following application of the granisetron patch at the patch size of 52 $cm^2$ (34.3 mg granisetron contained) to healthy subjects (males and females; N=24) for 7 days, which is the proposed clinical dose and dosing duration. Based on this data, exposure ratios of granisetron between humans and animals are calculated as shown in Table 1.

**Table 1: Relative exposure following application of the granisetron patch or continuous IV infusion in repeat dose toxicity studies**

| Species | Study duration | Dose | $C_{max}$ (ng/mL) | $AUC_{0-168}$ (ng.h/mL) | ER based on $C_{max}$ | ER based on AUC | Study |
|---|---|---|---|---|---|---|---|
| Rat | Two patches once weekly for 2 weeks | 10% BSA | 37 | 2306 | 7.4 | 4.4 | 19138/05 |
| Dog | Continuous IV infusion for 2 weeks | 1, 3, 9 mg/kg/day | 7.4, 22, 63 | 1063, 3108, 9461 | 1.5, 4.4, 13 | 2.0, 5.9, 18 | 19293/05 |
| | Two patches once weekly for 14 days | 10% BSA | 79 | 6177 | 16 | 12 | 19140/05 |
| | Continuous IV infusion for 2 weeks | 0.3, 1, 3 mg/kg/day | 3.7, 9.8, 35.5 | 522, 1475, 4669 | 0.7, 2.0, 7.1 | 1.0, 2.8, 8.8 | 19336/05 |
| Human | A single patch for 7 days | 52 $cm^2$ | 5.0 | 530 | - | - | 392MD/26/C |

BSA: Body surface area, ER: Exposure ratio

## Toxicology

### *General toxicity*

Systemic and local toxicity was studied with the patch in rats and dogs with consecutive applications of a granisetron patch at the patch size of 10% body surface area (BSA) once weekly for 2 weeks. In addition, systemic toxicity was also studied by continuous IV infusion to achieve sustained exposure to granisetron in these species. The patch was also assessed for phototoxicity, photoallergenicity and photogenotoxicity in appropriate *in vitro* assay or animal models (discussed under *Phototoxicity* below). The studies were adequately performed and parameters examined were extensive.

### *Local tolerance and skin sensitisation*

Effects of the granisetron patch at 10% BSA were compared with those of the placebo control patch in both sexes of rats and dogs, following application once weekly for 2 weeks. In all animals including the placebo patch group, erythema was observed at the patch site. The severity of erythema was greater in rats (well defined to moderate/severe) than in dogs (very slight to well defined) for the test group. In rats, oedema was not seen macroscopically but was observed in both groups (except for females in the placebo patch group) by microscopic examination, whilst the opposite finding (oedema seen in the macroscopic examination, not in the microscopic examination) was observed in dogs. In the microscopic examination, an increased incidence of inflammatory reactions localised at the patch site was observed in the test group of rats, compared to that in the placebo control group, which is consistent with macroscopic observation (increased severity of erythema) in this species. However in dogs, no differences were found in the incidence or severity of inflammatory reactions between the placebo and test patch groups. Nevertheless, the severity of all incidents was minimal to mild (score ≤ 2 out of the range 0-4) in both groups of both species in the microscopic observation although higher scores were recorded by macroscopic examination (score 1-4 in rats and 1-2 in dogs out of the range 0-4).

In the skin sensitization study conducted in male guinea pigs, neither the placebo control nor test patch (granisetron TDS) caused any skin reactions at the Induction and Challenge Phases, whilst all animals had skin reactions in the positive control group. Therefore, the patch is not considered to have sensitising potential.

***Systemic effects***

Systemic toxicity of granisetron has been assessed in previous applications for the oral and IV dosage forms. In the new studies provided in this submission, no new systemic toxicity was observed in the patch and continuous IV infusion studies with sustained exposure to granisetron at up to 18 times the expected clinical exposure based on AUC. The only finding that was probably related to treatment was mild hepatic lesions (lympho-histiocytic infiltration, mixed cell foci and fatty infiltration) in rats with the patch and IV and/or PO dosing. The liver was identified as the target organ in previously evaluated studies in rats by the IV and PO routes.

***Genotoxicity and carcinogenicity***

No new data were provided, except for a photogenotoxicity study. However, these toxicities of granisetron have been assessed previously. In the newly provided data, granisetron was found to be photogenotoxic and details of this toxicity is discussed in the Phototoxicity section below.

***Phototoxicity***

Unlike from IV or oral administration of a drug substance, patch application related concerns include sustained high concentrations of the drug substance on the skin. To investigate the phototoxicity of granisetron in the proposed TDS, two *in vitro* and one *in vivo* studies were performed.

Granisetron did not display phototoxicity in the 3T3 NRU assay, which is an acceptable *in vitro* assay for testing phototoxicity. The granisetron base was not cytotoxic in mouse fibroblasts in the presence of UV-A (5 J/cm$^2$) at concentrations of up to 1000 µg/mL in the 3T3 NRU *in vitro* assay. However, in another *in vitro* study, granisetron was positive in a chromosomal aberration assay performed in Chinese hamster ovary (CHO) cells following UV irradiation. For the experiment, cells were exposed to the test article for 3 hours in the absence or presence of UV-A/UV-B (700mJ/cm$^2$) and harvested after recovery for 17 hours. In irradiated cells, a statistically significant increase in the percentage of cells with chromosomal damage was observed at granisetron concentrations of 200 and 300 µg/mL (13 and 33 % of cells respectively, as compared to 2.5 % in irradiated vehicle control cells). This result indicates that granisetron base is photogenotoxic. Therefore patients should avoid exposure to UV light, including sunlight, during application of the granisetron patch and for a period of time until the drug is completely cleared from the skin after patch removal. The sponsor proposed 10 days of protection of the patch application site after patch removal (proposed Product Information). The adequacy of the proposed period of protection from sunlight should be confirmed by clinical data.

Photoirritation and photosensitization were tested in guinea pigs following application of placebo and test patches (10 cm$^2$/each) for several periods of days over a total testing period of 31 days with/without exposure to UV-A/UV-B (15-17 J/cm$^2$ for UV-A and 0.1-0.2 J/cm2 for UV-B) four times at defined intervals. In this study, there were no skin reactions in any of the groups tested and therefore placebo and test patches were considered not to be photoirritating or photosensitising. The study was adequately performed with appropriate controls.

***Excipient***

The adhesive contained in the granisetron TDS is an adhesive copolymer manufactured from 2-ethylhexylacrylate, vinyl acetate, 2-hydroxyethylacrylate and glycidylmethacrylate. This substance has been registered as a proprietary ingredient on the ARTG and was used in other TD patches, which had subsequently been cancelled by their sponsor from the ARTG. However the weekly dose of the adhesive to be administered by the granisetron TDS is approximately twice that (maximum 118.4 mg/unit twice weekly) administered by other TD patches.

In the repeat dose toxicity studies provided in this submission, the animals were given placebo or drug patches and no control patch for the adhesive (that is, a patch without the adhesive or no patch applied) to assess the effects of this excipient contained in the placebo patch. As indicated above, erythema and oedema were observed at the patch application site in both rats and dogs treated with the placebo and test patches.

In regard to cytotoxicity, it was explained that the adhesive was not cytotoxic when tested according to the United States Pharmacopoeia Minimal Essential Medium Elution Method in the sponsor's *Nonclinical Expert Report* but the study report was not provided.

In regard to systemic effects, the adhesive is a copolymer which has a large molecular weight and is unlikely to be absorbed through the skin. The potential systemic effects of residual monomers in the adhesive were assessed and the proposed limits are toxicologically acceptable.

## Nonclinical Summary and Conclusions

Absorption of granisetron from the TD patch was demonstrated in rats and dogs, the animal species used in toxicity studies. Sustained systemic exposure was attained in both species following application of the patch or continuous IV infusion. Although there were differences in plasma granisetron concentrations between male and female animals in each study, plasma $C_{max}$ and AUC in all studies were high relative to those observed in humans at the proposed clinical dose.

Following application of a granisetron patch at the patch size of 10% BSA once weekly for two weeks to rats, all animals had erythema at the patch site with an increased severity (well defined to moderate/severe) in the test group, compared to that (very slight to well defined) in the placebo patch group. In dogs, oedema was also seen, but there was no difference in severity (very slight to well defined) in the placebo and test patch groups. These observations were confirmed by the microscopic findings, such as minor degrees of inflammatory reactions localised at the patch site in both species, with a higher incidence in rats. Granisetron was negative in a skin sensitisation test conducted in guinea pigs.

No significant systemic toxicity was observed in rats and dogs due to the administration of granisetron by the patch or continuous IV infusion at systemic exposures up to 18 times the clinical exposure based on AUC. No new toxicity was observed in rats and dogs with the patch dosage form. The only finding that was probably related to treatment was mild hepatic lesions (lympho-histiocytic infiltration, mixed cell foci and fatty infiltration) in rats with the patch and IV and/or PO dosing. Liver was identified as the target organ in previously evaluated studies in rats by the IV and PO route.

Granisetron was not phototoxic in an *in vitro* test and not photoallergenic in guinea pigs. However, granisetron was photogenotoxic in an *in vitro* chromosomal aberration assay conducted in Chinese hamster ovary cells. Therefore, patients should avoid exposure to UV light including sunlight during application and for a period of time until complete clearance from the skin after removal of the patch. The adequacy of '10 days' of protection

from sunlight following patch removal proposed in the draft Product Information should be assessed by the clinical evaluator.

The adhesive is an adhesive copolymer consisting of 2-ethylhexylacrylate, vinyl acetate, 2-hydroxyethylacrylate and glycidylmethacrylate. This substance appeared on the ARTG and had been used in other transdermal (TD) patches, which are no longer registered in Australia. Since no studies specifically investigating the toxicity of this adhesive were provided and there was no control group for the placebo patch in the dermal studies, it was difficult to assess the toxicity of the adhesive in the proposed product. However, there were well-defined or moderate/severe erythema at the patch site in rats and dogs following application of the placebo patch containing the adhesive once weekly for two weeks. In addition, the polymer is not expected to be absorbed dermally. The proposed limits of residual monomers contained in this excipient are toxicologically acceptable.

The granisetron TDS is a new dosage form. The dose of granisetron (3.1 mg/day) in the proposed TDS is lower than the maximum dose (9 mg/day) recommended for the registered IV injection and tablet formulations.

There were no nonclinical objections to the registration of the proposed product.

# IV. Clinical Findings

## Introduction

A total of five studies were provided in this submission. Study 392MD4C (Study 4) and Study 392MD11C (Study 11) were two trials in healthy subjects to determine the relevant pharmacokinetics for the granisetron transdermal system. Study 392MD26C (Study 26) was also a study in healthy subjects to determine potential sensitivity of the transdermal patches. Studies 392MD8C (Study 8) and 392MD15C (Study 15) were two clinical trials to compare the potential of the granisetron transdermal system to placebo (Study 8) or oral granisetron (Study 15).

## Pharmacokinetics

Pharmacology for oral and intravenous granisetron has been evaluated in previous submissions. Details regarding relevant absorption, distribution and metabolism and elimination of granisetron with these formulations has been previously submitted and assessed.

The current submission provides information on granisetron pharmacokinetics from the five clinical studies indicated above. Principal pharmacokinetic studies in this submission involved Study 4 and Study 11.

### *Study 4*

Study 4 was a single centre single dose study in 12 healthy subjects (six males and six females) to evaluate the systemic bioavailability of 15 $cm^2$ granisetron TDS and to determine the pharmacokinetic profile over an application period of five days on the abdomen. The dermal irritation potential as well as patch adhesiveness was also assessed. A placebo patch was administered concurrently to assess any differences in the dermal irritation potential and adhesivity versus the active one.

Thus the primary objective of this trial was to confirm the systemic bioavailability of granisetron from a transdermal patch. The secondary objectives were to assess the pharmacokinetic profile of granisetron delivered from the transdermal patch; to assess the dermal irritation potential of the transdermal patch compared to that of the placebo

transdermal patch. Also the local and systemic safety of granisetron transdermal patch was to be assessed.

The study was conducted in Germany with enrolment from 24 June 2003 to17 July 2003.

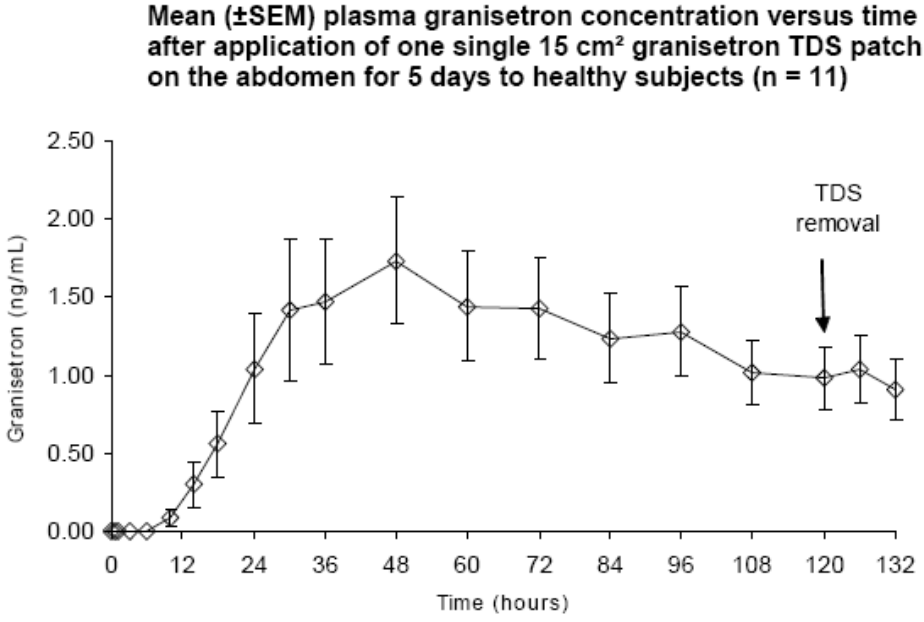
Pharmacokinetic criteria for evaluation included AUC. $C_{max}$, time to maximal plasma concentration ($t_{max}$), half-life ($t_{1/2}$), CL-F and V-F of granisetron in plasma were also assessed.

The mean age of all 12 subjects enrolled was 31.4 years with a mean weight of 68.3 kg and a mean body mass index (BMI) of 23.0 kg/m$^2$.

Granisetron was slowly absorbed through the skin with all subjects except one demonstrating quantifiable plasma concentration of granisetron within 24 hours after granisetron TDS application. In one subject the patch delivered 6.5 mg of granisetron, but the granisetron was not quantifiable in plasma at any time point. As a consequence this patient was excluded from the pharmacokinetic analysis.

Peak concentrations were observed within 24-30 hours after granisetron TDS application and the mean average concentration over the total period was 1.12 ng/mL (Figure 4). The concentrations declined slowly until patch removal at 120 hours after application. No significant decreases in granisetron concentrations were observed 12 hours after granisetron TDS removal. This pattern may be explained by the slow rate of passage of granisetron through the skin layers and continuous release of the drug into the blood stream.

**Figure 4: Granisetron concentration vs time**




The mean amount of granisetron remaining in the granisetron TDS 15cm$^2$ after removal was 44%, which corresponds to a measured flux of 1.11 mg/24 hours. This value was consistent with the estimated in vivo flux values calculated based on systemic granisetron exposure of 1.47 mg/24 hours.

This study therefore demonstrated the sustained bioavailability of granisetron via a patch. However the results showed that a larger patch size would be required to achieve comparable exposure to that obtained with a 2 mg dose of oral granisetron.

***Study 11***

The second pharmacokinetic study (Study 11) was a single centre open label four way crossover study to compare the bioavailability of granisetron after a single six day application of three doses of granisetron TDS to that of a 2 mg once daily oral dose of granisetron tablets for five days. This study also assessed the dose proportionality of granisetron pharmacokinetics after patch application. Also to be assessed were local tolerance, safety, tolerability and adhesion of the granisetron TDS.

A total of 12 healthy male subjects were to receive oral granisetron administered as 2 mg orally, once daily for five days and three doses of granisetron TDS (15, 33 and 52 $cm^2$) applied for six days to the upper outer arm. Each treatment was separated by a washout period of at least five days. The three doses of granisetron TDS were 34.3 mg with a 52 $cm^2$ patch, 21.8 mg with a 33 $cm^2$ patch and 9.9 mg with a 15 $cm^2$ patch.

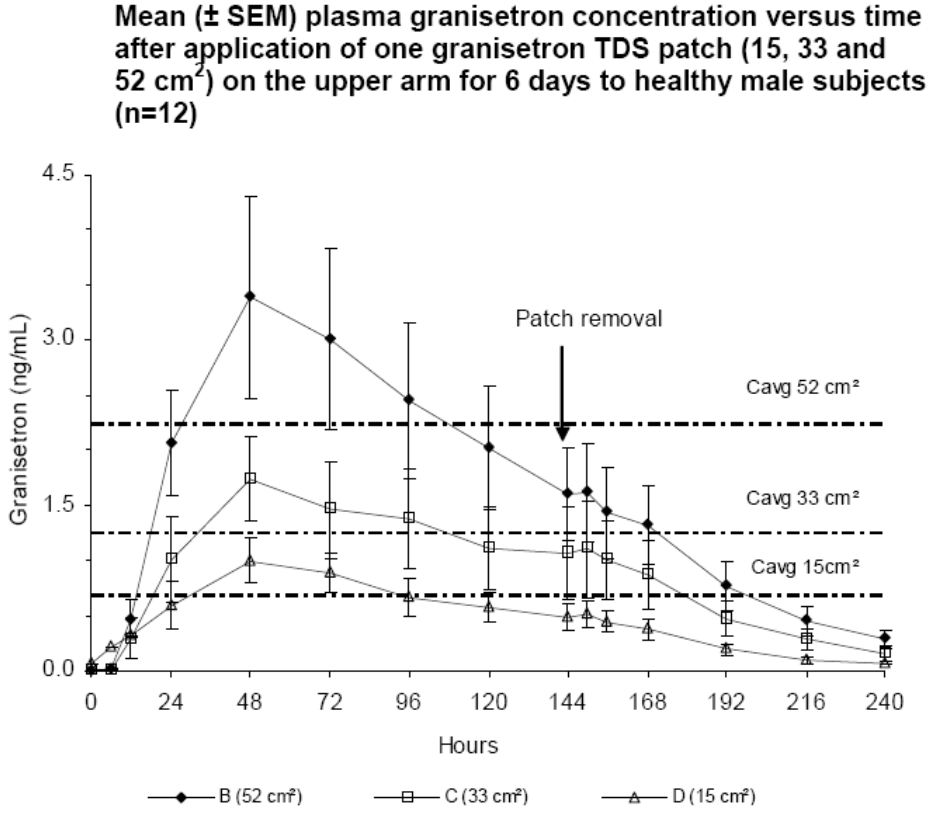
Pharmacokinetic parameters measured included $C_{max}$, $t_{max}$, $t_{1/2}$, $C_{avg}$ and AUC calculated as $AUC_{(0\text{-}24)}$ hours for oral dosing and as $AUC_{(0\text{-}144)}$ hours for TDS application.

Local tolerance was assessed by a scoring system, clinical examination and occurrence of adverse events.

The mean age of the 12 subjects entered into the study was 37.1 years and a mean weight of 76.8 kg and a mean BMI of 24.2 $kg/m^2$.

Mean granisetron concentrations vs time curves for the three granisetron TDS administrations are shown in Figure 5.

**Figure 5: Plasma granisetron concentration vs time**



During once daily dosing of 2 mg oral granisetron for five days, granisetron steady state was reached after the second dosing day. No accumulation of granisetron was observed either on $C_{max}$ or AUC after multiple oral dosing; the overall exposure after five days was 302 ng/mL.hour. The terminal half-life of granisetron was similar after single and multiple oral dosing with a mean value of 6.4 – 7.9 hours. At steady state mean average ($C_{avg}$) and maximal ($C_{max}$) plasma concentrations of granisetron were 2.60 and 5.5 ng/mL respectively. In-between subject variability the oral granisetron pharmacokinetics was high as shown by between subject co-efficient variations (CV) which ranged from 42-68% for $C_{max}$ and from 80-120% for AUC.

With granisetron TDS application for six days, granisetron was slowly absorbed with a maximum concentration reached 48 hours post application with mean values of 1.15, 2.08 and 3.85 ng/mL for the 15, 33 and 52 $cm^2$ patches respectively. Concentrations decreased until patch removal which took place at 144 hours.

Within 24 hours of patch removal a decrease of 18-23% was observed in plasma granisetron concentrations which then increased according to a monophasic profile.

Elimination half-life after granisetron TDS was higher than after oral dosing and ranged between 30.9-35.9 vs 6.4-7.9 hours seen following oral administration.

The absorption of granisetron after patch application was slow and the elimination of granisetron was artificially prolonged due to continued absorption from the skin leading to increase apparent elimination half-life.

The mean $C_{avg}$ for granisetron was 0.68 ng/mL, 1.24 ng/mL and 2.23 ng/mL for the 15 $cm^2$, 33 $cm^2$ and 52 $cm^2$ patch sizes respectively. Based on $C_{avg}$ , 52$cm^2$ granisetron TDS applied for six days resulted in similar $C_{avg}$ concentrations to those obtained with once daily oral dosing of 2 mg granisetron.

The between subject variability of the granisetron pharmacokinetics after patch application was high but of similar magnitude to that seen after oral dosing. This is shown by between subject coefficient variations (CV) ranged from 83-110% for $C_{avg}$ and 72-95% for AUC after granisetron TDS and ranging from 80-110% for $C_{avg}$ and 96-120% for AUC for oral granisetron.

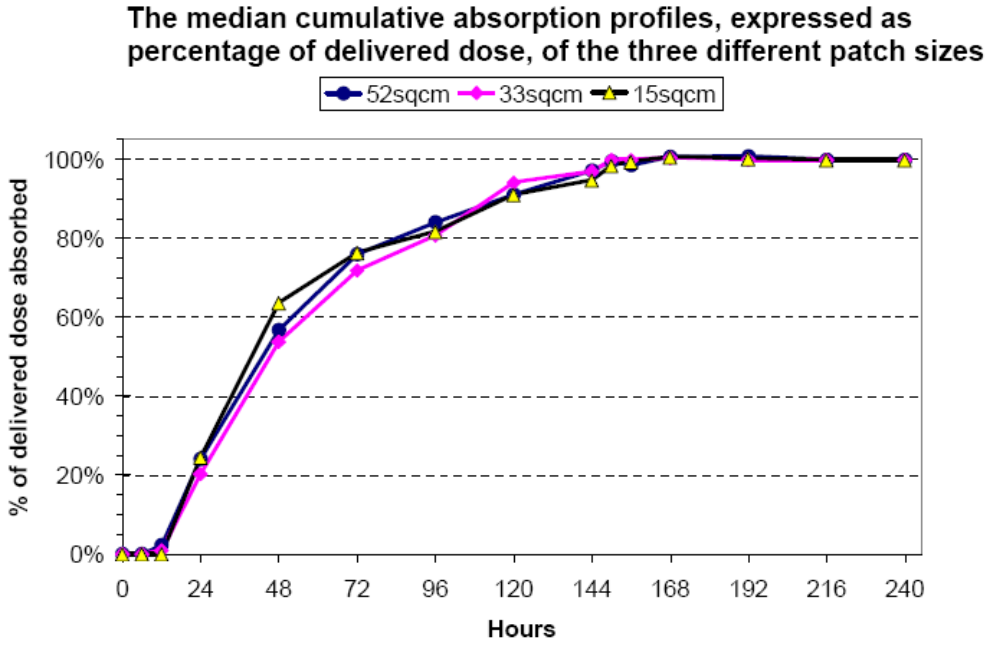
After a single six day application of three doses of granisetron TDS, average granisetron plasma concentrations as well as the area under the concentration time curve from time zero to infinity ($AUC_{0-\infty}$) and *in vivo* flux increase proportionally with the dose study of the patch area. Terminal half-life of granisetron was similar for the three doses with an overall mean of 33 hours. The mean average of granisetron plasma concentrations reached a maximum on the third day following application. However statistically there are no significance differences between the mean granisetron $C_{avg}$ achieved on Day 2 with that on Days 3-6.

The mean percentage of the granisetron dose remaining in granisetron TDS patches after removal was 36, 42 and 36% which corresponded to mean *in vitro* flux of 1.06, 2.10 and 3.68 mg for 24 hours for the 15, 33 and 52 $cm^2$ patch sizes respectively. These values were consistent with *in vivo* flux values calculated based on systemic granisetron exposure ($C_{avg}$ x intravenous granisetron clearance) of 1.02, 1.90, 3.30 mg/day for the three patch sizes. This similarly suggested that after granisetron TDS application the entire granisetron dose absorbed went into the bloodstream.

The median cumulative absorption profile was expressed as percentage of delivered dose of the three different patch sizes were superimposable (Figure 6). Approximately 20% of the released dose from the patch was absorbed over the first 24 hours and a further 60% being absorbed in the next 24 hours. The median percentage absorption after six days

applications was 97% of the total release suggesting that a small proportion of the release dose remain as reservoir in the skin and was absorbed over the next 24 hours.

**Figure 6: Median cumulative absorption profiles**




At 144 hours post dose, at the time of patch removal, a median of 97.2% of the release dose had been absorbed into the bloodstream leaving a small residual 2.8% in the skin to be absorbed over the next 24 hours.

*Evaluator's comment*

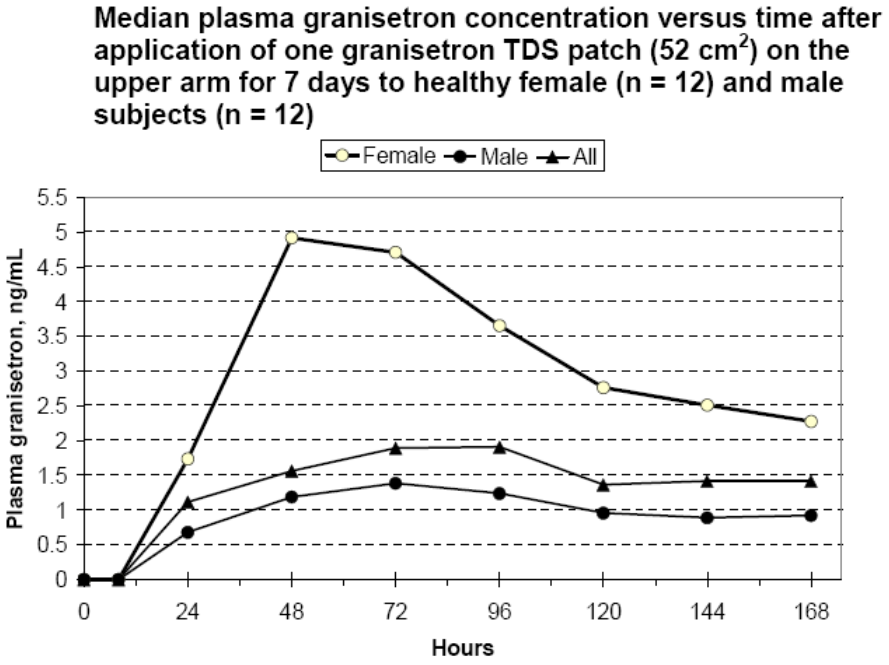
> This study has confirmed that *in vivo* a 52 $cm^2$ granisetron TDS achieved a similar exposure as determined by $C_{avg}$ to that of a 2 mg oral dose of granisetron. The study also confirmed that the optimal time of patch application for further study is 24-48 hours before chemotherapy.

***Study 26***

Pharmacokinetic evaluations were also conducted in relation to Study 26, which was a double blind placebo controlled study to assess the skin irritation and sensitisation potential of granisetron TDS in healthy subjects. The full design of the trial is presented in the relevant section but this study was in essence divided into two phases, the first being the Induction Phase during which a 52 $cm^2$ granisetron patch and placebo patches were applied simultaneously to the upper arm of the subjects for a total duration of 21 days (three granisetron TDS and placebo patches applied for seven days each). This was followed by a Sensitisation Phase during which 52 $cm^2$ granisetron TDS and placebo patches were applied for two days on the back.

A total of 24 subjects had pharmacokinetic evaluations undertaken and there was a large difference between the sexes in the plasma granisetron concentrations (Figure 7). Female patients had higher plasma concentrations than the males. One female subject had a particularly high plasma concentration of 42.7 ng/mL compared with the mean $C_{max}$ in the female subjects of 7.6 ng/mL.

**Figure 7: Median granisetron concentrations vs time**




The mean average granisetron plasma concentrations ($C_{avg}$) reached the maximum on the third day following application. However statistically there was no significant difference between the mean granisetron $C_{avg}$ achieved on Day 2 with those of Days 3-7.

*Evaluator's comment*

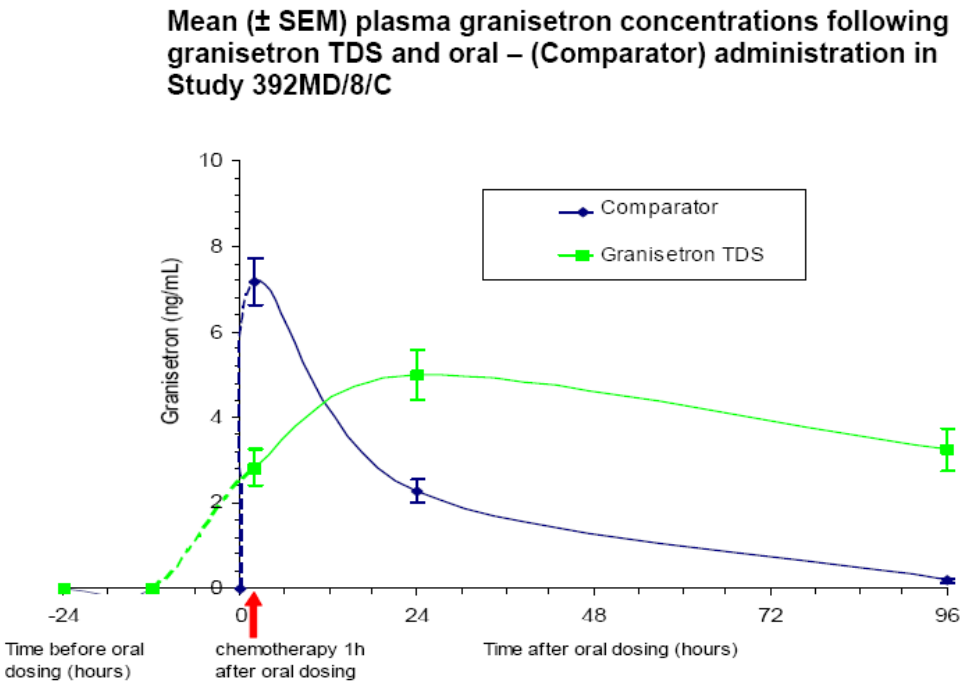
> This study confirmed the variability of the pharmacokinetics of granisetron overall in both male and female healthy subjects. It also showed that $C_{avg}$ did not significantly differ between Days 2-7. The *in vitro* calculation of flux from this study (3.1 mg per 24 hours) is the nominal strength of the product.

### *Study 8*

Pharmacokinetic studies were undertaken in the two trials involving cancer patients (Study 8 and Study 15). Study 8 was a multicentre double blind double dummy randomised parallel group Phase II study in chemotherapy naïve patients undergoing a single day regimen of chemotherapy with moderately emetogenic potential. It was initially intended to recruit 210 patients to this study but following an interim analysis closure of the study occurred after 179 patients had been recruited. In this study patients were randomised to receive granisetron TDS and oral placebo or the placebo patch and oral granisetron.

Twenty five hours after the application of active patch (Day 0) granisetron was quantifiable in the plasma in 86/88 patients with a mean value of 2.84 ng/mL (median 1.12 ng/mL). The maximal concentration was reached 48 hours after the patch application (Day 1) with mean value of 5.0 ng/mL (median 2.56 ng/mL) (Figure 8). Concentrations decreased slowly until patch removal on Day 4 with a correspondingly mean value of 3.26 ng/mL and median 1.76 ng/mL.

**Figure 8: Mean plasma granisetron concentrations vs time**




In patients treated with oral granisetron as a single 2 mg dose, the drug was rapidly absorbed and granisetron quantifiable in the plasma of 80 of the 83 patients two hours post oral granisetron administration on Day 0. This is also the time point at which maximum concentration is reached with a mean value of 7.17 ng/mL (median 7.71 ng/mL). By Day 1 or 24 hours post dose, the mean plasma concentration had substantially reduced to 2.28 ng/mL and by Day 4, 196 hours post dose 70% of the patients recorded plasma concentrations of granisetron below the limit of quantification (0.1 ng/mL).

In the oral granisetron group, one patient presented four days after dosing with a very high granisetron concentration of 349 ng/mL compared to the other patients with a range from the limit of quantification to 2.78 ng/mL. This value was suggestive of an additional granisetron dose having been taken just prior to the clinic visit and was therefore excluded from the subsequent analysis.

*Evaluator's comment*

> These data have confirmed that peak plasma concentrations achieved 24-48 hours after patch application highlighting that for further clinical studies the timing of patch application was optimal relative to the start of chemotherapy.

***Study 15***

The second cancer study, Study 15, was a randomised active control double blind double dummy parallel group multinational study to assess efficacy, tolerability and safety of granisetron TDS as a 52 $cm^2$ patch in chemotherapy induced nausea and vomiting (CINV), associated with the administration of moderately or highly emetogenic multiday chemotherapy. Over 600 patients were treated with granisetron; 316 were administered granisetron TDS and 321 with oral granisetron.

The granisetron plasma concentrations were determined in order to establish the level of granisetron and between patient variability. The mean plasma concentration following the granisetron TDS patch on Visit 1 was approximately 4 ng/mL and the concentration seen in males was higher than that in females. In both sexes the between patient variability

was high as indicated by the co-efficient of variation but the variability in the females was higher, CV 184% compared with CV 109% in males.

For oral granisetron the mean plasma granisetron concentration at Visit 1 was substantially higher than that seen after the patch. When subdivided by sex, females had a higher mean plasma concentration at Visit 1 (10.8 ng/mL) than males (6.7 ng/mL) but the variability in each sex, 94% for males and 92% for females was similar.

At Visit 1, 5% of patients taking granisetron TDS formulation were below the limit of quantification for granisetron compared to 2% of patients taking oral granisetron.

*Evaluator's comment*

> This study has confirmed the variability of the pharmacokinetics of granisetron overall and in both male and female cancer patients treated with oral granisetron and granisetron TDS. Median plasma concentrations at Visit 1 (anticipated peak plasma concentration) were higher for the oral granisetron than granisetron TDS.

The *in vitro* flux or the dose released per day overall can be compared across the studies (Table 2). The *in vitro* flux for Study 26 (7-day study) was re-calculated to be 3.1 mg/24 hours, the declared strength of the product.

**Table 2: In vitro flux of granisetron by study**

**Released dose of granisetron, *in vitro* flux, from granisetron TDS by study. For comparison the across studies the *in vitro* flux has been normalised to a dose of 34.3 mg, that is, a 52 $cm^2$ patch**

| Study | 392MD/4/C | 392MD/8/C | 392MD/11/C | | | 392MD/26/C |
|---|---|---|---|---|---|---|
| Patch, $cm^2$ | 15 | 52 | 15 | 33 | 52 | 52 |
| Days contact | 5 | 5 | 6 | 6 | 6 | 6 |
| Dose, mg | 9.9 | 31.8 | 9.9 | 21.8 | 34.3 | 34.3 |
| Subjects, n | 12 | 84 | 12 | 12 | 12 | 211 |
| Males, n | 12 | 27 | 6 | 6 | 6 | 53 |
| Females, n | 0 | 57 | 6 | 6 | 6 | 158 |
| | | | | | | |
| Flux, mg/day | | | | | | |
| Mean | 3.84 | 3.51 | 3.68 | 3.31 | 3.68 | 3.86 |
| SD | 0.46 | 0.90 | 0.77 | 0.81 | 0.51 | 0.64 |
| CV% | 12.0 % | 25.6 % | 21.0 % | 24.5 % | 13.8 % | 16.6 % |
| | | | | | | |
| Minimum | 3.40 | 0.73 | 2.02 | 1.94 | 2.63 | 0.95 |
| 1st Quartile | 3.45 | 2.93 | 3.42 | 2.86 | 3.46 | 3.47 |
| Median | 3.71 | 3.59 | 3.67 | 3.17 | 3.82 | 3.88 |
| 3rd Quartile | 4.07 | 4.11 | 4.17 | 3.64 | 3.91 | 4.32 |
| Maximum | 4.64 | 5.36 | 5.02 | 5.01 | 4.42 | 5.22 |

Note: studies 392MD/4/C, 392MD/11/C, 392MD/26/C included healthy subjects and 392MD/8/C cancer patients.

When the *in vitro* flux was dose normalised for comparison purposes to a dose of 34.3 mg (that is, the 52 $cm^2$ patch), the overall mean in vitro flux calculated across all the studies was 3.74 mg/day and it can be seen that the mean flux varied very little across the study with a minimum 3.31 mg/day and maximum 3.86 mg/day.

The median flux was similar in both sexes and healthy subjects (4.1 mg/day in males and 3.9 mg/day in females) and in patients (3.7 mg/day in males and 3.6 mg/day in females).

The release of granisetron from the granisetron TDS patch (*in vitro* flux [mg/day]) was measured *in vitro* as the initial dose in the patch minus the residual drug in the patch after removal. An *in vivo* flux was also estimated as the product of the average granisetron concentration of the plasma of the subjects and the plasma clearance.

The similarity in the mean measured *in vitro* flux and the calculated *in vivo* flux values (Table 3) suggests that all granisetron that is released from the granisetron TDS patch into the skin is absorbed and is available in the systemic circulation.

**Table 3: In vivo flux of granisetron by study**

**Released dose of granisetron, *in vitro* flux, from granisetron TDS by study compared with calculated *in vivo* flux.**

| Study | 392MD/4/C | 392MD/11/C | | | 392MD/26/C |
|---|---|---|---|---|---|
| Patch, $cm^2$ | 15 | 15 | 33 | 52 | 52 |
| | | | | | |
| Flux, mg/day | | | | | |
| *In vitro* | 1.11 | 1.06 | 2.10 | 3.68 | 3.86 |
| *In vivo* | 1.45 | 1.02 | 1.9 | 3.3 | 3.6 |

Review of between subject variability in absorption of granisetron revealed that it is large following both oral and granisetron TDS administration to healthy subjects. A coefficient of variation for both granisetron $C_{max}$ and AUC of the order of 80 or 100% was found for both routes of administration. Nevertheless comparing the mean extent of absorption of granisetron from granisetron TDS across the three studies undertaken in healthy subjects demonstrated the absorption was proportional to the area of the patch used and was similar in all three studies.

The mean average plasma granisetron concentration following oral administration of 2 mg/day for five days is 2.32 ng/mL and was 2.23 ng/mg when a 52 $cm^2$ granisetron patch was in place for six days. Thus the 52 $cm^2$ granisetron TDS patch delivers equivalent granisetron exposure to the clinically proven efficacious dose of 2 mg administered orally. This therefore supports the choice of the 52 $cm^2$ granisetron TDS patch for the clinical efficacy studies.

Regardless of whether the subjects or patients receiving granisetron as a patch or orally, the plasma concentrations and the pharmacokinetics of granisetron were very variable. This is true for all the clinical studies conducted with granisetron TDS. For example the coefficient of variation for $C_{max}$ following the 52 $cm^2$ patch in Study 11 was 77% and 68% on Day 5 after 2 mg oral concentration every 24 hours. The coefficient of variation for AUC was 89% following the patch and 120% after oral administration. This variability is a function of the drug substance and not dependent on the route of administration as has been previously noted in the literature.

It is unclear why granisetron exhibited this high variability. There are, however, no obvious patient related factors that contribute to this and in particular no consistent evidence to support that either absorption or elimination of granisetron is influenced by subjects' sex.

It is noteworthy that at the start of emetic chemotherapy the patients have sufficient exposure to granisetron to prevent nausea and vomiting and this exposure is sustained over the time course of chemotherapy. In the two studies (Study 11 and Study 26) in which the average plasma concentration of granisetron $C_{avg}$ was measured, granisetron TDS patch showed comparable concentrations to 2 mg oral granisetron on the second day after patch application. In addition, in Study 26, the average plasma concentration of granisetron was sustained at similar or higher concentrations for the seven days the patch was applied.

When administered for six days granisetron TDS 52 $cm^2$ patch delivers on average a dose of 3.6 mg of granisetron per day. This results in an average plasma concentration of 2.23 ng/mL. In the same subjects given 2 mg oral granisetron every 24 hours for five days, there is an average plasma concentration of 2.14 ng/mL after the first administration and 2.6 ng/mL following the final dose. Hence the granisetron TDS 52$cm^2$ patch delivers comparable average plasma concentrations to 2 mg oral granisetron every 24 hours. This further supports the choice of the 52 $cm^2$ granisetron TDS patch for clinical efficacy studies.

## Pharmacodynamics

There were no new pharmacodynamic data provided in the submission.

## Efficacy

The submission involved two trials assessing efficacy, the pivotal Phase III trial, Study 15 and a supportive Phase II trial, Study 8.

### *Study 15*

Study 15 was a randomised active controlled double blind double dummy parallel group multinational study to assess the efficacy, tolerability and safety of the granisetron transdermal delivery system (GTDS) in chemotherapy induced nausea and vomiting (CINV) associated with the administration of moderately or highly emetogenic multiday chemotherapy. A total of 61 centres were involved in this trial with patients enrolled between 24 January 2006 and 11 October 2006.

It is worth noting that in multiday chemotherapy regimens, the doses and agents used may vary from day to day and therefore the relevant level of emetogenic risk varies. Accordingly it is possible to consider that some chemotherapy regimens have some days associated with moderate emetogenic risk versus others with high risk. The trial was based on a decision that inclusion of cisplatin in any chemotherapy regimen indicated this to be a high emetogenic risk program and therefore patients were stratified accordingly.

The primary objective of the trial was to demonstrate non-inferiority of the GTDS efficacy compared with oral granisetron efficacy with regard to complete control (CC) of CINV from the first administration until 24 hours after the last administration of the moderately emetogenic (ME) or highly (HE) emetogenic multiday chemotherapy according to Hesketh classification.[2,3] The primary endpoint was the percentage of patients achieving CC as defined above.

Secondary objectives include:

- comparing TDS with oral granisetron with regards to the CC of CINV during successive 24 hour intervals from the first administration until 24 hours after the last administration of assorted toxic agents with ME or HE potential;

[2] CC was defined as no vomiting and/or retching, no more than mild nausea and no rescue medication

[3] One of the most common classification systems for emetogenicity of a chemotherapeutic agent is referred to as the Hesketh classification. The classification is based on the likelihood of a particular agent causing emesis in an adult patient who had not received the agent previously. The classification has 5 levels of which levels 3 and 4 are considered moderate and level 5 is considered high:
Level1: Less than 10% risk of patients experiencing emesis
Level 2: Agents within this class cause acute emesis in between 10 and 30% of patients.
Level 3: Agents within this class cause acute emesis in between 30 and 60% of patients.
Level 4: Agents within this class cause acute emesis in between 60 and 90% of patients.
Level 5: Agents within this class cause acute emesis in greater than 90% of patients.

- in the sub-group of patients receiving three and four day regimens to compare GTDS with oral granisetron with respect to CC in the period between 24 hours after the last administration of ME or HE multiday chemotherapy and patch removal;
- emetic episodes, time to first emetic episode and number of emetic episodes from the first administration until 24 hours after last administration of ME or HE multiday chemotherapy;
- complete response was defined as no vomiting or retching and no rescue medication of CINV from the first administration until 24 hours after last administration of the ME or HE chemotherapy and during successive 24 intervals from the first administration from the ME or HE chemotherapy until 24 hours after last administration of the ME or HE multiday chemotherapy;
- nausea episodes, severity of the nausea and frequency of more than mild nausea from the first administration until 24 hours after last administration of the ME or HE multiday chemotherapy;
- vomiting episodes, severity of vomiting from the first administration until 24 hours after last administration of the ME or HE multiday chemotherapy; rescue medication, time to first administration (from the first administration until 24 hours after last administration of the ME or HE multiday chemotherapy); patients global satisfaction with the anti-emetic treatment.

With respect to the safety comparison of GTDS with oral granisetron, secondary objectives were:

- analysis of adverse events;
- local tolerance issues in relation to patch application;
- changes from screening to end of treatment for vital signs, physical examination, electrocardiogram (ECG) and laboratory values.

It was also intended to assess the adhesion of the GTDS over a full seven day application period.

The main inclusion criterion for the trial include males or females aged at least 18 years; histologically and/or cytologically confirmed cancer and an ECOG status of 2 or less;[4] life expectancy of at least three months; assigned to receive the first cycle of a new multiday ME or HE chemotherapy regimen including the daily administration of cytotoxic regimen with a emetogenic potential of level 3-5 via the Hesketh classification from 3-5 days.

Main exclusion criteria included hypersensitivity to adhesive plaster; contraindication to $5HT_3$ receptor antagonist; any cause for nausea and vomiting other than CINV; any episode of retching, vomiting or uncontrolled nausea in the 72 hour period prior to chemotherapy administration; clinical relevant abnormal ECG parameters and/or baseline

[4] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

$QT_C$ >450 milliseconds (ms) for male patients or baseline $QT_C$ >470 ms for female patients; other $5HT_3$, NK1 or dopamine antagonist.

The study period involved a screening period of 4-12 days, a treatment period of seven days and a follow up period of 14 days.

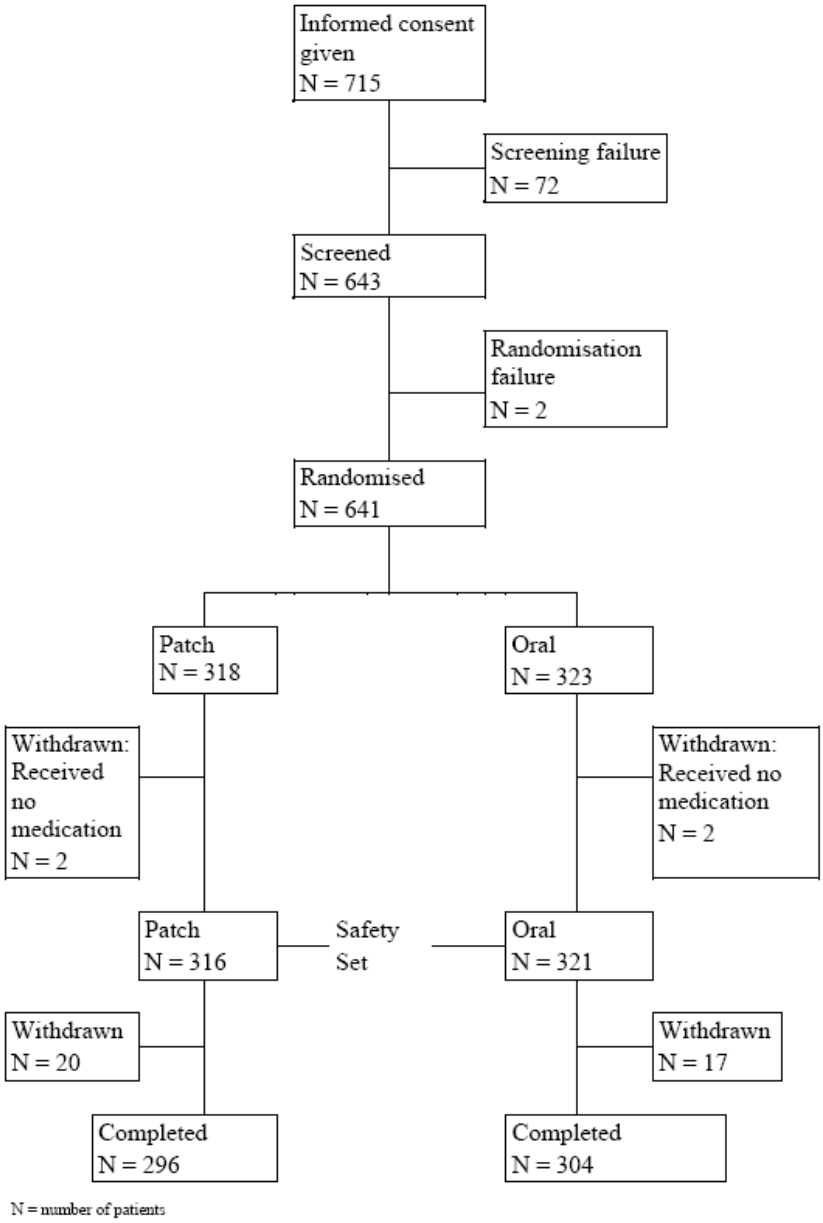
Patients were randomised to either oral placebo and an active patch (patch group) or oral active and a placebo patch (oral group). Oral active and oral placebo were taken one hour before administration with ME or HE chemotherapy. Patches were applied 24-48 hours before chemotherapy and remained *in situ* for seven days. The dose of granisetron per patch was 34.3 mg while the oral granisetron administered was 2 mg per day for 3-5 days.

Statistical methods related to the study being designed to establish whether GTDS was non-inferior to oral granisetron in the prevention of CINV associated with ME or HE multiday chemotherapy. As previously indicated the primary efficacy endpoint was the percentage of patients achieving CC from the first administration until 24 hours after start of the last day of administration of the multiday ME or HE chemotherapy regimen.

The null hypothesis was that the granisetron TDS was inferior to oral granisetron. The hypothesis was tested by the construction of a two sided 95% Confidence Interval (CI) (around the difference in percentage of CC between the two treatment groups). If the lower limit of this CI was greater than the non-inferiority margin the null hypothesis was rejected. Setting the reference rate for CC with oral granisetron to 50%, an absolute non-inferiority margin of 15% and 90% power, 576 patients (288 per group) were required.

Overall 715 patients were screened to yield 621 for the full analysis set and 582 for the per protocol set. This is summarised in Figure 9. The treatment and control populations were balanced with respect to baseline demographics.

**Figure 9: Disposition of patients in Study 15**




The analysis also revealed that the randomised populations were balanced with respect to the other major factors in the prognosis of CINV namely smoking and alcohol use, site of primary disease and chemotherapy naivety versus previous chemotherapy. Groups were also well balanced as per concomitant medications.

A summary of efficacy endpoints is shown in Table 4. The percentage of patients who achieved CC from the first administration until 24 hours after the start of the last day of administration of ME or HE chemotherapy regimen was comparable between granisetron

TDS and the oral groups with a point estimate of the difference between groups of -4.89%. The difference between the two treatments was calculated by logistic regression model, adjusted for treatment, gender, planned cisplatin and corticosteroid use, planned regimen duration and chemotherapy naivety as recorded in the interactive voice recognition system (IVRS). The lower bound of the 95% CI was -12.91%. Since the lower limit of this CI was above -15% the null hypothesis was rejected and the alternative hypothesis was accepted, that is, the granisetron TDS was non-inferior to oral granisetron.

**Table 4: Primary efficacy endpoint – Study 15**

| | Granisetron TDS (N = 284) | | Oral Granisetron (N = 298) | | Adjusted logistic regression[1] Difference (%) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | Estimate | 95 % CI |
| **Complete Control** | | | | | | |
| Yes | 171 | 60.2 | 193 | 64.8 | -4.89 | -12.91, 3.13 |
| No | 113 | 39.8 | 105 | 35.2 | | |

[1] Primary comparison estimated via a logistic regression model, adjusting for treatment, gender, planned cisplatin and corticosteroid use, planned regimen duration and chemotherapy naivety as recorded in IVRS.
CI: confidence interval
N: Number of patients in the respective treatment group
n: Number of patients
%: Percentage based on N

The generalisability of the primary endpoint results was examined using a breakdown by categories such as gender, actual cisplatin and corticosteroid use, planned duration of chemotherapy regimen and chemotherapy naivety. Analysis of the per protocol set (PPS) for the patients who achieved CC spilt by the strata as specified in the protocol showed no statistically significant differences between the two treatment groups for any of the strata, emphasising the robustness of the primary efficacy result. In addition to analyses by strata one further sub group was studied, that is, the effect of age by looking at the response to treatment in those under and over 65 years of age. The results showed no significant effects of age on CC of CINV.

Overall adhesion of the patch for the site of application was very good with over 75% of patch adherence in 90% of patients in the granisetron TDS group and 95% of patients in the placebo patch group. Of the 621 patients receiving either active or placebo patches <1% of patches became detached over a course of a seven day patch application period.

*Evaluator's comment*

> This study has demonstrated non-inferiority of the GTDS control granisetron and complete control of nausea and vomiting over a course of multiday HE and ME chemotherapy. GTDS delivered sufficient drug to provide $5HT_3$ receptor blockade and thus control of CINV similar to that resulting from multiple daily oral granisetron administration.

***Study 8***

Study 8 was a supportive efficacy study which was a randomised active control double blind double dummy multicentre Phase II study comparing the efficacy, safety and tolerability of granisetron TDS with oral granisetron in CINV following a single day administration of ME chemotherapy. The trial was constructed to allow study of both pre-

and post-24 hour phases of CINV following chemotherapy. The primary analysis was on total control (TC) of CINV for the period 24 -120 hours following chemotherapy administration. TC was defined as no nausea, no vomiting, no use of rescue medication and no withdrawal from the study.

The principal inclusion criteria for the trial were an ECOG status of 2 or less, life expectancy of at least three months, chemotherapy naive for at least six months since last chemotherapy; at least three weeks since last major surgery including thoracotomy, laparotomy, craniotomy or vascular surgery involving the major vessels, scheduled to receive a single day regimen of moderately emetogenic chemotherapy which included any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, mitozantrone, >250 mg methotrexate, cyclophosphamide <1500 mg, doxorubicin or cisplatin <50 mg infused over 1-4 hours.

Exclusion criteria included tumours of the head and neck or stomach, received radiation involving the abdomen or pelvis within the 48 hour period prior to or scheduled to receive such radiation during the treatment period.

The primary efficacy endpoint was the proportion of patients with total control (TC) of CINV. Based on a logistic regression model (treatment, centre, gender and use of nicotine as factors), the two sided hypothesis for granisetron TDS is not different to the single oral dose of granisetron (2 mg per day) was tested with an alpha level of 0.499 on data from the intention to treat (ITT) population.

Secondary endpoints were the proportion of patients achieving TC of CINV during the zero-24 hour time period post chemotherapy and the proportion of patients achieving TC of CINV during the 0-120 hour time period post chemotherapy.

In addition the following efficacy endpoints were assessed;

- the proportion of patients achieving a complete response (no emetic episode and no use of rescue medications) for the 0-24 hour period, 24-120 hours and 0-120 hours;
- the proportion of patients achieving complete control for the 0-24 hour, 24-120 hour and 0-120 hour period;
- treatment failure, that is, the occurrence of emetic episodes or use of rescue medication whichever occurred first;
- severity of nausea;
- first administration of rescue medication.

The trial was conducted at 21 sites in Germany. Patients were randomised to either oral placebo and an active patch (the patch group) or oral active and placebo patch (the oral group). Oral active and oral placebo were taken one hour before the administration of ME chemotherapy. Patches were applied 24 hours before chemotherapy and remained *in situ* for four days after chemotherapy (five days in total). Oral granisetron was administered at 2 mg/day for five days.

Depending on distribution, secondary and other efficacy parameters were analysed by logistic regression, analysis of covariance or the log rank test for time to failure data.

The response rate for a single oral dose of granisetron was assumed to be 50% for TC of CINV 24 hours post chemotherapy. Due to the sustained delivery of granisetron by granisetron TDS an increased response rate of 70% was expected. In the case of superiority for a two sided exact Fisher Test with an upper level of 0.05 and a power of 80%, 103 patients per treatment group were required.

A total of 210 patients were planned to be randomised. However an interim analysis of the results of all patients enrolled until 31 March 2005 (133 patients) suggested that although the granisetron TDS showed comparable efficacy to oral granisetron for the first 24 hours there was no evidence of superiority during the 24-120 hours post chemotherapy. Therefore patient recruitment was halted at the end of April 2005 at which time 179 patients had been randomised. The patients entered onto trial and disposition are shown in Table 5.

**Table 5: Patient disposition in Study 8**

| Population | Number (%) of patients | |
|---|---|---|
| | Granisetron TDS | Oral Granisetron |
| All enrolled patients | 93 (100.0 %) | 90 (100.0 %) |
| All randomised patients | 91 (97.8 %) | 88 (97.8 %) |
| Safety | 88 (94.6 %) | 85 (94.4 %) |
| ITT | 87 (93.5 %) | 84 (93.3 %) |
| PP | 80 (86.0 %) | 77 (85.6 %) |

There were no statistically significant differences between treatment groups for demographic parameters. The majority of patients (99.4%) were Caucasian and more female patients were recruited than male patients (63.2% vs 36.8%). Patients had a mean age of 60.6 years with a range of 33-83 years and mean BMI of 25.34 kg/m$^2$ with a range 15.59 – 39.21 kg/m$^2$. Approximately half of the patients were current smokers or who had smoked in the past, that is, 23.4% and 33.9% respectively.

Prior to patch application there were no clinically relevant differences between treatment groups for medical history, vital signs, ECG, laboratory parameters, tumour type, ECOG status or symptoms of nausea. In both groups the most common tumour types were breast cancer (46.2%) and lung cancer (33.9%).

The proportion of patients who achieved the endpoints of total control, complete response and complete control are shown in Table 6. There were no statistically significant differences between the treatment groups for the primary endpoint (p=0.6288). There were no statistically significant differences between treatment groups for the secondary endpoints concerning the total control, complete response or complete control of CINV.

Logistic regression analysis revealed a high risk of therapy failures between the 24-120 hour phase for patients receiving oral granisetron and for the granisetron TDS group and in women compared to men, but decreased risk in smokers compared to non-smokers.

Severity of nausea was generally similar between treatment groups with no statistically significant differences for the overall period. No statistically significant differences between the granisetron TDS and oral granisetron were observed for the number of emetic/vomiting episodes (mean 2.8 and 2.5 respectively).

Similar patients on granisetron TDS and oral granisetron groups experienced treatment failure, 66.7% and 61.9% respectively or received less chemotherapy, 56.3% and 48.8% respectively.

**Table 6: Efficacy results for Study 8**

| Endpoint | | Number (%) of patients (ITT population) | | |
|---|---|---|---|---|
| | | Granisetron TDS N=87 | Oral Granisetron N=84 | Total N=171 |
| Primary endpoint | Total control | | | |
| | 24 – 120 h | 28 (32.2 %) | 25 (29.8 %) | 53 (31.0 %) |
| Secondary endpoints | Total control | | | |
| | 0 – 24 h | 38 (43.7 %) | 44 (52.4 %) | 82 (48.0 %) |
| | Overall | 22 (25.3 %) | 21 (25.0 %) | 43 (25.1 %) |
| Additional endpoints | Complete response | | | |
| | 24 – 120 h | 40 (46.0 %) | 39 (46.4 %) | 79 (46.2 %) |
| | 0 – 24 h | 43 (49.4 %) | 52 (61.9 %) | 95 (55.6 %) |
| | Overall | 27 (31.0 %) | 32 (38.1 %) | 59 (34.5 %) |
| | Complete control | | | |
| | 24 – 120 h | 37 (42.5 %) | 34 (40.5 %) | 71 (41.5 %) |
| | 0 – 24 h | 42 (48.3 %) | 50 (59.5 %) | 92 (53.8 %) |
| | Overall | 26 (29.9 %) | 28 (33.3 %) | 54 (31.6 %) |

*Evaluator's comment*

This study has provided supportive data for the efficacy of granisetron TDS in the treatment of acute CINV during ME chemotherapy and appears at least equivalent to oral granisetron.

## Safety

### *Skin Irritation and Sensitivity Assessment – Study 26*

In order to assess the potential skin irritation and sensitisation associated with the GTDS a specific study was conducted. Study 26 was a double blind placebo controlled study to assess the cumulative skin irritation and sensitisation potential of the GTDS. This was a single centre study conducted between August 2006 and November 2006.

The primary objective of the study was to assess the incidence and prevalence of irritation at the time of application after repeated applications of the study drug materials (Induction Phase).

A further objective was to assess the incidence of sensitisation at an alternative skin site after another application of the study drug materials (Challenge Phase).

Secondary objectives were to assess the delivery of granisetron from the patch by determining the plasma granisetron levels in a subset of patients. These pharmacokinetic data have been discussed above.

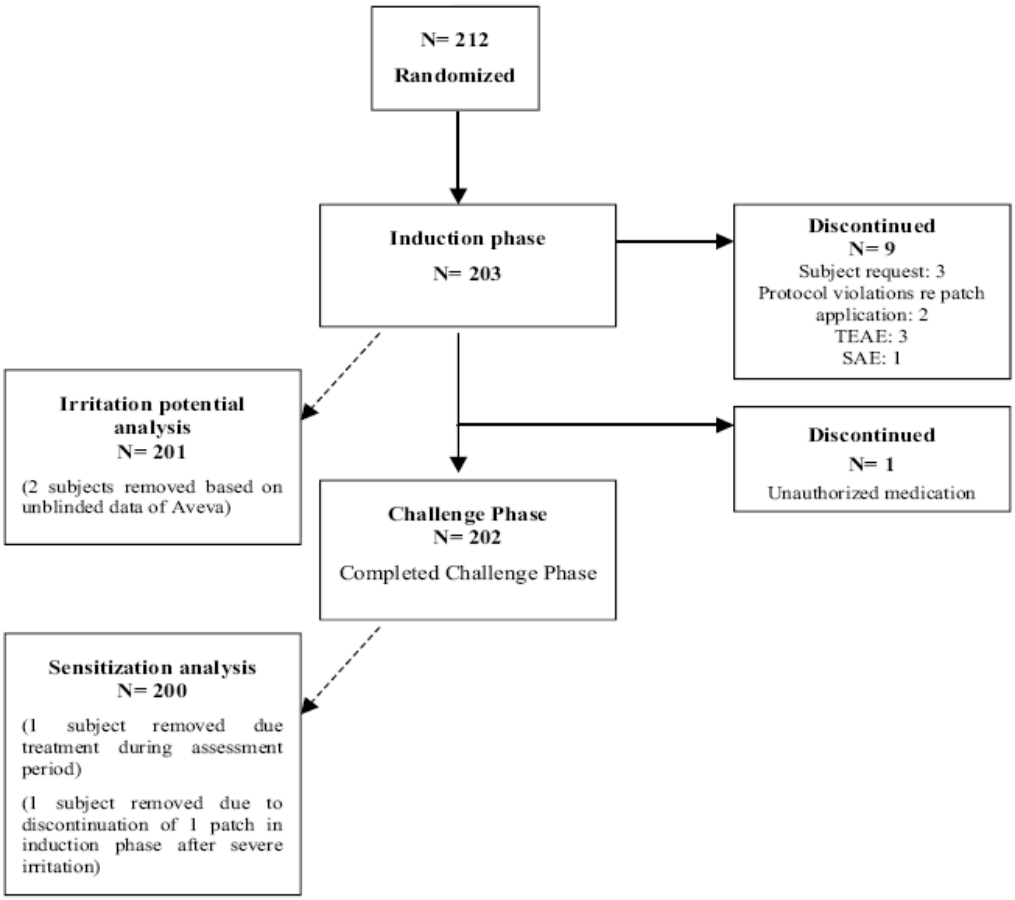
The study consisted of a 28 day screening period, a three week Induction Phase followed by a rest phase of two weeks and a subsequent Challenge Phase of six days. If required an additional one week Rechallenge Phase was to be completed. A 7-10 day follow up phase was completed by all subjects. During the Induction Phase a total of three applications of the two test products (active and placebo patches) were performed on the upper outer arms. The patches remained in place for one week. The skin reactions were assessed prior to patch application, Day 1 and 30 minutes after each patch removal on Days 8, 15 and 22. During the Challenge Phase, the two test products were applied for 48 hours on the back and skin sensitisation was scored 30 minutes, 24, 48 hours and 72 hours after patch removal. In case of an eventual rechallenge this procedure was to be repeated within 14 days. Additionally patch adhesion and objective assessments were evaluated

three times each week during the Induction Phase and after 48 hours during the Challenge Phase.

A scoring system was developed to assess local tolerance and a scale of assessment was developed to assess patch adhesion.

A total 252 subjects were screened and 212 randomised. This disposition of subjects is shown in Figure 10.

**Figure 10: Disposition of subjects in Study 26**




Review of irritations scores during the Induction Phase is shown in Table 7. Four subjects discontinued during the Induction Phase because of an occurrence of a serious skin reaction, that is, a score of 3. A total of 91 (45.3%) and 66 (32.9%) of patients respectively displayed no erythema on the active granisetron and placebo test sites at Day 8. This is the recommended duration of use in the target population. Skin reactions on the placebo patch a day were slightly higher for moderate or severe erythema being 45 subjects (22.4%) compared to 27 (13.5%) with the active granisetron patch. Severe erythema was reported in one active granisetron patch subject at Day 8. There were no reports of erythema with vesicles in either group.

**Table 7: Induction Phase – frequency of irritation scores**

| Parameters *n (%)* | Baseline *(N =201 )* | Day 8 *(N = 201)* | Day 15 *(N =201 )* | Day 22 *(N =201 )* |
|---|---|---|---|---|
| GTDS | | | | |
| *0: No reaction* | 201 (100.00) | 91 (45.27) | 104 (51.74) | 96 (47.76) |
| *1: Slight erythema* | 0 (0.00) | 83 (41.29) | 75 (37.31) | 80 (39.80) |
| *2: Moderate erythema* | 0 (0.00) | 26 (12.94) | 22 (10.95) | 25 (12.44) |
| *3: Severe erythema* | 0 (0.00) | 1 (0.50) | 0 (0.00) | 0 (0.00) |
| *4: Erythema with vesicles or erosion or bullae* | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| *Total N* | 201 (100.00) | 201 (100.00) | 201 (100.00) | 201 (100.00) |
| Placebo | | | | |
| *0: No reaction* | 201 (100.00) | 66 (32.84) | 65 (32.34) | 45 (22.39) |
| *1: Slight erythema* | 0 (0.00) | 90 (44.78) | 95 (47.26) | 100 (49.75) |
| *2: Moderate erythema* | 0 (0.00) | 39 (19.40) | 31 (15.42) | 45 (22.39) |
| *3: Severe erythema* | 0 (0.00) | 6 (2.99) | 7 (3.48) | 6 (2.99) |
| *4: Erythema with vesicles or erosion or bullae* | 0 (0.00) | 0 (0.00) | 3 (1.49) | 5 (2.49) |
| *Total N* | 201 (100.00) | 201 (100.00) | 201 (100.00)) | 201 (100.00) |

The incidence of irritation for each tested patch is defined as the percent of subjects with an irritation score >1 for the first time on study and is the percentage of new positive response at each time point. This is shown in Table 8. The prevalence of irritation for each patch tested is defined as a percent of subjects with irritation score >1 whatever the previous score for the same subject and is shown in Table 9. Of the 201 subjects, 174 or 86.6% displayed no irritation at the active granisetron site and 156 or 77.6% subjects displayed no irritation reaction at the placebo site at Day 8.

**Table 8: Incidence of skin irritation**

| Parameters n (%) | Day 8 | Day 15 | Day 22 |
|---|---|---|---|
| **GTDS** | *(N =201 )* | *(N =201 )* | *(N =201 )* |
| *Incidence* | 27 (13.43) | 12 (5.97) | 13 (6.47) |
| **Placebo** | *(N =201 )* | *(N =201)* | *(N =201 )* |
| *Incidence* | 45 (22.39) | 24 (11.94) | 32 (15.92) |

**Table 9: Prevalence of irritation**

| Parameters n(%) | Day 8 | Day 15 | Day 22 |
|---|---|---|---|
| GTDS | *(N =201 )* | *(N =201 )* | *(N =201 )* |
| *Prevalence* | 27 (13.43) | 39 (19.40) | 52 (25.87) |
| Placebo | *(N =201 )* | *(N =201 )* | *(N =201 )* |
| *Prevalence* | 45 (22.39) | 69 (34.33) | 101 (50.25) |

Review of the mean cumulative irritation scores and the total cumulative irritation scores for the two groups revealed that the transdermal products for the Induction Phase were considered better than or equivalent to the placebo patch for both of these measures (Table 10).

**Table 10: Equivalence tests between GTDS and placebo for score means**

| Parameters | Statistics | GTDS | Placebo | Non-inferiority Test *P* |
|---|---|---|---|---|
| *Mean cumulative irritation (MCI) score* | *Mean* | 0.64 | 1.00 | |
| | *Std* | 0.54 | 0.67 | P (t) < 0.0001 |
| | *Min* | 0.00 | 0.00 | |
| | *Median* | 0.67 | 1.00 | |
| | *Max* | 2.00 | 3.67 | |
| *Total cumulative irritation (TCI) score* | *Mean* | 1.92 | 3.00 | |
| | *Std* | 1.63 | 2.00 | P (t) < 0.0001 |
| | *Min* | 0.00 | 0.00 | |
| | *Median* | 2.00 | 3.00 | |
| | *Max* | 6.00 | 11.00 | |

Patch adhesivity was assessed three times a week during the Induction Phase to validate irritation assessments. A total of 94.5% of patients or subjects had >75% patch adhesion by Day 8 with GTDS. This confirms that the compliance was good and validates the Induction Phase results.

Subjective comments reported by the subjects as pruritus, stinging and burning sensation or others were recorded during the Induction Phase and are shown in Table 11. Pruritus was the most frequently reported subjective symptom. This may be attributed to the exclusive properties of the patch. Frequency of pruritus slightly decreases during the Induction Phase and was comparable between the two treatment groups.

**Table 11: Subjective symptoms during the Induction Phase on patch removal days**

| n (%) | Granisetron | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Days | | | Days | | |
| | 8 | 15 | 22 | 8 | 15 | 22 |
| Pruritus | 94 (46.77) | 96 (47.76) | 81 (40.30) | 100 (49.75) | 88 (44.00) | 88 (44.00) |
| Stinging | 20 (9.95) | 16 (7.96) | 12 (5.97) | 16 (7.96) | 12 (6.00) | 11 (5.50) |
| Burning | 6 (2.99) | 6 (2.99) | 2 (1.00) | 7 (3.48) | 6 (3.00) | 5 (2.50) |
| Others | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |

During the Challenge Phase 200 subjects were analysed for sensitisation potential. Only one positive sensitisation reaction to the active patch was observed during the Challenge Phase when the patches were applied to the subjects' backs. No sensitisation reaction was observed with the placebo. Frequency of skin reaction scores per assessment for each test product is shown in Table 12. Table 13 indicates the means of mean cumulative score and the total cumulative score by product and the equivalence test results for the Challenge Phase. The mean irritation score for the GTDS group has to be lower than that of the placebo group, the p-values for the tests imply that 95% upper confidence bounds defined to be <0. Therefore the transdermal product for the Challenge Phase is considered better than or equivalent to the placebo patch.

**Table 12: Skin reaction scores per visit during the Challenge Phase**

| Parameters<br>*N (%)* | 30 min<br>*(N =200)* | 24h<br>*(N = 200)* | 48h<br>*(N =200)* | 72h<br>*(N =200)* |
|---|---|---|---|---|
| GTDS | | | | |
| *0: No reaction* | 103 (51.50) | 127 (63.50) | 160 (80.00) | 184 (92.00) |
| *1: Erythema without edema* | 91 (45.50) | 69 (34.50) | 36 (18.00) | 14 (7.00) |
| *2: Erythema with edema or small papules* | 6 (3.00) | 4 (2.00) | 4 (2.00) | 1 (0.50) |
| *3: Erythema with individual vesicles* | 0 | 0 | 0 | 1 (0.50) (*) |
| *4: Erythema and swelling with blisters* | 0 | 0 | 0 | 0 |
| *Total N* | 200 (100.00) | 200 (100.00) | 200 (100.00) | 200 (100.00) |
| Placebo | | | | |
| *0: No reaction* | 64 (32.00) | 116 (58.00) | 146 (73.00) | 185 (92.50) |
| *1: Erythema without edema* | 119 (59.50) | 82 (41.00) | 50 (25.00) | 14 (7.00) |
| *2: Erythema with edema or small papules* | 17 (8.50) | 2 (1.00) | 4 (2.00) | 1 (0.50) |
| *3: Erythema with individual vesicles* | 0 | 0 | 0 | 0 |
| *4: Erythema and swelling with blisters* | 0 | 0 | 0 | 0 |
| *Total N* | 200 (100.00) | 200 (100.00) | 200 (100.00) | 200 (100.00) |

**Table 13: Non-inferiority tests between GTDS and placebo mean and total cumulative scores**

| Parameters | Statistics | GTDS | Placebo | Non-inferiority Test *P* |
|---|---|---|---|---|
| *Mean cumulative score* | *Mean* | 0.41 | 0.52 | P (t) < 0.0001 |
| | *Std* | 0.48 | 0.48 | |
| | *Min* | 0.00 | 0.00 | |
| | *Median* | 0.33 | 0.33 | |
| | *Max* | 2.67 | 2.33 | |
| *Total cumulative score* | *Mean* | 1.22 | 1.57 | P (t) < 0.0001 |
| | *Std* | 1.45 | 1.43 | |
| | *Min* | 0.00 | 0.00 | |
| | *Median* | 1.00 | 1.00 | |
| | *Max* | 8.00 | 7.00 | |

Patch adhesivity was assessed on Day 3 during the Challenge Phase to validate sensitisation assessments. A total of 89% of subjects who completed the Challenge Phase had >75% patch adherence with GTDS.

Pruritus was the main subjective symptom reported on Day 3 (17.50% granisetron, 21.0% placebo) and was not an unexpected event with inclusive patches.

*Evaluator's comment*

> This study has shown that the active patch was not significantly more irritant than the matching placebo patch. There was a slight irritant potential for both patches. Of the 200 subjects analysed only one positive allergic reaction was observed with the active patch. There is no evidence of increasing irritation with time and also placebo patches and active patches are not statistically different in terms of irritation they cause.

### *Integrated Safety Analysis*

An Integrated Safety Analysis from the five clinical trials was provided in this submission for the GTDS with safety data up to 14 May 2007. Overall 1056 healthy subjects and cancer patients were included in the database and 1046 healthy subjects and patients were included in the safety summary. In total 820 cancer patients and 236 healthy subjects were randomised. All of the healthy subjects have been included in the database whereas 10 cancer patients were excluded from the safety analysis generally because of withdrawal of consent.

In total 640 individuals were exposed to the granisetron TDS. The majority of healthy subjects wore the 52 $cm^2$ patch for a minimum of six days, range 1-23 days. All the cancer patients were exposed to 52 $cm^2$ patch size, most of these patients wore the patch for 5, 6 or 7 days. The majority of cancer patients exposed to oral granisetron received it for three days.

Patch adhesion was good in the treatment target population. Only four cancer patients on granisetron TDS group were withdrawn due to failure of patch adhesion in the clinical studies.

The cancer patient population included in this analysis was older than the healthy population with a mean of 55 years versus 37 years which is to be expected. However in all other demographic characteristics the groups were well balanced.

The analysis of adverse events is based on the assessment of treatment emergent adverse events (TEAE). The majority of TEAEs observed in the granisetron TDS and oral granisetron both in healthy subjects and cancer patients were mild to moderate in severity. Overall healthy subjects had a higher incidence of TEAEs to granisetron TDS (80%) compared with the cancer patients (42%). The reasons for this are not entirely clear. In cancer patients the overall incidence of TEAEs was comparable between the transdermal and oral groups. Within the cancer patient population similar numbers of patients on transdermal or oral granisetron withdrew from the study due to TEAEs.

The most common TEAEs reported by healthy subjects with the 52 $cm^2$ patch according to System Organ Classes (SOCs) included *Gastrointestinal Disorders* (70.5%), *Infections and Infestations* (17%), *Nervous System Disorders* (48.7%), *General Disorders and Administrative Site Conditions* (4.9%) and *Musculoskeletal System Disorders* (7.6%) (Table 14). Cancer patients had a similar pattern of adverse events to healthy subjects with the highest incidence being *Gastrointestinal Disorders* (20.5%), *General Disorders and Administrative Site Conditions* (10.4%), *Metabolism and Nutrition Disorders* (6.2%), *Nervous System Disorders* (5.0%) and *Blood and Lymphatic System Disorders* (7.4%). The principal TEAE in the *Blood and Lymphatic System Disorder* SOC was neutropenia and this was considered most likely related to chemotherapy rather than granisetron.

**Table 14: Granisetron TDS related TEAEs in cancer patients by SOC and frequency**

| System Organ Class | Common ≥ 1/100 to < 1/10 | Uncommon ≥ 1/1000 to < 1/100 |
|---|---|---|
| Metabolism and nutrition disorders | | Anorexia, decreased appetite |
| Nervous system disorders | | Headache |
| Ear and labyrinth disorders | | Vertigo |
| Vascular disorders | | Flushing |
| Gastrointestinal disorders | Constipation | Retching, nausea, aptyalism |
| Hepato-biliary disorders | | Alanine aminotransferase increased*, aspartate aminotransferase increased*, gamma-glutamyltransferase increased* |
| Skin and subcutaneous tissue disorders | | Application site pruritis*, skin irritation |
| Musculoskeletal and connective tissue disorders | | Arthralgia |
| General disorders and administration site conditions | | Generalised oedema |
| Investigations | | Weight decreased |

* Secondary SOC locations to those listed in Appendix 3 have been used for the highlighted terms, solely in the context of the SmPC, to make identification of adverse reactions simpler and clinically appropriate for the reader

Within the systems among the healthy patients the most common events were constipation and headache. These are well recognised adverse effects of $5HT_3$ antagonists. Among the cancer patients the most common specific symptoms indicated were again headache and constipation. Other less common symptoms are indicated in Table 14. The incidence of constipation in this group was 5.4% and was the predominant related adverse event for both granisetron TDS and oral granisetron patients. Again these were as

anticipated from previous experience with granisetron and no new safety issues were raised.

A total of 16 patients, 10 with granisetron TDS and six treated with oral granisetron died as a result of adverse events during the clinical trial. Cause of death was widespread with no particular trend. The most frequent cause of death was sepsis, stroke and febrile neutropenia. This included four patients on the granisetron TDS group and were all considered unrelated to treatment. In addition two patients suffered pulmonary embolism in the granisetron TDS group. Overall none of the deaths in the granisetron TDS group was attributed to treatment with granisetron TDS. In the oral granisetron population the cause of death was also widespread. Importantly there was one death in the granisetron oral group considered treatment-related and this was a patient who died of toxic megacolon.

Review of serious adverse events revealed that in the healthy subjects studies there was one report of a cerebrovascular accident considered unrelated to treatment. Among the cancer patients there were 36 serious adverse events (SAEs) in the granisetron TDS group and 33 in the oral groups. Four patients reported related events: three patients in the oral group had QTc prolongation reported as an SAE and one patient in the active patch group had constipation. An additional unrelated SAE of gangrene was reported in the granisetron TDS group. Overall no significant differences in the incidence of non-fatal serious adverse events were recorded between the groups. The three related SAEs of QTc prolongation for oral granisetron were followed up to investigation of site ECGs and centrally read ECGs and were subsequently noted as not being QTc prolongation.

Adverse events leading to treatment withdrawal occurred in 22 patients; 10 cancer patients were from the granisetron TDS group and six cancer patients were from the oral group while there were six healthy subjects who withdrew from study.

In the healthy subject group, three of these withdrawals were considered related to study medication and all were constipation. Three were unrelated. In the cancer patients most adverse events leading to withdrawal were assessed as not related to study medication but were related to either the medical condition or the chemotherapy administered. Exceptions to this included two patients both from the oral group with prolonged QT intervals on ECG and one patient in the oral group with headache. Overall the transdermal group had a similar adverse event profile to the oral treatment group.

Recognising that granisetron had been associated with rare cardiac events including atrial fibrillation and QT interval prolongation of unknown significance, there was a review of specific adverse events in relation to ECG analyses. Of the ECG recordings from Study 15, four patients had prolonged QT intervals all in the oral group. Review of these however suggested they were not true QT interval prolongation. There was no evidence in either the patch or oral groups of changes to heart rate, AV conduction, cardiac repolarisation or morphology. Overall review of ECG traces revealed that there were no apparent cardiac safety issues arising from these studies of granisetron TDS.

Review of gastrointestinal adverse events indicated that 5.4% of the cancer patients and 58.5% of the healthy patients experienced constipation while being exposed to granisetron. The difference can be explained by the fact that cancer patients have a high background incidence of gastrointestinal symptoms. The frequency of constipation in the patch treated cancer population was not significantly different to the oral group being 5.4% vs 3%. No cases of severe constipation were recorded in the oral group although one case of severe constipation occurred in the granisetron TDS groups. One patient in each group had a gastrointestinal serious adverse event deemed related to treatment. As

mentioned above, the serious adverse event for the patient receiving oral granisetron was toxic megacolon and resulted in death.

It would therefore appear that in the cancer patient population granisetron TDS poses no greater risk from constipation than the oral granisetron formulation and therefore no additional warnings or precautions appear to be required.

With regard to dermal tolerance and hypersensitivity, it is noted that rare cases of hypersensitivity had been recorded with granisetron TDS and occasionally they are severe.

The results of the dermal tolerance studies in both patients and healthy subjects suggested that patches had potential for mild irritation. The studies also suggest that hypersensitivity reactions are possible with one subject having such a sensitisation reaction. Accordingly it is appropriate that patients be warned about the potential for mild skin reactions and if severe skin reactions occur, then patches should be removed and health professional care sought.

A review of clinical laboratory evaluations showed there was no consistent pattern of changes in biochemistry and haematological assessments in the cancer patient treatment groups. Overall 17 adverse events were reported in the laboratory investigations of which five in the granisetron TDS group and five in the granisetron oral group were related. It would appear that potential for mild disturbances in hepatic function occurs on occasions and needs to be appropriately monitored.

A review of vital signs did not show any particular changes of concern in either the healthy subjects or cancer patients or in either the granisetron TDS or oral granisetron groups.

*Evaluator's comment*

> The data provided from this integration of data from the five clinical trials in relation to safety essentially confirm the known safety profile for granisetron, that is, the principal toxicities being constipation and headache. Much less common concerns relate to potential changes in QT intervals on ECG and very rare potential for hypersensitivity.
>
> There appears to be no obvious differences in potential for adverse effects related to granisetron TDS compared to oral granisetron and therefore no reasons arise for concern in potential registration of granisetron transdermal delivery system.

## Clinical Summary and Conclusions

This submission has provided five clinical trials to support the new granisetron transdermal system for use in patients receiving chemotherapy to prevent nausea and vomiting.

Study 4, which was single centre Phase I study assessed the pharmacokinetic profile of a granisetron patch with a strength of 9.9 mg. Patients showed quantifiable granisetron within 24 hours of the patch application and plasma concentrations reached the maximum in any subject of 5.2 ng/mL by 30 hours. This confirmed a sustained bioavailability of granisetron via a patch but also indicated that a larger patch size would be required to achieve a comparable exposure to that obtained with a 2 mg dose of oral granisetron.

Study 11, which was a single centre open label trial in subjects who received both oral granisetron administered at 2 mg daily/once daily dose for five days and three separate doses of granisetron at 15, 33 and 52 $cm^2$ or equivalent strengths of 9.9 mg, 21.8 mg and 34.3 mg applied for six days. Data revealed that granisetron was absorbed with peak

plasma concentrations reached 48 hours after application of the patch. Subsequently concentrations progressively decreased until patch removal at 144 hours.

The study confirmed that a 52 $cm^2$ granisetron TDS achieved a similar exposure to that of a 2 mg oral dose of granisetron. It also confirmed that the optimal primary patch application for the Phase III clinical study was 24-48 hours before chemotherapy.

Review of these data in conjunction with the data from the two studies involving cancer patients (Study 15 and Study 8) together with the skin sensitisation study (Study 26) has confirmed that when a granisetron TDS 52 $cm^2$ patch is applied and maintained for six days, on average a dose of 3.6 mg granisetron per day is delivered. This results in an average plasma granisetron concentration of 2.23 ng/mL and in patients who were treated with 2 mg oral granisetron every 24 hours for five days, this resulted in an average plasma granisetron concentration of 2.14 ng/mL after the first administration and 2.6 ng/mL following the final dose. Thus granisetron TDS 52 $cm^2$ patch delivers comparable average plasma concentrations to 2 mg oral granisetron every 24 hours. This suggests that sufficient drug should be released from the patch formulation to demonstrate efficacy.

The pivotal clinical trial (Study 15) was a randomised active controlled double blind double dummy parallel group multinational study to assess the efficacy, tolerability and safety of the granisetron transdermal delivery system in chemotherapy-induced nausea and vomiting associated with the administration of moderately or higher emetogenic multiday chemotherapy. The primary objective was to demonstrate the non-inferiority of the GTDS efficacy compared with oral granisetron efficacy with regard to complete control (CC) over CINV, being defined as no vomiting or retching and no more than mild nausea and no rescue medication, from the first administration until 24 hours after last administration of the moderately or highly emetogenic multiday chemotherapy. The primary endpoint was the percentage of patients achieving CC. Results revealed that 60.2% of patients receiving the patch achieved complete control compared to 64.8% of patients receiving oral granisetron. This essentially rejected the null hypothesis and confirmed that the GTDS is not inferior to oral granisetron for the control of CINV in multiday ME and HE chemotherapy. The best estimate of the difference was -4.89%. Review of various secondary objectives also confirmed this result. Stratification by various factors including gender, regimen of chemotherapy, duration of chemotherapy and prior chemotherapy history also showed no statistically significant differences between the treatment groups in any of the strata.

These data were supported by a Phase II trial (Study 8), which is a double blind double dummy randomised multicentre trial comparing the efficacy, safety and tolerability of a granisetron transdermal patch with oral granisetron in CINV following a single day administration of moderately emetogenic chemotherapy. The study involved random assignment of patients to receive either a granisetron transdermal patch and one placebo capsule or a placebo patch and one granisetron 2 mg capsule. The patch was maintained for a total of five days. The primary endpoint was the proportion of patients achieving total control of CINV, that is, no nausea, vomiting or use of rescue medication or withdrawal from study during the 24-120 hour period of assessment following chemotherapy. Results revealed that total control was achieved with the patch system in 32.2% of patients throughout the delayed phase of assessment compared to 29.8% of patients receiving the oral granisetron with a p-value of 0.6288. All other endpoints analysed also revealed comparable outcomes for the transdermal system compared to oral administration.

A further study (Study 26) assessed the cumulative skin irritation and sensitisation potential of the granisetron transdermal delivery system. This was a double blind placebo controlled study. The primary objectives were to assess the incidence and prevalence of

irritation at the site of application after repeated application of study drug (Induction Phase) and to assess the incidence of sensitisation on an alternative skin site after another application of the study drug (Challenge Phase). Assessment of the incidence and prevalence of skin irritation reactions showed the active granisetron patch was no more irritant than its matching placebo patch. The two patches proved to be slightly irritant with prevalence on Day 8 of 13% in the active group and 22% in the placebo group. There was one positive contact allergic reaction documented for those patients receiving the granisetron patch. Application of the patch was discontinued in five subjects due to serious irritant reactions at the original patch site and when a patch was applied to a different site in 4/5 subjects minimal irritation occurred. Assessment of patch adhesivity also demonstrated that 94.5% of patients with granisetron patch had >75% patch adherence up to Day 8. Therefore it can be concluded that the active granisetron patch and its matching placebo are slightly irritant when applied to healthy skin with a lower number of subjects reporting irritation of the active patch. There was a low sensitisation potential with only one patient having hypersensitivity reaction.

These data essentially indicated that the granisetron transdermal delivery system provides an appropriate level of granisetron when applied and maintained over a five day period utilising the 52 $cm^2$ patch with the highest drug concentration of 34.3 mg. The concentration of granisetron reached in systemic circulation is essentially equivalent to that obtained with oral administration over a five day period. The level of complete control achieved with these patches is comparable to the oral formulation in a large and relatively robust study.

A review of adverse effects occurring in all five clinical trials essentially confirms the known adverse effects associated with granisetron when administered by other routes, namely a particular potential for constipation and to a lesser degree headache. Other adverse effects such as mild disturbances of hepatic function and occasional ECG abnormalities were documented but generally not considered to be clinically significant in most circumstances. An occasional allergic reaction to the patch was also documented as discussed earlier. Overall the safety profile for the granisetron transdermal delivery system was essentially similar to that observed for other formulations of granisetron.

The data provided in this submission therefore essentially confirms the equivalent efficacy for the granisetron transdermal delivery system to other formulations of granisetron in relation to both efficacy and safety. The reviewer therefore considered that the proposed new indication for granisetron transdermal delivery system is appropriate in the context of the data provided:

*Granisetron transdermal system is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimes of up to five consecutive days duration.*

# V. Pharmacovigilance Findings

## Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

The sponsor nominated two potential risks for Sancuso granisetron patches:

1. Complications of severe constipation

2. Hypothetical risk of local photogenotoxicity potentially leading to skin cancer

Routine pharmacovigilance was proposed to monitor these potential risks for Sancuso.[5] The sponsor did not propose undertaking additional risk minimisation activities, apart from product labelling.[6] The RMP was accepted overall, however the sponsor was asked to provide a line listing or other suitable record of worldwide post marketing reports for Sancuso, which were not available at the time of RMP submission.

In addition, the sponsor was asked to clarify and provide further information on the following issues:

1. Does the patch contain any metal components?

2. Does the presence of excessive hair on the outer arm impact on the bioavailability of the patch? Should patients with excessive hair be advised to clip the hair or place patch on a hair-free area?

3. Can the sponsor provide an update with regard to the status of the EU application and outline any issues or concerns raised by the Agency which may have prolonged the evaluation period?

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

The quality evaluator raised concerns regarding poor pharmaceutical characterisation and routine control of manufacturing. The application was considered by the Pharmaceutical Subcommittee at its November 2010 meeting. The Subcommittee also raised concerns regarding the high degree of variability in bioavailability, and the absence of *in vivo – in vitro* correlation data. The application was reconsidered by the PSC at its January 2011 meeting. The PSC concluded that there should be no objection on pharmaceutic and biopharmaceutic grounds to the approval of this application provided all outstanding issues were addressed to the satisfaction of the TGA.

## Nonclinical

There were no nonclinical objections to registration. The evaluator noted that for the currently registered granisetron products, dosage regimes of up to 9 mg per day by IV or oral administration are approved. The systemic exposure to granisetron with the patch product will be significantly less and therefore there are unlikely to be any new issues related to systemic toxicity.

The submission included several studies examining local tolerance, skin sensitisation and phototoxicity. The product demonstrated mild skin irritation but no evidence of skin sensitisation was demonstrated in a guinea pig model. There was some evidence of photogenotoxicity in a chromosomal aberration assay. The draft product information

[5] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[6] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

recommends avoidance of exposure of the application site to sunlight for 10 days after patch removal.

## Clinical

### *Clinical Evaluation*

The clinical evaluator recommended approval of the application.

### *Pharmacokinetics*

PK data were available from three studies in healthy volunteers and two studies in patients.

In **Study 4**, a 9.9 mg (15 $cm^2$) patch was applied to healthy volunteers for a total of 5 days. Systemic absorption of granisetron was demonstrated.

In **Study 11**, the PK of three different patch strengths was compared with that of a 2 mg granisetron tablet given daily for 5 days, which is the approved dose for oral granisetron in Australia. The three patch strengths studied were 9.9 mg (15 $cm^2$), 21.8 mg (33 $cm^2$) and 34.3 mg (52 $cm^2$). The average concentration achieved with the 34.3 mg (52 $cm^2$) patch (2.23 ng/mL) was comparable to that achieved with the 2 mg tablet (2.14-2.60 ng/mL).

With application of the 34.3 mg (52 $cm^2$) patch, the average concentration was reached with 24 hours and the maximum concentration in 48 hours. These data support the proposed dose regimen of patch application 24-48 hours prior to chemotherapy.

In **Study 26**, the effect of gender on the PK of granisetron delivered by the patch was examined. It was shown that females have a much greater systemic exposure than males (AUC 800 vs 254 ng/mL.hr).

**Study 8** enrolled patients receiving moderately emetogenic chemotherapy. At 48 hours after patch administration, the granisetron concentration was 5.0 ng/mL, which is comparable to 48 hour concentration seen in healthy volunteers (3.85 ng/mL) in Study 11.

**Study 15** enrolled subjects receiving moderately or highly emetogenic chemotherapy. Subjects were randomised to receive either the patch or oral granisetron. The only PK data collected were from a single sample taken one hour after the oral dose or 24-48 hours after patch application.

### *Efficacy*

Evidence for efficacy came primarily from a single pivotal, randomised, double blind, controlled trial (**Study 15**). The trial enrolled adult patients receiving their first cycle of either highly emetic or moderately emetic chemotherapy (HEC or MEC) as defined by levels 3, 4 or 5 of the Hesketh classification. Patients were scheduled to receive multiday chemotherapy regimens (lasting 3, 4 or 5 days).

Subjects were randomised to receive either the patch or oral granisetron (2 mg once daily). The patch was applied 24-48 hours prior to chemotherapy, whereas oral granisetron was administered 1 hour prior to chemotherapy. The primary efficacy endpoint was the proportion of patients who achieved "complete control" – defined as no vomiting/retching, no rescue therapy and no more than mild nausea from the first administration of chemotherapy until 24 hours after the last administration of chemotherapy. The study was designed as a non-inferiority trial. Non-inferiority would be concluded if the lower bound of the 95% CI for the difference in complete control rate (patch minus tablet) was greater than -15%. For the per-protocol population, the difference in response rate was -4.89% (95% CI: -12.91 to +3.13 %). Non-inferiority was

therefore concluded. Efficacy was also comparable in the subgroup of patients who received HEC (cisplatin).

There were multiple secondary endpoints used in the study. The results suggest broadly comparable efficacy. However, there is some suggestion of lower efficacy in the patch group by Day 5 in patients receiving 4 or 5 day regimens.

**Study 8** was a supportive randomised, double blind, controlled Phase II efficacy study conducted in patients scheduled to receive a single day MEC regimen. Subjects were randomised to receive either the patch or oral granisetron (2 mg single dose). The patch was applied 24 hours prior to chemotherapy, whereas oral granisetron was administered 1 hour prior to chemotherapy.

The objective of the study was to examine the efficacy of the patch in preventing *delayed* nausea and vomiting (in the period 24-120 hours after chemotherapy administration). The primary efficacy endpoint was the proportion of patients who achieved "total control" – defined as no vomiting, no nausea, no rescue therapy and no withdrawal from the study in the period 24-120 hours after administration of chemotherapy. There was no difference between the treatment arms for the primary endpoint.

The secondary/additional endpoints demonstrated numerically *inferior* results for the patch in the 0-24 hour period after chemotherapy. In this study, the patch was applied only 24 hours prior to chemotherapy, whereas in Study 15 it was applied 24-48 hours prior. Given that $C_{max}$ occurs at 48 hours, it may be preferable to recommend administration of the patch at 48 hours before chemotherapy, rather than 24-48 hours.

***Safety***

Approximately 640 subjects were exposed to the patch in the submitted studies, including approximately 400 patients receiving chemotherapy. Studies 15 and 8 compared the safety of the patch with oral administration of granisetron. The overall safety profiles of the two dose forms appeared comparable. The incidences of individual adverse events were also comparable.

The submission also included a skin sensitisation study (**Study 26**). Healthy subjects had the granisetron patch applied to one upper arm and a placebo patch to the other. Patches were left in place for seven days for each of three consecutive administrations (total = 21 days). Subjects were then rechallenged after a two week rest period.

On Day 8 (which corresponds to the longest period the patch will be applied in clinical practice):

- 41 % had slight erythema;
- 13 % had moderate erythema; and
- 0.5% had severe erythema.

The incidence of irritation was higher with the placebo patch.

Only one subject (of 200) developed evidence of sensitisation when rechallenged with the patch.

## Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was found to be acceptable by the TGA's Office of Product Review (which has replaced OMSM). The questions raised by the RMP evaluator were satisfactorily addressed by the sponsor.

## Risk-Benefit Analysis

### *Delegate Considerations*

#### Overall risk benefit

The submitted pivotal study has demonstrated efficacy and safety comparable to a registered oral granisetron regimen. The patch is associated with some mild to moderate local skin toxicity. Overall the Delegate considered that the product has a favourable risk benefit ratio and proposed to approve the application.

#### Variability in bioavailability

One of the concerns raised by the PSC was that the product displays a high degree of between-subject variability in bioavailability. In response, the sponsor provided evidence that the bioavailability of granisetron is also highly variable when administered orally or intravenously. In clinical use, between-subject variability in bioavailability would manifest as poor efficacy in those subjects in whom bioavailability was low. The pivotal clinical study demonstrated that the proportion of patients in whom granisetron was ineffective was comparable across the patch and tablet treatment groups. The clinical data therefore provides reassurance that the variability does not result in clinically significant consequences.

#### Combination with other anti-emetic agents

In current clinical practice, the prevention of CINV typically involves combination of a 5-$HT_3$ receptor antagonist with other agents (for example, dexamethasone and aprepitant). The pivotal study in this submission examined use of granisetron alone in both treatment arms. Granisetron is metabolised in part by cytochrome P450 (CYP) 3A4 and administration of other drugs such as aprepitant (a CYP3A4 inhibitor) could alter the PK of the drug. However, it would appear unlikely that such effects would be greater or smaller with the transdermal preparation than with other formulations of granisetron. The Delegate therefore considered it would be reasonable to extrapolate the findings of the pivotal study to combination use.

#### Increased exposure in females

Study 26 demonstrated that female patients experience significantly greater systemic exposure to granisetron than males. The pivotal study demonstrated that efficacy was not reduced in males. However, it is possible that female patients may experience greater toxicity than males with this product. *In the pre-ACPM response the sponsor was requested to comment as to whether there was any evidence of increased toxicity in females in the pivotal trial (Study 15).* As systemic granisetron exposure with this product is likely to be considerably lower than that seen with approved dosage regimens for the IV products, the Delegate did not consider this issue to be a barrier to registration.

The Delegate proposed to approve the application, subject to resolution of the quality issues to be considered by the PSC prior to the ACPM meeting. The advice of the Committee was requested.

***Response from Sponsor***

In its pre-ACPM response, the sponsor discussed a number of issues which had been raised during the evaluation

**Variability in Bioavailability**

*Intersubject variability in pharmacokinetic studies*

The wide range of inter-subject variation in blood granisetron levels is a characteristic of granisetron that has been noted from its earliest development. The available literature indicates that the variability observed with the Sancuso patch formulation is essentially similar to the variability that has been observed with both oral and intravenous administration (% CV 60 – 100). Therefore, inter-subject variability is not dependent on dosage form and route of administration.

It is important to highlight that the pivotal clinical study (Study 15) demonstrated comparable efficacy and safety to a registered oral granisetron regimen and as acknowledged by the Delegate this study also demonstrated that the proportion of patients in whom granisetron was ineffective was comparable across the patch and oral tablet treatments which provides reassurance that there are no clinical consequences as a result of the variability observed.

It is also relevant to consider that although the quality reviewer recorded some concern about the variability of bioavailability in Study 4, this was a small study, conducted in the early stages of development, using smaller 15 $cm^2$ patches manufactured using semi-automated equipment. As such more emphasis should be placed on PK Studies 11 and 26 which were larger and used the patch formulation (52 $cm^2$) and method of manufacture proposed for registration.

**Pharmaceutical characterisation and control of manufacturing**

The sponsor described details of the characterisation of the drug in the patch matrix. The sponsor also described details of the control of the finished product and consistency in manufacture. In addition, the sponsor described details of its investigation of crystalline particles in patch matrix.

To ensure consistency of drug release the manufacturer has developed an *in vitro* dissolution test which is adequately discriminatory and designed to provide a quality control tool with which to assess the reproducibility of finished product batch manufacture.

**In vivo/in vitro correlation**

The sponsor reiterated its reasoning for not conducting an *in vitro/in vivo* correlation study. It further noted that an *in vitro/in vivo* correlation is not a standard requirement for Category 1 applications which are primarily supported by sponsor-conducted clinical efficacy and safety studies. It was also recognised within the pharmaceutical industry and the regulatory community that the generation of *in vitro/in vivo* correlation using matrix transdermal products has met with a very poor success rate because the *in vivo* performance of such a product depends upon the absorption of the drug from the skin rather than release from the patch itself. It was considered, however, that the product gives a very consistent *in vitro* dissolution profile and that any variation in the finished product that would cause a difference in clinical performance would be noted during routine dissolution testing during batch analysis.

### Combination with other anti-emetic agents

Both highly and moderately emetogenic chemotherapy regimens were given to patients in the pivotal efficacy and safety study 15. Use of corticosteroids with individual patients was at the decision of the individual investigator and decided prospectively. Aprepitant (NK1 receptor antagonist) could not be used because it was not approved in all regions where the study was conducted and had not been adopted into CINV treatment guidelines. Various CINV treatment guidelines recommend use of 5-HT3 receptor antagonists alone and also in combination, depending on the individual risk of CINV. To provide guidance to the prescriber the sponsor proposed to make appropriate changes to the PI.

### Increased exposure in females

Increased exposure in females could potentially result in safety differences. A *post hoc* analysis of the safety set of Study 15 shows the AE rate to be very similar between males and females within the Sancuso treated group (38.5% vs 42.5% respectively). Severe adverse event rates and adverse reaction rates are also very similar between the male/female populations (7.1%, 7.5% and 7.1%, 8.8% respectively). When the nature of the adverse reactions is examined the rates are very similar between male/female groups, and predominantly constipation (5.8%, 7.5% respectively).

The pharmacokinetic findings in healthy subjects in Study 4 were that the mean plasma granisetron $C_{max}$ and AUC in the healthy male subjects was greater than that seen in the females, however in Study 26 (also in healthy subjects) the mean plasma granisetron $C_{max}$ and AUC were higher in females compared to males. In Study 26 the apparent gender difference may be due to outlying PK values for a single female subject.

Experience in cancer patients receiving Sancuso (Study 15) was consistent with the Kytril US prescribing information as mean plasma granisetron concentrations were higher in males than in females, although it was interesting to note that levels were higher in females than males for the oral granisetron group in Study 15. Differences between studies can be explained by higher inter-patient variability in PK values, and small patient numbers in some studies leading to apparent gender differences.

Overall there is no consistent PK or clinical evidence to support the assertion that the absorption or elimination of granisetron is influenced by a subject's gender.

#### *Advisory Committee Considerations*

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission as a new dosage form and new route of administration for the indication:

*For the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.*

ACPM noted that no data on the effect of this product on the coadministered chemotherapy were provided.

The ACPM also noted that all testing had been carried out with the patch affixed to the upper arm and that patch adherence was an issue which may be of practical consideration in warmer climates or weather.

The Committee also recommended a number of changes to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sancuso transdermal system containing granisetron 3.1 mg/24hours 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.*

As a condition of registration the Risk Management Plan of June 2007, as agreed with the Office of Product Review, must be implemented.

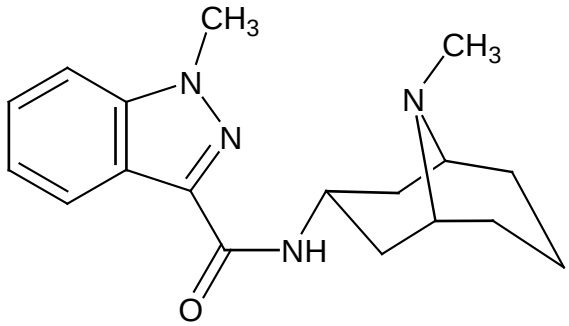
# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

## Product Information

### Name of the medicine
Sancuso® (Granisetron Transdermal Drug Delivery System).

### 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. The CAS number for granisetron is 109889-09-0. 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. 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.

### Pharmacology

### 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$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, or 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.

### 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.

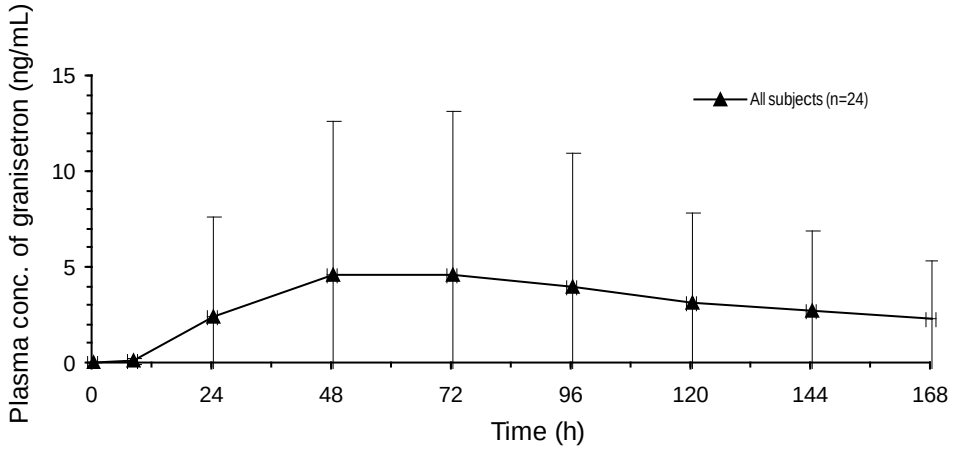
**Pharmacokinetics**

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 $AUC_{0\text{-}168hr}$ was 527 ng-hr/mL (CV:173%).

**Mean Plasma Concentration of Granisetron (mean ± SD)**




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

Distribution

Granisetron is extensively 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.

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. *In vitro* studies with human liver microsomes and expressed human CYP450 isoforms show that the metabolism of granisetron is mediated mainly by CYP1A1 and CYP3A4. Animal studies suggest that some of the metabolites may also have 5-$HT_3$ 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 faeces. The half-life of granisetron following IV administration is approximately 9 hours. The apparent terminal half-life after removal of the Sancuso patch is approximately 36 hours.

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.

*Paediatrics*

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

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.

**Clinical trials**
The effectiveness of Sancuso in the prevention of chemotherapy-induced nausea and vomiting (CINV) was evaluated in a multinational Phase 3 randomized, parallel group, double-blind, double-dummy study. 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.

**Indications**
Sancuso® (Granisetron Transdermal Drug Delivery 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.

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

**Precautions**

**Gastrointestinal**
Granisetron may reduce lower bowel motility and therefore may mask a progressive ileus and/or gastric distension caused by the underlying condition.

**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.

**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 **Precautions - Phototoxicity**).

**ECG Abnormalities**
As for other 5-$HT_3$ antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. The ECG changes were minor, generally not of clinical significance and specifically, there was no evidence of proarrhythmia. However, in patients with pre-existing arrhythmias or cardiac conduction disorders, this might lead to clinical consequences. Therefore, caution should be exercised in patients with cardiac co-morbidities, on cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities.

**Effects on Fertility**
Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/$m^2$/day, about 18 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 293 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.

**Use in Pregnancy (Category B1)**
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 26 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/$m^2$/day, about 366 times the recommended human dose with Sancuso, based on body surface area). Reproduction studies have also been performed in pregnant rabbits at intravenous doses up to 3 mg/kg/day (36 mg/$m^2$/day, about 18 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 187 times the human dose with Sancuso based on body surface area). These studies did not reveal any evidence of teratogenic effects 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.

**Use in Lactation**
A study in lactating rats showed that the rate of excretion in milk after IV dosing is less than 1% of the dose per hour, and at least some of this is absorbed by the offspring. It is not known whether granisetron is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when Sancuso is administered to a nursing woman.

**Paediatric Use**
Safety and effectiveness of Sancuso in paediatric patients under 18 years of age have not been established.

**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.

**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 **Pharmacology - Pharmacokinetics**).

**Carcinogenicity**
In a 24-month carcinogenicity study, rats were treated orally with granisetron in the diet 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. 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 15 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 73 times the recommended human dose with Sancuso, on a body surface area basis). No increase in liver tumours was observed at a dose of 1 mg/kg/day (6 mg/m$^2$/day, about 2.9 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 15 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 293 times the recommended human dose with Sancuso, on a body surface area basis) produced hepatocellular adenomas in male and female rats while no such tumours were found in the control rats.

In a mouse carcinogenicity study, animals were treated with granisetron in the diet at 1, 5 or 50 mg/kg/day (3, 15 or 150 mg/m$^2$/day) for 24 months. There was a statistically significant increase in the incidence of hepatocellular carcinoma in males and hepatocellular adenomas in females dosed with 50 mg/kg/day (about 73 times the recommended human dose with Sancuso, on a body surface area basis). No increase in liver tumours was observed 1 mg/kg/day (1.5 times the recommended human dose with Sancuso).

Because of the tumour findings in animal studies, Sancuso should be prescribed only at the dose and for the indication recommended (see **Indications**, and **Dosage and administration**).

**Genotoxicity**
Granisetron was not mutagenic or clastogenic in an *in vitro* Ames test, a mouse lymphoma cell forward mutation assay, an *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (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.

**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 UV irradiation.

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 photosensitisation. No phototoxicity studies have been performed in humans.

**Interactions with Other Medicines**
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 *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation and N-demethylation of granisetron. 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.

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*.

**Adverse effects**

**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**<br>**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-$HT_3$ receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities (see **Precautions**). 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.

**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 have been observed in clinical trials at varying incidence rates both in comparative and non-comparative studies using other formulations of granisetron. The causality for all these adverse events has not necessarily been established. The adverse events reported are listed below categorised by frequency according to the following

definitions: common events reported at a frequency of greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 patients.

**Body as a whole:** *Common:* fever, asthenia.

**Cardiovascular:** *Common:* hypertension; *Rare:* hypotension, arrhythmias, sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy, including non-sustained tachycardia, ECG abnormalities, angina pectoris, syncope.

**Gastrointestinal:** *Common:* constipation, diarrhoea, abdominal pain

**Hypersensitivity:** *Rare:* hypersensitivity reactions (e.g. anaphylaxis, shortness of breath, hypotension, urticaria).

**Hepatic:** *Common:* transient increases in AST and ALT. These are generally within the normal range and have been reported at similar frequency in patients receiving comparator therapy.

**Nervous system:** *Common:* headache, agitation, anxiety, CNS stimulation, dizziness, insomnia, somnolence; *Rare:* extrapyramidal syndrome (only in presence of other drugs associated with this syndrome).

**Dermatological:** *Common:* skin rashes.

**Special Senses:** *Common:* taste disorder.

Other common events often associated with chemotherapy also have been reported: leukopaenia, decreased appetite, anaemia, alopecia, thrombocytopaenia.

**Dosage and administration**

The transdermal drug delivery 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 oily, recently shaved, red, irritated or damaged. Sancuso should also not be applied to areas that have been treated with creams, oils, lotions, powders or other skin products that could keep the patch from sticking well to the skin.

Showering and washing normally can be continued while wearing Sancuso. Activities such as swimming, strenuous exercise, and using a sauna or whirlpool should be avoided as it is not known how these activities may affect Sancuso.

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

The patch should not be cut into pieces.

**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.

Clinical experience is based on use of Sancuso® alone and in combination with corticosteroids. The use of Sancuso® in combination with corticosteroids and other recognised antiemetic agents should be considered depending on the emetogenicity of the anticancer agents used, the individual patient's risk factors, and relevant therapeutic guidelines.

**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.

**Presentation and storage conditions**
Sancuso (Granisetron Transdermal Drug Delivery System) is supplied as a 52 $cm^2$ 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 sachet.

Sancuso is available in a pack size of 1 patch.

Store below 25°C.

Sancuso should be stored in the original packaging.

**Name and address of the sponsor**

**Manufactured by:**
Aveva Drug Delivery Systems Inc.,
Miramar
FL 33025
USA

**Supplied by:**
Invida Australia Pty Limited
Level 8/67 Albert Avenue
Chatswood
NSW 2067

**Poison schedule of the medicine**
Prescription Only Medicine

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Sancuso is a trademark owned by the ProStrakan group of companies

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
**www.tga.gov.au**

Reference/Publication #