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APPLICATION NUMBER:

22-198

MEDICAL REVIEW(S)

Division Director Review

Date	September 12, 2008
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-198
Supplement #	
Applicant Name	Strakan International Ltd.
Date of Submission	June 29, 2007
PDUFA Goal Date	May 2, 2008
Proprietary Name / Established (USAN) Name	Sancuso
Dosage Forms / Strength	Transdermal delivery system
Proposed Indication(s)	Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration
Recommended Action	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Karyn Berry, MD/Hugo Gallo-Torres, MD, Ph.D., PNS
Statistical Review	Wen-Jen Chen, Ph.D./Mike Welch, Ph.D.
Pharmacology Toxicology Review	Sushanta Chakder, Ph.D.
CMC Review	Rao Puttagunta, Ph.D./Moo-Jhong Rhee, Ph.D.
Clinical Pharmacology Review	Tien-Mien Chen, Ph.D./Sue-Chih Lee, Ph.D.
DDMAC	Samuel Skariah, PharmD
OSE/DMEP	Richard Abate/Kellie Taylor/Denise Toyer/Carol Holquist/
OSE/DPV I	Ann Corken Mackey, RPh, MPH/Mark Avigan, MD

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEP=Division of Medication Errors Prevention
 DPVI= Division of Pharmacovigilance I

Division Director Review

1. Introduction

The applicant proposes to market a transdermal patch formulation of granisetron, a 5-HT₃ antagonist that is currently approved in intravenous and oral formulations for prevention of nausea and vomiting associated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). The already approved granisetron formulations are only approved for prevention of acute, not delayed phase, nausea and vomiting associated with chemotherapy. The application is a 505b2 NDA. The primary endpoint utilized in the prior approvals of granisetron were consistent with the endpoint evaluated by the applicant in the major study that supports this application – proportion of patients with no emesis, no more than mild nausea, and no use of rescue medication – although the “name” attached to that endpoint by the applicant differs from that utilized in the prior applications. The applicant refers to the endpoint as “Complete Control”, whereas in prior applications it was called “Complete Response”. The prior approvals focused on efficacy in the first 24 hours after administration of the first dose of chemotherapy. In contrast, because the single patch delivers granisetron over a course of 5-7 days (in the therapeutic range for 5 days), the primary endpoint of the major trial that supports this application evaluates control of nausea and vomiting (as defined above) for the entire administration cycle of the chemotherapy regimen (3-5 day regimens) up to 24 hours after the last dose of chemotherapy in the regimen.

The major review issue identified was whether the single major study submitted in this application provided adequate strength of evidence to support product approval - specifically, whether the study was adequately designed to establish noninferiority to the active control, a different formulation of the same active drug.

2. Background

Granisetron is a 5HT-3 antagonist antiemetic. The innovator product has been marketed under the name Kytril as intravenous and oral formulations. Generic granisetron products are currently marketed. The product submitted for review in this 505b2 NDA is the first transdermal formulation of granisetron, and if approved, will be the first marketed antiemetic transdermal product for chemotherapy induced nausea and vomiting (CINV).

The major review issue was whether the active control trial design of the major phase 3 trial submitted to support approval, Study 392MD/15/C, was adequate to establish that this product is noninferior to the approved oral granisetron 2mg dose. The biostatistics reviewers expressed concern that the statistical plan and trial design were not adequate to establish noninferiority to the approved active control, oral Kytril. The primary medical reviewer, Dr. Karyn Berry, and by the biostatistical reviewer, Dr. Wen-Jen Chen, PhD, did not identify evidence in their reviews that the Agency had agreed to the design and statistical plan for this

study. However, a record of communication of clear disagreement with the plan was not identified either. This application was associated with a number of interactions with the agency: a pre-IND meeting January 11, 2005, phase 3 protocol submission in December 30, 2005, FDA response to the IND submission's phase 3 protocol on January 23, 2006, protocol amendment (to address additional safety monitoring with ECGs and vital signs) on January 27, 2006, FDA comments on the phase 3 protocol on June 6, 2006, and a pre-NDA meeting on February 22, 2007.

In the January 11, 2005 pre-IND meeting the Agency recommended that at least two adequate and well controlled trials be conducted to support the proposed indication.

After review of the IND protocol, on January 23, 2006 the Agency requested that the applicant revise the protocol to incorporate assessments of vitals signs and 12-lead ECGs to measure QTc. The ECGs were to be performed, at a minimum, at baseline, at time of anticipated C_{max} and at time of patch removal. The reason given in the correspondence for this revision was "Since the GTDS is expected to result in sustained plasma levels of granisetron, and another drug in the 5HT3 class, that has a long half life, has demonstrated an adverse effect on QTc, the protocol defined safety assessments must be revised...." The applicant was also advised to review the ICH guidelines regarding clinical evaluation of QT/QTc interval prolongation, and "Prior to submitting an NDA you should review your existing data to determine whether any additional studies are necessary for satisfying current ICH guidelines."

Additional protocol design comments were conveyed to the applicant on June 6, 2006. These comments included:

- 1) Reiteration that two clinical trials were recommended. Concern was raised that two populations of patients, those being treated with moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC), would be enrolled in the single study. The division told the applicant that if both populations were to be enrolled in the same study, the study would need to be appropriately powered.
- 2) Comments were provided regarding the protocol plan to enroll patients on chemotherapy regimens that ranged in duration from 3-5 days. There was concern expressed that the applicant might be attempting to study delayed phase nausea and vomiting control within the context of this noninferiority study. Because the active comparator did not have that indication, the design would only support an acute nausea and vomiting claim.
- 3) The division expressed concern about the multiple stratifications proposed for the randomization procedure, which included sex, cisplatin chemotherapy, non-cisplatin chemotherapy with or without corticosteroids, duration of the chemotherapy regimen – naïve vs. non-naïve.
- 4) The division recommended that corticosteroid use in the study be standardized.

- 5) The division recommended that enrollment be limited to either one of chemotherapy naïve or non-naïve patients.

On October 30, 2006, additional protocol comments were conveyed to the sponsor.

- 1) Because there are chemotherapy regimens that include drugs that might be classified as either HEC or MEC, the Division recommended that the emetogenicity classification be based on the most emetogenic drug in the combination. The Division recommended prospective classification of regimens to allow for accurate and consistent stratification by MEC or HEC classification.
- 2) A question was raised regarding the plan to apply the patch 2 days prior to chemotherapy in patients receiving 5 day chemotherapy regimens.

At the pre-NDA meeting held February 22, 2007, the FDA agreed with a waiver for children younger than 13 years of age, but stated that there might be a role for the product in children 13 years of age and older.

In summary, in my review of the communication record between the applicant and the agency, I found no discussion of the statistical plan for noninferiority analysis or substantive discussion of the active control trial design to establish noninferiority.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and substance. Manufacturing site inspections were acceptable. Although the applicant proposed a _____ expiration for the to be marketed product, stability testing only supports an expiry of 24 months _____
_____ The applicant developed a specification for _____
specification for previously approved transdermal patches.

b(4)

In the development of the product, the applicant noted that exposure to sunlight or artificial sunlight leads to degradation of the granisetron product. For this reason, the applied patch should be covered with clothing while wearing the patch. Conceivably, any residual product within the skin after patch removal could also be degraded by sun exposure. Based on these concerns and the UV light exposure concerns raised by the Chinese hamster ovary cell *in vitro* assay (see Section 4 of this review, below), labeling will state that the area of skin exposed to the patch should remain covered for 10 days after patch removal.

The removable release liner, which is in contact with the granisetron/adhesive matrix while it is in the package, is coated with a _____ lining that contains _____. The chemistry reviewer indicates that this component is made up of a polyester _____ and a _____ coating. _____

b(4)

_____ The chemistry reviewer found the _____ content acceptable because the release liner is removed from the matrix prior to application to the skin. Dr. Moo Jong Rhee, PhD, also pointed out that even if some of the

b(4)

_____ in the _____ lining were to migrate into the adhesive matrix, it would be a small amount, and _____ would be highly unlikely to migrate into skin. The cited CFR content is for food additives, in which exposures for transfer into body would be via gastrointestinal mucosal surfaces. I concur that the _____ in the _____ liner of this transdermal patch is not a significant concern, as any migration that might occur would be expected to be minimal.

b(4)

b(4)

The inspections of the drug substance manufacturer and packager in _____ was found Acceptable, as was the inspection of the finished dosage manufacturer and packager in Miramar, Florida.

b(4)

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with his recommendations for revisions to the proposed product labeling. Those changes were incorporated into the final version of the label. Although this was a 505b2 application, the applicant did submit new nonclinical data for review. These studies included an ADME study and a two-week bridging toxicology study comparing the patch with IV and orally administered granisetron in rats and dogs. In the bridging studies fatty infiltration in the liver, associated with AST elevation, was observed in all three granisetron dosage forms. In rats, cardiac lymphocytic infiltration was observed in all three dosage form groups – patch, continuous IV granisetron administration, and oral. Interstitial nephritis was observed in rats exposed to the patch and IV granisetron. Dr. Chakder concluded that no new target organs of toxicity were identified for the patch formulation of granisetron.

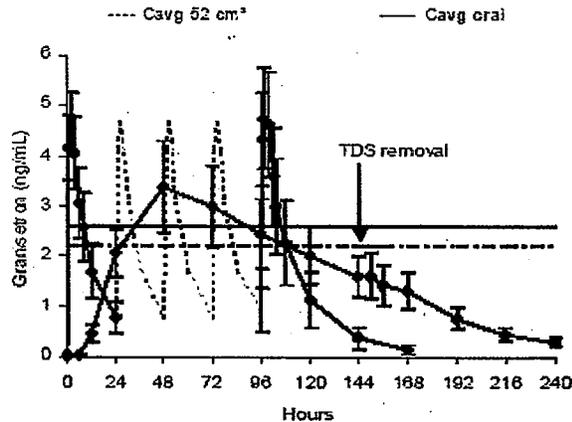
Granisetron was noted to be positive in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells (CHO) in the presence of UV irradiation. Results were negative in the absence of UV light. These findings resulted in labeling to inform physicians and patients that patients should avoid exposure of the area of patch application to sunlight, including for at least 10 days after patch removal.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the labeling recommendations of the Clinical Pharmacology reviewers and I concur with their recommendations that the applicant should commit to performing additional pharmacokinetics studies post approval to investigate the impact of varying degrees of subcutaneous adiposity/skin integrity on the pharmacokinetics of the transdermal granisetron patch.

The reviewers noted that a significant subcutaneous fat store of granisetron is associated with this delivery system. This is shown in Figure 1 in Dr. Chen's review, which I have reproduced from his review below. The graph of granisetron concentration over time shows that significant serum concentrations are sustained after patch removal at 144 hours post application. This indicates there is continued release from the subcutaneous compartment after removal of the patch.

Figure 1. Mean (\pm SEM) plasma granisetron concentration-time profiles for the 52cm² granisetron TDS (filled diamonds) and 2 mg oral granisetron (open diamonds) once daily dosing x 5 days (Study 392MD/11/C)



Given this depot effect, questions were raised about whether patients at extremes of nutritional status, either obese or cachectic, might experience significant changes in granisetron pharmacokinetics with this delivery system. The major concern was that these changes might have an impact on efficacy, and the reviewers believed that these studies should be performed as postmarketing commitments, not as postmarketing requirements under FDAAA. The reviewers also asked whether skin changes that occur with age in the elderly might have an impact on this depot effect. They recommended a postmarketing commitment study to evaluate the pharmacokinetics in a population of elderly individuals to determine whether there are pharmacokinetic difference secondary to age related skin changes. The applicant agreed to conduct the following studies to address these issues, as postmarketing commitments:

1. A clinical pharmacokinetic study to assess granisetron exposure in human subjects with differing levels of body fat.
Protocol Submission: by October 2008
Study Start: by February 2009
Final Report Submission: by December 2009
2. A clinical pharmacokinetic study to assess granisetron exposure in elderly individuals (over 65) that includes an even age distribution across the geriatric population.
Protocol Submission: by October 2008
Study Start: by February 2009
Final Report Submission: by December 2009

I concur with the clinical pharmacology reviewers' additional recommendation that the applicant should conduct a phase 4 study to evaluate the impact of heat on drug delivery. A validated in vitro model might be sufficient to provide this information. The applicant committed to conduct the following additional study as a postmarketing commitment:

An appropriate in vitro or clinical pharmacokinetic study to determine the impact of heat on the delivery of granisetron from the transdermal system.

Protocol Submission: by October 2008
Study Start: by December 2008
Final Report Submission: by March 2009

The clinical pharmacology reviewers carefully evaluated the appropriateness of the applicant's recommendation for timing of patch application prior to administration of chemotherapy, i.e. 24-48 prior to administration of chemotherapy. They also explored the evidence of efficacy in the first 24 hour after starting chemotherapy to see if they could correlate efficacy to timing of patch application. I concur with their conclusion that the applicant's recommendation for timing of patch application is supported by the data submitted in this NDA.

I concur with the reviewers' labeling recommendations for clarifying the amount of drug delivered from the patch vs. the nominal amount loaded. I also concur with their recommendation that labeling should reflect the apparent 3-fold higher exposure to granisetron observed in females vs. males wearing the patch. Even when a female who had an outlier 8 fold higher plasma level was excluded from the analysis, females had an 80% higher C_{max} and AUC than males. Please refer to section 8. Safety of this review for a discussion of additional pharmacokinetic analyses conducted by the clinical pharmacology reviewers to explore exposure/response issues as they relate to safety.

6. Clinical Microbiology

The chemistry review states that since the matrix component of the patch is an organic solvent blend, the microbial loading of the product "will be low". He considered the microbial limits adequate for a topical product, and because the formulation _____, microbial loading was not a concern.

7. Clinical/Statistical-Efficacy

The applicant proposes an indication for prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days. The patch will be applied a minimum of 24 hours prior to chemotherapy and removed a minimum of 24 hours after the last dose of chemotherapy. The patch is to be worn a total of no more than 7 days.

Two studies were submitted in support of this indication. One was a randomized phase 2 study that compared the patch to oral granisetron 2mg in the period of 24-120 hours following a single dose of moderately emetogenic chemotherapy, a time period utilized to evaluate antiemetic control of the delayed nausea and vomiting phenomenon associated with some chemotherapeutic agents.

The second study, Study 392MD/15/C, is the major study supporting this application. It was a randomized, active control, phase 3 noninferiority trial comparing the 52 cm² patch (containing 34.3 mg of granisetron) to oral granisetron 2 mg/Day in patients treated with multi-day (3-5 day) regimens of moderately or highly emetogenic chemotherapy. The study utilized a double-blind, double-dummy, parallel group design. The active control was a capsule containing two Kytril 1mg tablets. The primary endpoint was the proportion of patients with no emesis, no more than mild nausea and no rescue medication over the entire duration of their chemotherapy administration regimen, including up to 24 hours after the last administered dose of chemotherapy in that treatment cycle. This acute phase assessment differs from the usual antiemetic trial assessment of nausea and vomiting in the first 24 hours after a dose of chemotherapy, as it incorporates the entire 3-5 day regimen in the assessment period.

The granisetron 2 mg oral dose comparator in both studies is approved for treatment of moderately (MEC) and highly emetogenic chemotherapy (HEC). The labeled dose and administration instructions for this oral formulation state that the oral product should be administered up to 1 hour before chemotherapy, only on the days of chemotherapy administration. The label clearly states that the product has not been found to be useful on the days patients are not receiving chemotherapy, i.e. for the delayed nausea and vomiting period. The regulatory basis of approval of the 2 mg granisetron oral dose comparator is summarized below. Because the studies that were conducted to support its approval were built on a comparison to the granisetron 1 mg PO BID dose regimen, the regulatory/scientific basis of the approval of that comparator granisetron regimen is also provided.

Granisetron 1 mg PO BID was approved for prevention of nausea and vomiting secondary to both moderately and highly emetogenic chemotherapy on the basis of the following studies:

- 1) A dose ranging study that demonstrated that for moderately emetogenic chemotherapy (MEC), granisetron 1 mg BID was superior to the lowest dose tested, granisetron 0.25 mg BID, and a 0.5 mg BID dose. (81% vs. 70% for the 0.5 mg dose, p<0.009)
- 2) A superiority trial comparing granisetron 1 mg PO BID to prochlorperazine BID in patients treated with moderately emetogenic chemotherapy (MEC), which demonstrated superiority of granisetron. [Complete Response 74% vs. 41%, p = <0.001 (n=111 on prochlorperazine arm)]
- 3) A superiority trial that compared oral granisetron 1 mg po BID (in combination with dexamethasone) to metoclopramide (in combination with dexamethasone) in patients treated with highly emetogenic chemotherapy (HEC). Although the granisetron + dexamethasone arm was associated with a numerically higher complete response (65% vs. 52%), it appears from the statistical review that the Agency didn't concur with the applicant that the difference observed was statistically significant. In a comparison of

the trial's oral granisetron-only arm (N=119) to a historical placebo control, the complete response associated with granisetron 1 mg BID (52%) was found to be superior. The placebo complete response rate (N=14) used in this comparison, 7% (95% CI = 0.2 - 33.9), was derived from the results from the control arm of a previous study of IV granisetron. This comparison to historical placebo is found in the product label supporting use of oral granisetron 1 mg BID with "high-dose" cisplatin.

Granisetron 2 mg PO per day was approved based on:

- 1) A moderately emetogenic chemotherapy study that compared granisetron 2 mg to a **historical** prochlorperazine 10 mg BID control. The observed complete response rate associated with granisetron 2 mg (58%) was deemed superior to the prochlorperazine **historical** control (41%) – see granisetron 1 mg BID vs. prochlorperazine superiority study above
- 2) A moderately emetogenic chemotherapy study that compared granisetron 2 mg to granisetron 1 mg BID and a prochlorperazine 10 mg BID **historical** control. Both granisetron arms were found superior to the prochlorperazine control: complete response rate 69% for granisetron 1 mg BID, 64% for granisetron 2 mg q D, and 41% for the prochlorperazine **historical** control – see granisetron 1 mg BID vs. prochlorperazine superiority study above.
- 3) A highly emetogenic chemotherapy study that compared granisetron 2 mg to granisetron 1 mg BID and a placebo **historical** control. The complete response associated with granisetron 2 mg was 44% compared to the 7% placebo **historical** control. The placebo control complete response was derived from the control arm of a previous study of IV granisetron, as described above.

In summary, the granisetron 1 mg BID regimen approval for moderately emetogenic chemotherapy (MEC) was based on demonstration of its superiority compared to low dose granisetron and prochlorperazine. The highly emetogenic chemotherapy (HEC) indication was based on its superiority to a placebo historical control, utilizing the granisetron 1 mg BID data from a randomized comparison to metoclopramide plus dexamethasone. The granisetron 1 mg BID NDA approval was critical to the subsequent approval of the granisetron 2 mg per day regimen, as the 2 mg product was deemed effective based on historical comparisons to the historical placebo data used in the granisetron 1 mg BID application, and the historical prochlorperazine data from the studies submitted in the granisetron 1 mg application. Although the studies submitted in the granisetron 2 mg application package compared the 2 mg product to 1 mg granisetron BID, noninferiority was not formally established. The label deems the two oral granisetron regimens "comparable".

Because the major trial that supports this application is a noninferiority comparison to the active control granisetron 2 mg/D, it is key to be able to establish the treatment effect of granisetron 2mg relative to placebo. Importantly, the applicant proposes two populations in the proposed indication, moderate and highly emetogenic chemotherapy. Hence, two issues arise from the regulatory/scientific history associated with the active comparator, granisetron 2 mg, if a formal claim of noninferiority is to be supported/established:

- 1) What evidence exists that granisetron 2 mg is superior to placebo in moderately emetogenic chemotherapy (MEC), and what is the treatment effect relative to placebo?
- 2) What evidence exists that granisetron 2 mg is superior to placebo in highly emetogenic chemotherapy (HEC), and what is the treatment effect relative to placebo?

As summarized above, the studies that supported approval of granisetron 2 mg, for both MEC and HEC indications, utilized a superiority comparison to a historical control. For the MEC indication, the historical comparison was to the active prochlorperazine arm data from a previous granisetron 1 mg BID study. The reviewers of the granisetron 1 mg BID application cited a review article by G. Wampler [Drugs 25(Suppl.1) 35-51, 1983] as evidence that prochlorperazine is itself superior to placebo. That publication noted that prochlorperazine was superior to placebo in all placebo controlled trials they identified, except for two. Review of that publication's summary tables of prochlorperazine trials suggests that the total number of placebo controlled prochlorperazine trials included for analysis were 9. For the granisetron HEC indication, the historical comparator was placebo.

The historical evidence of the treatment effect that can be expected with placebo in either the setting of MEC or HEC was a key review issue in the current application, and in the previous granisetron applications. There are sparse data available that establish the placebo effect in the setting of HEC, given the ethical issues of utilizing a placebo to evaluate antiemetics in the setting of chemotherapy trials, particularly with highly emetogenic chemotherapy. The current availability of highly effective antiemetics makes such a design impossible today, and the previous placebo data are derived from studies performed in the 1980's. Comparability of the data from those trials to current studies is questionable, given differences in cisplatin doses, cisplatin administration schedules and the definitions of efficacy, i.e. primary endpoints, utilized in those previous studies. Those comparability issues were discussed in detail in the biostatistical review of the granisetron 1 mg BID application. The major sources of evidence of placebo effect in the setting of HEC in that review were:

- 1) a placebo controlled trial of IV granisetron vs. placebo (Study 43694A/012)
- 2) a published placebo controlled trial reported by Gralla, et al. NEJM, Vol 305, No. 16, pp 905-909, 1981.
- 3) a published placebo controlled trial reported by Cubeddu, et al. NEJM, Vol 322, No. 12, pp 810-816, 1990.

The summary descriptions of the trials are provided in the table below, a table reproduced from the biostatistical reviewer's, Dr. Milton Fan, Ph.D, granisetron 1 mg review. The studies vary in proportion of enrollment of females (a higher risk group for chemotherapy induced nausea and vomiting), age range (elderly people have less risk for chemotherapy induced nausea and vomiting), mean dose of cisplatin, and cisplatin infusion times. The statistical reviewer reported that the primary endpoints utilized in these trials also could not be established.

		Study 012 IV Granisetron vs. Placebo	Gralla (1981)	Cubeddu (1990)
		Placebo N = 14	Placebo N= 10	Placebo N=14
Gender	Male	57%	100%	30%
	Female	43%	0%	70%
Age		49-76 yo	21-66 yo	18-68 yo
Cisplatin dose (mg/m ²)	mean	81	120	73
	range	46-100	120	50-120
Cisplatin infusion time (hr)		1.75-3	0.3	1

Dr. Fan explored the historical placebo data in a number of ways in the granisetron 1 mg application. He evaluated the 14 patient IV granisetron study data as stand alone data, given that the definition and method of evaluation of the primary endpoint were known and had been previously reviewed by the Agency. In addition, the placebo data from the 3 historic sources were pooled by the applicant and presented with 99% CI for comparison to granisetron 1 mg BID. Those results, with associated confidence intervals are summarized in the table below, also reproduced from Dr. Fan's review of the granisetron 1 mg PO BID NDA. Note, given the small numbers of placebo treated patients in these historical studies, the confidence intervals around the point estimates are quite large. Also shown in the table is the conservative analysis of the Study 012 data, which was performed by using the 99% confidence intervals.

	Study 012	Study 012	Study 012+Gralla + Cubbedu
Number of pts	14	14	38
	(95% CI)	(99% CI)	(99% CI)
Complete Response (%)	7% (0.2 - 33.9)	7% (0.04-42.4)	3% (0.01 - 17.98)

As can be seen, to maximize the number of patients available historically to obtain a point estimate for "complete response" for a placebo, the pooled placebo data from the 3 studies results in a conservative (99% confidence interval) estimate that the placebo effect in the setting of HEC (with cisplatin) is, at best, an 18% response. Use of a 95% confidence interval reduces that upper limit estimate of placebo effect in this setting. This estimate of placebo effect should be kept in mind when selection of noninferiority margin is discussed below.

Placebo control data reviewed by the agency in the past do exist in the ondansetron application. However, those data are from the setting of MEC and different primary endpoint definitions were utilized. For the subset of placebo patients that received cyclophosphamide doses >600 mg/m² in two ondansetron studies, the complete response, defined as no vomiting (a different endpoint), was 12% (3/25) in one study and 12% (3/26) in another study. In a European study submitted in that same application, which did not appear to have been reviewed, a higher placebo response (BUT defined only as "no vomiting") was noted - 61% in 18 patients treated with CHOP chemotherapy (cyclophosphamide dose >600 mg/m²).

The major trial that supports this application was presented by the applicant as a noninferiority study. As outlined in the ICH guidelines E10 Choice of Control Group and Related Issues in Clinical Trials, studies designed to show that a product is not inferior to an active control should incorporate the following features in the design of the study:

1. Determine that historical evidence exists to support the effect of the active comparator.
2. The trial design should adhere to the design of the trials used to establish the effectiveness of the active comparator.
3. An acceptable noninferiority margin should be prospectively defined and should be based on the historical data that show that the active control "can be consistently distinguished from placebo in appropriately sized trials of design similar to the proposed trial and should identify an effect size that represents the smallest effect that the active control can reliably be expected to have". This margin, referred to as the "delta", is the degree of inferiority the trial will attempt to exclude by showing that the lower bound for the confidence interval of the delta between the treatment effect of the test drug and active comparator does not cross the prespecified "line". The guideline states the margin is generally selected based on past experience in placebo-controlled trials, in order to assure that the desired effect size of the active control relative to placebo is retained, however dose response and active control superiority studies can be supportive.

As summarized earlier, the treatment effect of the oral granisetron 2 mg control group selected for the major trial supporting this application relative to placebo has not been robustly defined in a "head to head" comparison. The historical placebo control data is limited to the small number of patients (particularly if the single IV granisetron placebo controlled data is utilized) and the questionable comparability of the outcome data (if the pooled data from the published literature is utilized). This places a limit on how well the study submitted in this NDA can address the 3 bulleted design items from the ICH guidelines.

The applicant in this NDA utilized a 15% margin for the noninferiority analysis. There is no record of an agreement between FDA and the applicant regarding this margin. In response to an information request from the biostatistical team to provide the derivation and justification of the margin, the applicant informed the reviewers that it was based on the following factors:

1. They could not identify studies of the granisetron comparator with a placebo arm in multi-day dosing.
2. The only placebo controlled granisetron study that they could identify was the IV granisetron single dose study mentioned in the discussion above.
3. They cited a report in the NEJM by Herman TS, et al. (Superiority of Nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy NEJM 300 (23), 1295-1297) in which a study was mentioned that treated 70 patients with prochlorperazine or nabilone for prevention of emesis during cisplatin chemotherapy, and found 0/70 completed the entire

- course without nausea and vomiting. The study that was the subject of this publication, however, was not that placebo controlled trial.
4. They cited the IV granisetron efficacy reported from two 5-day cisplatin chemotherapy regimen studies in the consensus statement from a 2004 consensus conference in Perugia (MASCC, 2006. Prevention of chemotherapy and radiotherapy induced emesis: Results of the 2004 Perugia International Antiemetic Conference. Ann Onc, 17, p 20-26.) in which complete responses of 47% and 54%, respectively, were reported. Based on this, they concluded that the lower bound for the 95% confidence interval for the treatment effect of IV granisetron is 39%.
 5. They cited evidence that a 15% margin had been utilized in the studies that supported approval of palonosetron, in particular the noninferiority analysis comparing palonosetron with ondansetron for HEC. In fact the product label does clearly state that a noninferiority margin of -15% was utilized for these trials, and review of the regulatory record indicate that the division has accepted that margin for antiemetic development subsequent to the palonosetron approval. The palonosetron label does report, however, that a relatively more conservative 97.5% confidence interval around the delta between study drug and active control was utilized.
 6. They reported published trials have utilized a 15% noninferiority margin.
 7. They reported that they had asked advisory boards and the principal investigator for the IV granisetron placebo controlled trial about whether 15% was an adequate margin, and were told that it was.
 8. They concluded that if the reference product was found to be noninferior to the comparator by 15%, that the patch could be considered superior to placebo by at least 35%. (15% + 35% = 50%). **The reference 50% treatment effect of oral granisetron relative to placebo was “assumed” by the applicant “based informally on the information” available.**
 9. In an effort to be “more conservative” they presented a calculation of retained treatment effect by replacing the 50% treatment effect in #8 with the 39% lower bound for the effect associated with IV granisetron in #4. With a 39% treatment effect minus the 15% lower bound loss, the applicant proposed that a 24% retained effect would be assured relative to placebo.

The biostatistical reviewers noted that this series of explanatory points does not constitute a formal analytical and mathematical approach for defining a margin - where the treatment effect of the comparator relative to placebo is defined, and the margin of noninferiority selected based on assuring that the lower bound of the confidence interval of the projected difference of the treatment effect between the patch and the active control preserves a clinically relevant proportion of that treatment effect.

The applicant's noninferiority trial (Study 392MD/15/C) included 637 patients who received at least one dose of study drug (641 were randomized). All patients were treated with either MEC or HEC multi-dose regimens of 3-5 day duration. The patch was applied 24-48 hours prior to initiation of chemotherapy and worn until 24 hours post completion of the last dose of chemotherapy in the patient's cycle regimen. The oral granisetron was administered daily, 1

hour before daily chemotherapy administration. Oral granisetron was not administered on the days following completion of chemotherapy. The total 2 mg oral granisetron dose was administered within a single capsule. The primary endpoint was proportion of patients who experienced no vomiting, no more than mild nausea, and required no rescue medication during the entire course of chemotherapy up to 24 hours after the last dose of chemotherapy in the patient's regimen cycle. This endpoint was called "complete control" by the applicant, but has been called "complete response" in prior approved granisetron labels.

b(4)

The per protocol dataset was the prespecified dataset used for the primary efficacy analysis, which is appropriate for a noninferiority analysis. The demographic breakdown of the per protocol dataset was well-balanced between study arms, similar to the distribution between arms in the full analysis dataset, which is shown in tabular form in Dr. Berry's review.

The results for the primary efficacy analysis in this study, as presented by the applicant, using an adjusted logistic regression analysis, were:

	Patch	Granisetron 2 mg PO q D	Difference*	
	N = 284	N = 298	Estimate	95% CI**
Complete [†] Control	60.2%	64.8%	-4.89%	-12.91, 3.13

[†] Complete Control = No vomiting, no nausea worse than mild nausea, no use of rescue medication

* Difference = (Patch) – (Oral Granisetron)

** Confidence interval of the Difference

The point estimates were very similar, and the lower bound for the difference between the two arms was -12.91%, which fell within the applicant's pre-defined noninferiority lower bound of -15%. The biostatistical reviewer performed an exploratory analysis utilizing an un-adjusted analysis and obtained similar results. He also re-examined the data, utilizing a tighter confidence interval, 99.75%, given that this study represented a single study to establish effectiveness. On that exploratory analysis, the lower bound of the confidence interval dropped below the -15% margin to -17.0%. The biostatistical team stated that this conservative confidence interval was most appropriate for a single study since the 2-sided 99.75% confidence interval corresponds to a one-sided alpha level of 0.0025. They did calculate the lower bound, utilizing a 2-sided 97.5% confidence interval and found that it would be -13.5%.

The biostatistical reviewer did not consider this robust evidence of noninferiority. He was concerned that the ICH guidelines for designing a noninferiority trial had not been followed, and that the margin had been derived primarily based on "clinical judgment". His concern was not dispelled when, on his more conservative exploratory analysis utilizing a 99.75% confidence interval, the lower bound of the confidence interval of the difference between the patch and oral granisetron dropped below the applicant's specified 15% lower bound. Despite this, the biostatistical reviewers stated in the biostatistical review that this did not mean that the patch was not effective in preventing nausea and vomiting. The reviewer calculated the point estimate for the primary endpoint of complete control for the granisetron patch arm of the study with its 95% confidence interval, shown in the table below (Table 3.1.4.3 of Dr.

Wen-Jen Chen, PhD's biostatistical review), and pointed out that the lower bound of the confidence interval around the point estimate of the primary endpoint of complete control (no vomiting, no more than mild nausea, and no rescue medication) was 54%. He concluded that although this major study did not provide strong evidence that the transdermal granisetron patch is noninferior to the 2mg oral dose of granisetron, given the relatively high (>50%) complete response associated with the patch, he was comfortable deferring to the clinical review team's judgment of whether that proportion of the response in patients treated with either MEC or HEC is higher than would be expected in patients treated with placebo.

	Complete Control Rate of Granisetron Transdermal Patch	95% Confidence Interval
Per Protocol Population	60%	(54%, 66%)
Full Analysis Set Population	60%	(54%, 66%)

The clinical reviewers were convinced by the comparable outcome observed between the two study arms and the high point estimate of complete control observed with the transdermal patch that the granisetron transdermal patch is more effective than placebo in preventing nausea and vomiting in patients treated with MEC and HEC. The lower bound of the confidence interval is higher than the placebo response the clinical reviewers expected in patients treated with MEC and HEC. Certainly the lower bound of the confidence interval around the point estimate exceeds that upper bound from the placebo control arm of the IV granisetron study, Study 012, discussed earlier in this section of the review. In fact, the majority of the patients (2/3) in Study 392MD/15/C were treated with 3 day chemotherapy regimens, and the majority of those patients (3/4) were treated with HEC. In the per protocol population, the proportion of the 144 transdermal patch arm patients who experienced no vomiting and required no rescue medication while taking a 3 day HEC regimen was 59%. This is higher response than the clinical reviewers would expect from placebo in patients treated with HEC. Approximately 3/4 of the patients who were treated with 5 day chemotherapy regimens on the transdermal patch arm were also treated with HEC. The proportion of those sixty patients who experienced no emesis and no need for rescue medication was 53%, similar to that observed in the shorter duration HEC regimens.

I concur with the biostatistical reviewer that the second study submitted by the applicant to support the approval of the granisetron transdermal patch for prevention of nausea and vomiting associated with MEC, a randomized phase 2 study, is inadequate to support its approval. Study 392MD/8/C, which enrolled 171 patients (ITT population), was designed to evaluate the effectiveness of the patch relative to oral granisetron 2 mg in controlling nausea and vomiting in the delayed phase, 24 - 120 hours following a single day of MEC. The primary endpoint was defined differently in this study, compared to the phase 3 trial - no vomiting, no nausea and no rescue medication. (The primary endpoint of the major phase 3 trial was no vomiting, no more than mild nausea and no rescue medication.) The proportion of patients that experienced "total control of emesis" during the delayed phase (no nausea, vomiting or rescue medication) was similar between study arms - 32% with the patch and 30% with oral granisetron. Because oral granisetron is not indicated for prevention of delayed nausea and vomiting associated with chemotherapy, the outcome of this trial could only be

meaningful if the patch was found to be superior to oral granisetron in this setting. The biostatistician performed an exploratory analysis of the data from this study to evaluate the relative complete control (no vomiting, no more than mild nausea, and no rescue medication – the primary endpoint utilized in the phase 3 study) between the patch and the oral granisetron in the first 24 hours after chemotherapy. He found that the proportions of complete control were 48% on the patch and 60% with oral granisetron. The difference (Patch minus Oral granisetron) was -12%, with a lower bound of -26%, which he concluded _____

_____ This was, however, an exploratory analysis and the population in this phase 2 study, 171, is less than half of the number in the per protocol population of the phase 3 noninferiority study, N=582. The populations differed between the two studies as well. About half the patients in the Study 392MD/15/C were female (a higher risk group for chemotherapy induced nausea and vomiting relative to males), while a higher proportion in the smaller 392MD/8/C study, approximately 2/3, were female.

b(4)

8. Safety

The most common treatment emergent adverse event associated with the granisetron transdermal patch was constipation, which occurred in a higher proportion of patients in the integrated safety database than with granisetron 2mg oral dosing – 8.7% vs. 4.9%. There were 36 SAEs reported, of which 4 were considered drug related. Those events included 3 QTc prolongations (all in patients treated with oral granisetron) and one constipation (in a patient treated with the transdermal patch). A similar proportion of serious adverse events occurred in patients exposed to the patch and those exposed to oral granisetron 2 mg. There were 10 deaths observed in the studies submitted in patients treated with the patch compared to 6 deaths in patients treated with the oral dose. The most common cause of death was sepsis, which is expected in patients treated with chemotherapy. There were 5 deaths secondary to infection in patients treated with the patch and 2 deaths (one coded “neutropenia”) in patients treated with the oral formulation. There were two deaths from pulmonary embolus in the patch treated group, one of which was also coded as acute myocardial infarction, and a death from toxic megacolon in the oral formulation group. Of the 3 remaining deaths in patients treated with the patch, one death was coded intestinal obstruction, one “anemia, asthenia, dysphagia”, and one “chest pain”. The remaining deaths in patients treated with oral granisetron were coded as chronic active hepatitis, hemolytic uremic syndrome, and tumor hemorrhage. None of these events are unusual in patients with an underlying malignancy.

In the major phase 3 study submitted, the proportion of patients that withdrew from the study was similar between arms, as were the reasons for withdrawal. There were, however, two patients treated with oral granisetron who dropped out of the study due to QT prolongation, coded as severe. The phase 3 study was designed to evaluate ECGs and QT interval over the treatment period. Patients had a baseline ECG performed 1) at the time of screening, 2) at Visit 1 prior to administration of chemotherapy, 3) at the time of anticipated C_{max} of drug (one hour post administration for the oral formulation and 24-48 hours post patch application in patients who were treated with the patch formulation), and 4) at 120 hours post treatment (Visit 6). The ECGs were sent to a central laboratory for high resolution measurement of cardiac intervals, where they were read by a cardiologist blinded to study treatment. Because

the study lacked a placebo control and moxifloxacin active control, the design limited evaluability of the impact of granisetron on cardiac intervals. The fact that all patients were also being treated with a variety of chemotherapeutic agents further impacted the interpretability of the results.

A total of 588 patients had ECGs performed, but only 468 contributed to the ECG evaluable dataset. In the applicant's Cardiac Safety Report, prepared by Joel Morganroth, MD, the following changes in QTcF were noted:

	Patch Visit 1	Oral Granisetron Visit 1	Patch Visit 6	Oral Granisetron Visit 6
Sample Size	273	278	268	287
N				
QTcF mean change in ms	-1.5	0.2	0.2	0.2
QTcF new >500 ms	0	0	0	0
QTcF new >480 ms	0	0	0	0
QTcF new >450 ms	1	4 (1%)	3 (1%)	4 (1%)
QTcF 30-60 ms change from baseline	13 (5%)	18 (6%)	22 (8%)	19 (7%)
QTcF >60 ms change from baseline	0	1	1	2
New ST depression	1	2	6 (3%)	9 (4%)
New negative or biphasic T wave	4 (2%)	3 (1%)	9 (3%)	5 (2%)

Shifts in the QTcF were observed in both granisetron formulation arms in this study, as well as some changes in the ST segment and T waves. These changes were not considered clinically relevant by the central cardiologist reviewer, who noted in his review comments that with the limited number of ECGs and the lack of a control group, these data "should be interpreted with caution".

There are no thorough QT studies available for granisetron IV or oral. The heart has serotonin receptors. A published meta-analysis by Navari, et al in Ann Pharmacother 2003 reported that changes in ECG intervals are a class effect, but not supported as clinically relevant by clinical experience. A drug in the 5HT3 inhibitor class, dolasetron, carries a warning in its label that it can cause ECG interval changes, and that heart blocks or cardiac arrhythmias have been reported. In 2006, the Division of Drug Risk Evaluation conducted a search of the Adverse Event Reporting System (AERS) for cases of cardiovascular adverse events associated with 5HT3 serotonin antagonists. The search terms included cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, supraventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, death, electrocardiogram repolarization abnormality, cerebral infarction, syncope, transient ischemic attack and pulmonary edema.

From the time of granisetron's approval in 1995 to the time of the 2006 review, 40 reports were identified, but 9 were excluded because they were temporally related to the chemotherapy, 9 were excluded because events were attributed to the patient's underlying condition, 7 excluded because they were attributed to an allergic reaction, 2 were excluded because they occurred prior to administration of drug, and a remaining 4 were excluded for assorted reasons, including too little information. Of the remaining 9 cases, the following events were reported: myocardial infarction (2), cardiac arrest(1), ventricular fibrillation (1), ventricular tachycardia (1), asystole (1), supraventricular fibrillation (1), atrial fibrillation (1), coronary spasm (1), bradycardia (1), tachycardia (1), seizure, loss of consciousness (3), hypotension (1), cerebral infarction (1), ejection fraction decreased (1), dyspnea (1), hypoxia (1). Time to onset included immediately (1), soon (1), 7 hours (1), 2-3 days (2), unknown (4).

The ventricular fibrillation occurred in a 22 year old female who experienced bradycardia that deteriorated into ventricular fibrillation and asystole immediately after receiving IV granisetron for post operative nausea and vomiting. The event resolved without defibrillation. The single death in this group occurred in a 31 year old male who experienced cardiac arrest 7 hours after being treated with IV granisetron 1 mg. He was resuscitated and survived, but developed renal failure and hepatic failure and subsequently died due to hepatic failure.

An updated review of the AERS database was requested during this review cycle. That review, completed September 11, 2008, used cardiac disorders and vascular disorders as MedDRA search terms, and covered the time period of May 1, 2006 to July 15, 2008. Events that were temporally related to a concomitant drug were excluded, as were events that resulted from an underlying condition. Specific terms targeted for review included: *angina pectoris, bradycardia, cardiac arrest, cardio-respiratory arrest, cyanosis, myocardial infarction, myocardial ischaemia, tachycardia, ventricular fibrillation, pulmonary artery thrombosis, angiopathy, circulatory collapse, flushing, hypertension, hypotension, pallor, shock and thrombosis.*

Although 27 unduplicated reports were identified over the time period queried, 22 were excluded because the events were related to allergic reaction or other concomitant medication, or the event was considered secondary to the patient's underlying condition. Two of the 22 were excluded because the events are already found in the granisetron product labels – atrial fibrillation and angina pectoris. Five remaining cases – all foreign reports - were considered serious and granisetron could not be excluded as the cause of the event. There were 2 reports of cardiac arrest, one syncope, 1 ventricular fibrillation, and a single QT prolongation/bradycardia in a patient on multiple concomitant medications. The ventricular fibrillation also occurred in a patient on multiple concomitant medication who had underlying heart failure. One of the cardiac arrests occurred 24 hours after granisetron administration and was suspected to be secondary to aspiration. In the other patient with cardiac arrest, the patient had received IV granisetron, and a positive rechallenge – another episode of cardiac arrest – was reported when granisetron was administered again alone (the first episode occurred with administration of a combination of granisetron with paclitaxel). Two of the five cases occurred in patients treated for PONV. A similar AERS search for the same time period for other 5HT3 antagonists identified (without removal of duplicate cases): 300 reports for ondansetron, 15 reports for dolasetron, and 35 reports for palonosetron.

The reviewer concluded, based on this updated search of the AERS database, that a causal role for granisetron in cardiovascular events cannot be ruled out and that these events are adequately reflected in granisetron product labels.

The reviewers carefully considered the implications of the lack of a thorough QT study prior to approval of this transdermal formulation of granisetron. The documented QT changes in the ECGs captured in this NDA's major study revealed similar changes in the two granisetron formulations. Granisetron is currently approved in both intravenous and oral formulations, and there are marketed generics. The review team evaluated whether pharmacokinetic differences exist that suggest there would be a greater risk for QT changes with the transdermal formulation than the oral formulation. The table below, taken from the clinical pharmacology reviewer's (Dr. Chen) review provides a "head to head" comparison of PK parameters between the transdermal granisetron patch (column 4, Patch size 52 cm²) and oral granisetron 2 mg per day x 5 days. Although the C_{max} achieved with oral granisetron is higher than the patch, the AUC exposure for the patch is higher than with oral dosing. On Day 5 of oral dosing the AUC 0-24 is 62 ng-hr/ml compared to 321 ng-hr/mL for the patch (AUC 0-144 for 6 days). Note that the AUC for the patch is expressed over 144 hours (compared to 24 hours for the oral dose). The C_{avg} is similar between the two formulations, though somewhat higher with the patch.

Table 2. Mean (%CV) Granisetron PK Parameters for Three Patch Sizes and Oral Granisetron

Parameter	Study 392MD/11/C				
	15	33	52	Oral QD Dosing x 5 days	
Patch Size, cm ²					
Nominal Dose, mg	9.9	21.8	34.3	2 (per day)	
C _{max} , ng/mL	1.15 (73)	2.08 (110)	3.85 (77)	5.25 (42%) (Day 1)	5.50 (68%) (Day 5)
T _{max} , hr ¹	48 [48-96]	48 [24-150]	48 [24-168]	1.5 [1-4]	2 [1-4]
T _{1/2} , hr	30.9 (32)	30.9 (21)	35.9 (35)	6.4 (74%)	7.9 (74%)
AUC _{0-t} , ng-hr/mL ²	98 (83%)	179 (110%)	321 (89%)	51 (80%)	62 (110%)
C _{avg} , ng/mL ²	0.68 (83%)	1.24 (110%)	2.23 (89%)	2.14 (79%)	2.60 (108%)

¹ Median [range].
² AUC_{0-t}: AUC₀₋₁₄₄ for patch application for 6 days and AUC₀₋₂₄ for QD oral dosing.
³ C_{avg} was calculated as (AUC₀₋₁₄₄)/144 hr for patch application and (AUC₀₋₂₄)/24 hr for oral dosing.

A dose escalating daily exposure x 7 days study was reviewed in the original safety review of granisetron 1 mg oral dosing. The safety data was considered relevant, although there wasn't a structured ECG evaluation, for evaluation of the need for a thorough QT study given the documented differences in the pharmacokinetics of the patch and oral dosing. In Study 43694A/020, placebo and oral granisetron at doses 2.5 mg BID, 5 mg BID and 10 mg BID doses were administered for 7 days after an initial IV loading dose of 40 micrograms/kg. There was one death on the placebo arm, 3 in the 2.5 mg arm (2.3%), 5 on the 5.0 mg arm (3.6%) and 9 on the 10 mg arm (6.9%). The primary medical reviewer of that NDA could not

establish that the deaths were related to granisetron. Causes of death included hypertension/CVA, respiratory failure, myocardial infarction, mesenteric infarction, and cardiovascular failure of unknown origin.

Ultimately, given the differences in pharmacokinetics and the questions raised regarding potential class effects, the review team recommended that the applicant conduct a thorough QT study post approval. Because the review team concluded after their review of the ECG data collected systematically in the major study supporting this NDA, the granisetron postmarketing safety record and the adverse events reported in oral dosing dose escalation trial described above (Study 43694A/020) that a signal for cardiac events related to QT prolongation had not been established, they did not feel a preapproval thorough QT study was necessary.

Exposure/response relationships for safety were also carefully considered in light of the Office of Surveillance and Epidemiology Division of Medication Error Prevention reviewers' recommendation (in their product name review) that the applicant, at product launch, attempt to make healthcare practitioners and patients aware that the patch contains granisetron, to avoid concomitant administration with other granisetron products. The clinical and clinical pharmacology reviewers carefully considered the safety impact of concomitant administration of the patch with another granisetron formulation and discussed their review findings the Office of Surveillance and Epidemiology Division of Medication Error Prevention team. These analyses and discussion points are summarized in the following paragraphs and table. The summary table was created by Dr. Tien-Mien Chen, Ph.D.

To address the safety of concomitant administration of granisetron formulations, the clinical pharmacology reviewers presented the expected C_{max} and AUC exposures with the worst case scenario of combining intravenous and transdermal granisetron. The oral combination wasn't explored because the C_{max} associated with an IV dose of granisetron exceeds that of oral granisetron. The data utilized for these analyses were the pharmacokinetic data for the patch – a 7 day application in healthy volunteers (study 392MD/26/C from NDA 22-198) and the pharmacokinetic data from a 1 mg intravenous injection of granisetron over 30 seconds in postoperative nausea and vomiting patients (Study 285 from NDA 20-239). The PK study that was utilized to provide the comparative exposure/safety context was Study HP/88/69 from NDA 20-239, in which healthy volunteers were administered relatively high dose intravenous infusions (over 3 minutes) of 160 mcg/kg twice a day x 15 doses.

Intravenous granisetron is approved for treatment of chemotherapy induced nausea and vomiting (CINV) at a dose of 10 mcg/kg, and for postoperative nausea and vomiting (PONV) at a dose of 1 mg. Although the IV product label reports the C_{max} after 3 and 5 minute infusions, the intravenous product administration is labeled as a 30 second infusion for the 1 mg and 10 mcg/kg doses (although the diluted 10mcg/kg CINV dose is also labeled for infusion over 5 minutes). The pharmacokinetics of the 1 mg dose approved for PONV are relevant for exploration of potential risk in the CINV setting, where at the approved dose of 10 mcg/kg, only a 100 kg person would be dosed at the 1 mg PONV dose. The vast majority of individuals treated for CINV are less than 100 kg, so the 1 mg dose exceeds the maximum dose that would be expected to be administered intravenously in the majority of that

population, and given the fact that the 1 mg IV dose in the referenced pharmacokinetic study in PONV (Study 285 in the table below) was a flat dose, the data from that study reflect a higher actual mcg/kg exposures than would be expected utilizing the CINV labeled dosing by weight (10 mcg/kg). The components of the combined patch + IV exposure exploration conducted were as follows:

1. The C_{max} and $AUC_{0-\infty}$ data for granisetron 1 mg dose administered IV in a 30 second injection in the PONV granisetron NDA (20-239/SEI-008, October 19, 2001), presented in the table below, were mean $C_{max} = 75.5 \text{ ng/mL}$ and mean $AUC_{0-\infty} = 72.2 \text{ ng-hr/mL}$.
2. Given that a 1 mg dose is equivalent to 20 mcg/kg in a 50-kg patient, the clinical pharmacology reviewers estimated that for a 10-mcg/kg dose (the approved IV dose for CINV) administered to a 50 kg patient, the C_{max} and AUC could be derived by halving the PONV data above - 37.8 ng/mL and 36.1 ng-hr/mL , respectively.
3. The reviewers then adjusted the estimated average potential exposures upward to take into consideration the impact of cross study comparisons and differences in patient populations (PONV vs. CINV), different assay methods, and possible sampling time errors. This adjustment resulted in estimated exposures for a 10 mcg/kg IV dose in a 50 kg patient of: mean $C_{max} = 50 \text{ ng/mL}$ and $AUC_{0-\infty} = 45 \text{ ng-hr/mL}$.
4. The C_{max} and AUC values utilized for the transdermal patch component of combined exposure equation were determined from the transdermal patch study 392MD/26/C. As shown in the table below, the clinical pharmacology reviewers estimated the $AUC_{0-\infty}$ for granisetron patch, utilizing the measured AUC_{0-168} data, and found the $AUC_{0-\infty} = 1000 \text{ ng-hr/mL}$ for the healthy volunteers studied and 1500 ng-hr/mL for patients. Similarly the C_{max} was normalized upward to 8 ng/mL . (The normalized C_{max} of 8.0 ng/mL was selected utilizing the observed C_{max} in females, 7.6 ng/mL , in order to present the "worst case scenario".) The higher $AUC_{0-\infty}$ was extrapolated based on the longer $t_{1/2}$ in patients relative to healthy volunteers.
5. The estimated total C_{max} and AUC in a patient wearing a transdermal patch who is mistakenly treated with a single 10 mcg/kg intravenous granisetron dose concomitantly was calculated by adding the C_{max} associated with each formulation and AUC associated with each formulation. The estimated total C_{max} and AUC that results from adding the adjusted values for the IV and transdermal exposures are $C_{max} = 58 \text{ ng/mL}$ ($50 \text{ ng/ml} + 8 \text{ ng/ml} = 58 \text{ ng/ml}$) and $AUC = 1545 \text{ ng-hr/mL}$ ($45 \text{ ng-hr/ml} + 1500 \text{ ng-hr/ml} = 1545 \text{ ng-hr/ml}$). The clinical pharmacology reviewers also included a total estimated AUC for a situation where intravenous granisetron is administered in error x 5 days, which can be found in the last cell in the table below: $AUC = 1725 \text{ ng-hr/mL}$.

Summary Table: Studies Supporting Additional Pharmacokinetic and Safety Analysis of Granisetron Formulation Coadministration

Study No.	Dose	Dosing Regimen	Subjects	Mean C_{max} ng/mL (CV%)	Mean $AUC_{0-\infty}$ ng-hr/mL (CV%)	Normalized ^b Mean C_{max} ng/mL (CV%)	Normalized $AUC_{0-\infty}$ ng-hr/mL (CV%)	Mean
HP/88/69 (NDA 20-239)	160µg/kg BID x 15 doses, i.e., a total dose of 120 mg for a 50-kg subject	3-min short-term IV infusion	16 M healthy volunteers	SD: 92.4 (48%) SS: 166 (67%)	SD: 194 (75%) SS: 241 (91%)	SD: 92.4 (48%) SS: 166 (67%)	3,000 calculated form 0-12 hours to cover 15 doses	
285 (NDA 20-239)	SD, 1 mg	30-sec IV infusion	17 PONV patients	75.5 (67%) at 1 min	72.2 (49%)	A 0.5-mg dose for a 50-kg patient (10µg/kg): SD: ≈40 SS: ≈50 (AC: 1.25)	A 0.5-mg dose for a 50-kg patient (10µg/kg): SD: ≈36 SS: ≈45 (AC: 1.25)	
392MD/26/C (NDA 22-198)	34.3-mg G patch	One patch for 7 days	12M+12F healthy volunteers	M+F: 5.0 (170%) F: 7.6 (150%)	M+F: 527 ³ (170%) F: 802 ³ (150%)	8.0 ⁸	1000 ⁴ 1500 ⁵	
IV+Patch (in patients)	0.5 mg+21.7 mg =22.2 mg	-----	-----	-----	-----	50+8=58	SD: 1500+45=1545 SS: 1500+225 ⁷ =1725	

1. HP/88/69: Estimated total $AUC_{0-\infty} \rightarrow 194 + (194+241) \times 7 + 241 = 2957 + 43$ (last-dose $AUC_{12-\infty}) \approx 3,000$
 2. Accumulation ratio: 1.25 estimated based on a longer T1/2 in patients (10 hrs)
 3. For GTDS: AUC_{0-168} (healthy subjects).
 4. For GTDS: extrapolated to $AUC_{0-\infty}$ (healthy subjects).
 5. Extrapolated to CINV patients.
 6. "Normalized" refers to estimated values for a 50-kg subject
 7. 225 = the estimate exposure contributed by intravenous granisetron if it was administered in error, concomitantly x 5 days.
 8. 8.0 ng/ml selected for worst case scenario, utilizing the female mean C_{max}

The safety of this level of exposure was evaluated by examining the adverse event data associated with a 160 mcg/kg dose administered BID over 3 minutes x 7.5 days in a study that enrolled healthy volunteers, Study HP/88/69 (from NDA20-239 IV injection). The reviewers found the normalized steady state C_{max} was 166 ng/ml and the normalized $AUC_{0-\infty}$ was 3000 ng-hr/ml - approximately double what they had estimated for concomitant administration of 10 mcg/kg intravenous granisetron and transdermal granisetron to a 50 kg patient, as calculated above. Dr. Karyn Berry reviewed the clinical safety reported in Study HP/88/69 - which administered 160 mcg/kg IV (3 minute infusion) BID x 7.5 days. She found that in the 18 healthy male volunteers there were no deaths or serious adverse events. Nine subjects had ECG changes observed in the study, and in two the changes were considered artifact. In the remaining 7 subjects, only two were considered to have had events to be clinically significant in the study report - a case of 1st and 2nd degree heart block and a subject with an unconducted p wave. Both of those subjects had a 72 hour holter monitor performed 4-6 weeks after study end, and both had similar findings on the holter, suggesting that the ECG events detected on study were not new findings in those individuals. There were two additional subjects who had "sinus arrest" detected on ECG during the study. It is not clear what those events were, but they were not considered clinically significant, and upon review of the adverse event data listings, Dr. Berry found no evidence of syncopal episodes on the trial. The AEs listed for the two subjects with "sinus arrest" were lower abdominal pain, constipation and flatulence.

Given the lower exposure anticipated with unintended concomitant granisetron formulation administration relative to the granisetron exposure in Study HP/88/69 and the lack of serious cardiac events and other serious adverse events observed in that same study, the review team and the reviewers from the Office of Surveillance and Epidemiology Division of Medication Error Prevention agreed that the applicant did not need to submit a communication plan for FDA review prior to product launch regarding how they planned to inform health care providers that Sancuso contains granisetron, which is also available in intravenous or oral formulations. In a discipline review letter dated September 10, 2008, the applicant was informed that the proposed proprietary name is acceptable and that, given that the transdermal patch is a new granisetron dosage form, the Division of Medication Error Prevention and Analysis recommends that they include in their product launch a component aimed at healthcare practitioners' awareness that the Sancuso patch contains granisetron and that practitioners should avoid administering other granisetron containing products to patients wearing a granisetron patch.

Skin sensitization to patch application was an additional safety issue identified in this application. Dermal tolerance studies were conducted in both healthy volunteers and in patients, including a large 212 subject skin irritation and sensitization study that included an induction phase, rest phase, challenge phase and rechallenge phase. These evaluations indicated that the patches can be associated with skin irritation, and in the 200 subjects evaluable for sensitization ("allergic contact reaction"), there was one positive for sensitization in the challenge phase. That subject's reaction was described as erythema, vesicles, pruritis at the site, with some extension to surrounding skin. Pruritis was the most common symptom in the trial subjects. Change in site skin pigmentation was noted in 36 participants. "Skin

irritation" was reported in nearly twice as many subjects exposed to the placebo patch as those exposed to the granisetron patch.

In summary, the most common adverse event associated with the granisetron transdermal patch was constipation, which is a known side effect of granisetron. Unique to the patch formulation are the local skin effects – irritation and sensitization. It is unknown whether granisetron has QT effects, but it is approved and marketed in IV and oral formulations (including generics), for which review of AERS reports does not reveal a signal of Torsades. Examination of the pharmacokinetics of granisetron patch reveals that the C_{max} associated with this product is lower than the approved 2 mg dose, which could imply that it has lower associated risk. Exposure, as measured by AUC, with the patch is higher, but it is unknown whether that overall exposure in the face of a lower C_{max} would impact relative risk of QT effects. The review team concluded that a thorough QT study should be performed, but that it could be done as a post marketing required study under FDAA. I concur with that decision, given the absence of a signal in postmarketing data from other granisetron products and the lower C_{max} associated with the patch.

9. Advisory Committee Meeting

There was no advisory committee for this application. Granisetron is not an NME.

10. Pediatrics

The applicant's pediatric development plan was taken to the PeRC review committee. Members of the committee felt strongly that a patch formulation offered a new option of drug delivery for control of nausea and vomiting associated with chemotherapy, and strongly recommended that the applicant have a development plan that encompassed both the very young children and older children/adolescents, as long as there were no safety concerns that precluded proceeding with studies in children. After review of the regulatory record for granisetron and the QTc data from the serial ECGs collected during the major trial that supports this application, the review team concurred that it would be prudent to conduct a thorough QT study to evaluate granisetron and the patch prior to initiating the pediatric studies. Given that the patch has different pharmacokinetic profile for oral granisetron, with a higher AUC, though lower C_{max} , there was concern that the cardiac question should be thoroughly studied before initiating studies in children, particularly since removal of the patch does not result in immediate removal of the drug (depot in skin tissue). Pediatric studies will be waived for ages 0 to 2 years because the necessary studies are impossible or highly impracticable. The studies in the age group 2-17 years were deferred and will not be initiated until the thorough QT study results are available for review.

There are two deferred required postmarketing studies:

1. A deferred pediatric study under PREA for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days in pediatric patients ages 2 to 17. A study to examine the pharmacokinetics of granisetron transdermal system (Sancuso) compared to IV dosing in 48 pediatric patients aged 2 to 17 years.

2. A deferred pediatric study under PREA for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days in pediatric patients ages 2 to 17. A study of the efficacy and safety of transdermal granisetron (Sancuso) compared to intravenous granisetron for the prevention of chemotherapy induced nausea and vomiting in 200 pediatric patients aged 2 to 17 years and over 400 patient treatment periods.

11. Other Relevant Regulatory Issues

Dr. Berry noted in her review that for the major study submitted in this application, the applicant provided certification that they had not entered into financial arrangements with their clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. They certified that each clinical investigator had no proprietary interest in the product or significant equity in their company, and that no clinical investigator was the recipient of a significant payment of any other sort.

The review team did not request a DSI audit of any study sites because the reviewers did not have concerns regarding the outcome data from any one of the sites.

12. Labeling

The major physician labeling issues that were discussed with the applicant during the course of the review were 1) how to refer to the study's primary endpoint in the label, 2) how to describe the efficacy observed in the major study supporting the application, 3) how to address low incidence adverse events in the label, and 4) how to describe the amount of drug delivered by the patch.

A major review issue was how to describe the effectiveness of the product and the major study's noninferiority design. Because the biostatistical reviewer was concerned that based on a single trial the finding of actual noninferiority was not robust, the reviewers and applicant

_____ The biostatistical reviewers worked with the clinical reviewers to define language in the clinical trials section of the label to describe the product's effectiveness. _____ The clinical reviewers were confident that efficacy had been established because the observed effect in the major study supporting the application (comparing two formulations of granisetron) fell within the applicant's prespecified noninferiority margin and they believed

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the evidence provided was adequate to conclude that the granisetron patch is more effective than placebo.

The reviewers believed that it was important to include in the granisetron patch label the uncommon adverse events that appear in the Kytril label, which were not observed (except in very small numbers) in the transdermal patch clinical trials. They felt that the low rate observed in the patch study may have been secondary to the smaller overall size of the safety database compared to the innovator product studies. Importantly, the major trial supporting this application compared the patch to an oral dose of Kytril, and for the more uncommon events cited in the Kytril label, the events appeared in a rate similar between the two granisetron arms in this study. The reviewers asked that the less common adverse events that appear in the Kytril label also be presented in the granisetron patch safety labeling, as adverse events that have been reported with use of granisetron.

The clinical pharmacology reviewers worked with applicant to modify the product description in the label to more accurately and clearly describe the amount of drug delivered from the total amount contained in the patch.

The Office of Surveillance and Epidemiology Division of Medication Error Prevention reviewers stated in their review that the proposed name, Sancuso, doesn't "appear vulnerable to name confusion that could lead to medication errors." However, since the product contains granisetron, which is available in other formulations under different names, to reduce the possibility of a patient being treated with the granisetron patch and another formulation of granisetron concurrently, they recommended that the applicant implement an educational campaign at launch to attempt to make healthcare practitioners and patients aware of the potential for inadvertent concomitant therapy with other granisetron products. They also made labeling recommendations regarding the product packaging, PPI and physician's labeling.

Reviewers from the Division of Drug Marketing, Advertising and Communications also reviewed the labeling and provided suggestions for modifications.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval
- Risk Benefit Assessment

I recommend approval of the transdermal granisetron patch for prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days. The product is a new formulation of granisetron. The previously approved granisetron formulations were approved for prevention of both highly and/or emetogenic chemotherapy. The applicant showed that the new transdermal patch formulation of granisetron has efficacy comparable to the approved oral dose of granisetron, in a study design that they considered a

noninferiority design. The difference in treatment effect between the two granisetron products fell within the applicant's prespecified noninferiority margin, -15%, a margin that the agency has previously accepted in prior approvals of antiemetic products. The clinical reviewers support the approval of the product and concluded that it is both effective and safe.

Although the biostatistical reviewers expressed concern about the noninferiority design, and concluded that the _____

_____, they did express confidence that the proportion of patients treated with the transdermal formulation who would be expected to have no vomiting, no more than mild nausea and no use of rescue medication within 24 hours of last dose of chemotherapy is greater than 50% (the lower bound of the 95% confidence interval associated with the proportion of patients who met the primary endpoint of response on the granisetron patch was 54%). The statistical reviewers supported approval of the product if the clinical reviewers deemed this rate of response to be higher than would be expected with a placebo. The clinical reviewers evaluated the data available to them from placebo controlled trials, including a placebo controlled trial of intravenous granisetron, and concluded that the response on the transdermal granisetron arm in this study was in fact higher than would be expected with placebo. They expressed confidence in the treatment effect of the transdermal product and strongly advocated for its approval.

I support the clinical reviewers' recommendation for approval. The applicant's noninferiority margin was met, the margin was prespecified, and the margin utilized has been the basis of previous antiemetic products approved by the Division. The responses in the two arms were comparable, 60.2% on the patch and 64.8% with the oral product, a difference of -4.89 (95% CI= -12.01, 3.13). I concur that the response observed in the trial is higher than would be anticipated with placebo, as the lower bound of the confidence interval around the response is 54%. The majority of the patients in this study were treated with highly emetogenic chemotherapy. I agree with the clinical reviewers' conclusion that this product is more effective than placebo in patients treated with highly emetogenic chemotherapy. In keeping with the review concerns expressed by the biostatistical reviewer, and discussed at length in my review, I concur, however, with the biostatistician's recommendations to: _____

_____ The product was a single study submitted to support noninferiority and when its robustness for establishing noninferiority was tested utilizing a 99.75% confidence interval around the difference in treatment effect between the two granisetron arms, the lower bound of the confidence interval dropped below the prespecified margin of -15%.

There were no safety concerns identified in the review that preclude approval.

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- Recommendation for Postmarketing Risk Management Activities and Postmarketing Study Requirements

Because there are known cardiac effects associated with some of the drugs in the class to which granisetron belongs, the 5HT₃ inhibitors, and because no thorough QT study has been conducted with any granisetron product, the applicant will be required to conduct a thorough QT study of the patch and intravenous granisetron. Although the C_{max} associated with the patch does not exceed the C_{max} associated with the currently approved oral granisetron, the AUC exposure associated with the patch is higher, and removal of the patch does not result in immediate removal of drug exposure because of the depot effect in the skin. A thorough QT study in volunteers not receiving chemotherapy, with a placebo and active control (moxifloxacin) will enable an accurate characterization of any QT effects that may be associated with granisetron and the transdermal granisetron patch. Because of safety concerns regarding “pushing” the granisetron dose to the supratherapeutic levels generally used in a thorough QT trial using the patch formulation (given the depot effect in the skin, which does not allow immediate discontinuation of the drug), the trial will include the patch, at the approved dose. IV granisetron will be utilized to achieve the supratherapeutic exposure levels. The required study, pursuant to section 505(o)(3) of the FDCA, and its timetable for completion are:

A single-site, randomized, cross-over, thorough QT study that evaluates placebo, active control, bolus infusion granisetron, and transdermal granisetron in healthy volunteers.

Protocol Submission:	September 30, 2008
Trial Start:	March 31, 2009
Final Report Submission:	December 31, 2009

As discussed in the Pediatrics section 10 above, the pediatric studies will be deferred until the thorough QT study has been completed so that the safety of proceeding with the pediatric studies can be adequately assessed. There are two required postmarketing studies:

1. A deferred pediatric study under PREA for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days in pediatric patients ages 2 to 17. A study to examine the pharmacokinetics of granisetron transdermal system (Sancuso) compared to IV dosing in 48 pediatric patients aged 2 to 17 years.
2. A deferred pediatric study under PREA for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days in pediatric patients ages 2 to 17. A study of the efficacy and safety of transdermal granisetron (Sancuso) compared to intravenous granisetron for the prevention of

Division Director Review

chemotherapy induced nausea and vomiting in 200 pediatric patients aged 2 to 17 years and over 400 patient treatment periods.

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this page is the manifestation of the electronic signature.**

/s/

Donna Griebel
9/12/2008 04:42:00 PM
DIRECTOR

Clinical Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROENTEROLOGY PRODUCTS MEDICAL OFFICER'S SECONDARY REVIEW

Date: July 19, 2008

From: Hugo E Gallo-Torres, MD, PhD, PNS
Medical Team Leader
Division of Gastroenterology Products
HFD-180

To: Division Files, NDA 22-198
Granisetron [Trade Name: Sancuso], a 5-HT₃ receptor antagonist
Sponsor: Strakan Pharmaceuticals Ltd.
Galashiels TD1 1QH, UK
Formulation: Transdermal Delivery System [TDS]
Indication: Prevention of nausea and vomiting in persons receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.
Dosing Regimen:
Apply a single patch to the upper outer arm a minimum of 24 h before chemotherapy. The patch may be applied up to a maximum of 48 h before chemotherapy as appropriate. Remove the patch a minimum of 24 h after completion of chemotherapy. The patch can be worn for up to 7 days depending on the duration of the chemotherapy regimen. The intended population is adults, aged 18 years and older.

Subject: Recommendations for Regulatory Action

I. BACKGROUND/INTRODUCTION

The object of the present application is granisetron, a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist currently marketed in the United States under the name of Kytril¹. Kytril is indicated for a) the prevention of chemotherapy induced nausea and vomiting (CINV); b) post operative nausea and vomiting (PONV) and c) radiation induced nausea and vomiting (RINV). Kytril is available in injectable, tablets, and oral solution forms. Through the current submission, the sponsor is requesting approval of SANCUSO, a transdermal system [TDS] of granisetron. The proposed indication for SANCUSO [granisetron TDS] is the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 days.

In support of their application, Strakan submitted results of two studies designed to evaluate the clinical efficacy and safety of SANCUSO (granisetron TDS) 52cm² for the prevention of CINV in patients receiving moderately and/or highly emetogenic (ME and/or HE) chemotherapy for up to 5 consecutive days. Pivotal Phase 3 study 392MD/15/C was designed to demonstrate non-inferiority between SANCUSO (granisetron TDS) and oral granisetron, the active comparator. At least 2/3 of the patients randomized in this trial received HE chemotherapy at appropriate infusion rates. Supportive Study 392MD/8/C compared the efficacy, safety and tolerability of a granisetron TDP with oral granisetron in CINV. It was conducted in cancer patients undergoing single day ME chemotherapy. A total of 810 patients were enrolled in these pivotal and supportive cancer trials (404 patients in the granisetron TDS group and 406 patients in the oral granisetron group). Three additional Phase 1 studies (392MD/4/C, 392MD/11/C and 392MD/26/C), enrolling a total of 236 healthy subjects, were included in the safety assessment of granisetron TDS.

II. MULTIDISCIPLINARY REVIEWS

Approvability recommendations/remarks from individual discipline reviewers are listed in Table 1.

Table 1
NDA 22-198 [SANCUSO; granisetron transdermal system = GTDS]
List of Individual Reviews

REVIEWER	DISCIPLINE	REMARKS
1. Dr. Karyn Berry	Clinical	Recommends approval
2. Dr. Tien-Mien Chen	Clinical Pharmacology	Acceptable
3. Dr. Wen-Jen Chen	Statistics	See Section III.3. below
4. Dr. Sushanta Chakder	Pharmacology/Toxicology	Recommends approval
5. Dr. Rao Puttagunta	Chemistry	Recommends approval
6. Dr. Samuel M Skariah	DDMAC	These two disciplines provided labeling comments
7. Dr. Richard Abate	Div Med Error Prevention	
8. Ms. Sharon R Mills	DRISK	Reviewed Patient Labeling

¹ There are currently four (4) 5-HT₃ antagonist drugs that are FDA approved for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy. These are: Ondansetron, Granisetron, Dolasetron and Palonosetron. All four of these 5-HT₃ receptor antagonists are available in injectable (Intravenous) formulations and all except palonosetron are available in oral formulations. None of these four 5-HT₃ antagonists is available in patch form.

III. HIGHLIGHTS of REVIEWS from INDIVIDUAL DISCIPLINES

Included in this Section of the MTL's review are salient comments/conclusions/ recommendations from individual disciplines [Table 1] regarding approvability of the submission and Labeling and Patient Labeling revisions.

1. CLINICAL

Included here are highlights from Dr. Berry's Clinical Review on SANCUSO's Efficacy and Safety as presented by the sponsor in their submission under NDA 22-198/000.

Pivotal Study 392/15/C was a randomized, active control, double-blind, double-dummy, parallel group, multi-national study that assessed the efficacy, tolerability and safety of the granisetron TDS in CINV associated with the administration of ME or HE multi-day chemotherapy. The endpoint of efficacy was the proportion of patients achieving Complete Control (CC²) of CINV from the first administration until 24 h after the start of the last day's administration of the ME or HE chemotherapy regimen. Treatment success rates at 0 to 24 h after chemotherapy administration were 60.2% in the granisetron TDS group and 64.8% in the oral granisetron comparator group. The treatment difference (95% CI [-12.91, 3.13]) was within the predefined non-inferiority margin of 15%. The primary efficacy endpoint analysis during the acute phase of HEC/MEC chemotherapy) demonstrated non-inferiority between granisetron TDS 52 cm² and daily oral granisetron 2 mg.

Supportive study 392MD/8/C had a different primary efficacy endpoint than study 392MD/15/C. The results of the secondary endpoint analysis of complete control during the acute phase demonstrated no significant statistical difference between granisetron TDS 52 cm² and daily oral granisetron 2mg.

From a clinical standpoint, the MOR concluded that granisetron TDS treatment success rates were similar to oral granisetron 2 mg daily in the prevention of CINV in moderately and/or highly emetogenic chemotherapy over a 5-day period. The MTL agrees with this conclusion.

The MOR review revealed that adverse events in the granisetron TDS clinical development program were similar to those attributable to other formulations of granisetron, with the exception of dermal tolerance. The majority of AEs were gastrointestinal related. The most common related adverse event reported was constipation, which occurred in 5.4% of the granisetron TDS group and 3.0% in the oral granisetron group. Of the 36 SAEs reported in the cancer patient studies, the sponsor reported that four events were drug related. These 4 SAEs were 3 QTc prolongations in the oral granisetron group and one constipation in the granisetron TDS group. The MOR reviewer concluded and the MTL agrees that while overall, the patches were well tolerated, the results of the dermal tolerance studies in both healthy subjects and cancer patients suggest that the patches have the potential of mild irritation. Study 392MD/26/C

²CC was defined by Strakan as no vomiting and/or retching, no more than mild nausea and no rescue medication, but in reality, the Applicant used different terminology to describe the endpoint than that used by the innovator, Kytril tablets. Kytril defined no vomiting, no moderate or severe nausea and no rescue medication as "Complete Response."

also suggest that hypersensitivity reactions are possible with the granisetron patch, since one subject had a sensitivity reaction.

The dose of granisetron TDS selected for both the Phase 2 and Phase 3 studies was based on results of the Phase 1 (healthy subjects) dose ranging study (392MD/11/C) which compared 15 cm², 33 cm² and 52 cm² patches with 2 mg oral granisetron. The proposed 52 cm² patch is ca. equivalent to the 2 mg oral granisetron dose. The Applicant reported that no studies were conducted to specifically investigate the potential for granisetron TDS to cause or result in drug-drug interactions. Granisetron is not known to induce or inhibit CYP-450 drug metabolizing enzyme systems in vitro. Regarding special populations, the MOR notes that a granisetron I.V. has been studied, the safety and effectiveness of granisetron TDS has not been adequately assessed in sufficient numbers of patients with renal insufficiency, hepatic insufficiency, age \geq 65 years, age < 18 years, Blacks or in women who are pregnant or nursing. Safety and effectiveness of granisetron TDS (Sancuso) in pediatric patients (under 18 years of age) have not been established.

As noted by the MOR, although, as a class, the available 5-HT₃ receptor antagonists are generally perceived as safe, they have been infrequently associated with cardiovascular AEs, consisting mainly of hypertension, QT prolongation and rarely arrhythmias, such as atrial fibrillation.

It is however important to mention that, as noted in a WARNINGS section of its labeling, dolasetron [ANZAMET], one of the approved drugs in this class, can cause EKG interval changes (PR, QTc, JT prolongation and QRS-widening). These changes are related in magnitude and frequency to blood levels of the active metabolite. These changes are self-limiting with declining blood levels... but heart blocks or cardiac arrhythmias have rarely been reported. The PRECAUTIONS Section of the Package Insert indicates that dolasetron should be administered with caution in patients who have or may have prolongation of cardiac conduction intervals, particularly QTc... Considering these findings, although both, the 100mg and the 200mg dose levels of dolasetron were found to be effective in the prevention of MECINV and prevention of PONV, the 200mg dose is not recommended. In addition, the European Medicines Agency (EMA) has contraindicated the use of dolasetron in pediatric patients because of serious cardiovascular events associated with its use. Although, in the clinical trials, no instances of QTc prolongation were reported to occur in association with granisetron TDS, three cases of QTc prolongation in the oral granisetron group that were assessed as drug-related were reported. Considering PK characteristics, including the lack of consistent correlation between any PK parameter and either efficacy and/or safety outcomes, there is need to explore the possibility that, under certain clinical circumstances [i.e., in the presence of contributing factors], granisetron TDS [or a metabolite of this drug] has the potential of prolonging the QTc. The MTL supports this exploration, perhaps through a thorough QTc study.

From her evaluation of the clinical data, Dr. Berry recommends that Sancuso (granisetron TDS) 52 cm² be approved for the prevention of prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days. The MTL agrees with this recommendation. There is no applicable activity related to risk management for this NDA. Safety and efficacy have not been established in pediatric patients. The MOR

recommends that pediatric studies in ages 0 to 23 months be waived and pediatric studies in patients between 2 to 17 years of age be deferred. Dr. Berry also agrees with the Clinical Pharmacology Division's recommendation to require additional pharmacokinetic studies to address the potential for altered delivery of granisetron TDS in patients with altered skin integrity, extremes in subcutaneous fat and to assess the impact of heat on the patch. The MTL agrees with these recommendations.

2. CLINICAL PHARMACOLOGY

The CPR reviewer, Dr. T-M Chen³ noted that granisetron has a well defined PK profile. The mechanism of action of granisetron TDS is thought to be through binding to 5-HT₃ receptors, blocking serotonin stimulation and thus preventing nausea and vomiting in response to emetogenic stimuli such as chemotherapy. The PKs of granisetron TDS were studied in five clinical trials. In summary, granisetron TDS is a dermal patch formulation containing a granisetron base⁴. Regarding PDs, it is noted that in most human studies, the approved granisetron formulations have had little effect on blood pressure, heart rate or EKG. Comments on exposure-response relationship were summarized as follows. The dose for the Phase 3 study was based on the PK data found in the Phase 1 dose ranging study (392MD/11/C). Average granisetron plasma concentrations and AUC_(0-∞) increased proportionally with granisetron TDS patch size (i.e. with dose). Terminal half-life of granisetron was similar for all three patch sizes with an overall mean of 33 hours. Based on C_{avg} measurements, the 52 cm² granisetron TDS applied for 6 days resulted in a similar granisetron exposure to that obtained with once-daily oral dosing of 2 mg granisetron. Thus, the 52 cm² patch size was selected for Phase 3. Granisetron has been associated with rare cardiac events, such as atrial fibrillation and QTc prolongation. To evaluate cardiac effects EKG readings were taken and assessed during study 392MD/15/C.

The CPR and the MOR offered the following detailed overview of EKG testing in the development program. EKGs were taken at the following time points: Baseline (screening); Visit 1 Prior to the administration of chemotherapy; at the expected peak drug concentration (24 to 48 h after patch application); 1 h ± 10 min after capsule administration; and at Visit 6 [120 h post treatment (end of study)]. Recordings were taken in a supine position after patients had been resting for at least 10 min. EKGs were recorded at the sites on each trial patient and retrospectively sent to a central laboratory for a high resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment⁵. A total of 641 patients were randomized in 60 centers in 9 countries. The Applicant's primary analysis was the mean change from baseline (a single EKG taken at screening) to each of the EKGs taken at time points, Visit 1 and Visit 6 (central tendency). For the outlier analysis results were presented for the EKG intervals of heart rate (HR), PR, QRS, QT, QTcB and QTcF. There were no controls and so the GTDS patch was compared to the oral granisetron. The applicant noted that some of these patients were admitted to the study prior to the study amendment detailing the collection of the additional EKGs that formed the basis of the cardiac report. Thus the EKG

³ More details of Dr. Chen's CPR are included in Dr. Berry's Clinical Review of NDA 22-198.

⁴ The patch consists of a matrix of granisetron base in a commercially available adhesive, _____
Granisetron TDS 52 cm² patch contains a nominal dose of 34.3 mg of granisetron. The formulation was designed to deliver granisetron for up to 7 days following dermal application. The patch releases a mean of 3.1 mg of granisetron per 24 hours for up to 7 days.

⁵ EKG measurements were performed using digitization software with magnification of the EKG and on screen calipers by experienced technicians and a centralized cardiologist who was blinded to the tracings

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evaluable dataset was 588 patients (286 patch and 302 oral). The analysis of change from baseline for morphological considerations had a smaller dataset due mostly to missing EKG leads. That dataset was 468 patients (230 patch and 238 oral). The Applicant did not observe clinically relevant differences in the EKG effects of the patch or the capsule method of granisetron delivery in this trial. There was no clinically relevant signal that either the patch or capsule when compared to each other caused a change in heart rate, atrioventricular conduction, cardiac repolarization or morphology. The applicant reported that the observed changes from baseline in heart rate, intervals (PR, QRS and QTc) and morphology were not clinically significant in either formulation.

Safety was also assessed in Study 392MD/26/C (skin irritation/sensitization study in healthy subjects). The safety assessment consisted of the evaluation of 1) local tolerance, 2) patch adhesion and 3) adverse events in 4 phases: a) Induction Phase, b) Rest Phase, c) Challenge Phase and d) Re-challenge Phase. Two hundred and twelve (212) healthy subjects between the ages of 19 to 63 years of age were randomized. Two hundred and one (201) subjects were eligible for assessing the skin irritant potential and 200 subjects were eligible for assessing the sensitization potential. The 2 patches were both found to be slightly irritant, with the prevalence at Day 8 of 13% (active) and 22% (placebo). The active patch induced one positive sensitization reaction observed during the Challenge Phase. No reaction was reported with the placebo. The applicant reported that the sensitization potential of the granisetron patch was estimated to be 0.5% (low sensitization potential). Pruritis was the most frequently reported subjective symptom in both the Induction Phase and Challenge Phase upon patch removal days. Pruritis was comparable between the two treatment groups. Application of a patch was discontinued in 5 subjects due to serious irritant reactions at the original patch site. The patch was applied at a different site in 4 out of the 5 subjects. Other skin reactions were modification of skin pigmentation observed during the follow-up in 36 subjects.

Patch adhesivity was assessed 3 times a week during the Induction Phase and at Day 3 (patch removal) during the Challenge Phase to validate the assessments. Reinforcement of the patches with adhesive dressings was authorized to ensure appropriate compliance where appropriate. In the Induction Phase, 94.5% of subjects had >75% patch adherence by Day 8 with the GTDS in the Induction Phase and 89% of subjects had >75% patch adherence with the GTDS in the Challenge Phase. The Investigator's description in the Case Report form of the one positive sensitization reaction (subject # 110) to the active patch during the Challenge Phase when the patches were applied to the subject's back is summarized below. The subject did not agree to be re-challenged.

"The reaction was clearly positive with erythema, vesicles, pruritus and extension of the reaction beyond the patch test site. A positive diagnosis of allergic contact reaction to the granisetron patch was based on the co-existence of the following symptoms:

- Skin reaction scored 3 (erythema with individual vesicles)
- Delayed marked pruritus (no score, reported after the Day 3 assessment)
- Extension of the reaction beyond the patch test site (on skin area where no test product was applied)
- Kinetics of the skin reaction"

Irritant potential (Induction Phase): number (N) of subjects = 201

Incidence and prevalence of skin irritation were calculated by the Applicant. Incidences of positive irritant reaction (percentage of subjects who experienced a skin reaction scored >1) are presented below for the two test products.

MOR's Table 33: Incidence of skin irritation (induction phase)

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)

Applicant's table Study 392MD/26/C
GTDS = granisetron transdermal system

Dr. Berry commented that the active patch appeared to be less irritant than the placebo patch at all time points. The Applicant notes that this probably reflects the suppression of cutaneous flare reactions by 5-HT₃ receptor antagonists. This seems like a plausible explanation of the finding. The active patch induced one positive contact allergic reaction, while no reaction was reported with the placebo, a finding that suggests that hypersensitivity reactions are possible with the granisetron patch. The most common subjective symptom during the induction phase for both active and placebo patches was pruritus, followed by stinging.

In addition, the sponsor reported that no studies were conducted to specifically investigate the potential for granisetron TDS to cause or result in drug-drug interactions. Granisetron is not known to induce or inhibit CYP-450 drug metabolizing enzyme systems in vitro. Finally, there is evidence to suggest that female subjects had higher granisetron concentrations following patch application. Based on the Phase 3 trial results, it appears that any gender differences in PK did not translate into clinical efficacy outcome.

From the OCP standpoint, the clinical pharmacology section of the NDA is acceptable. The labeling comments on p. 17 [Of Dr. T-M Chen's review dated July 3, 2008] should be communicated to the Medical Officer Reviewer and sponsor.

NOTE: Dr. T-M Chen's Question Based Review portion of his review is included, in its entirety, as Appendix 1 to the current MTL's review,.

The CPR listed required Phase 4 commitments, a recommendation supported by the MO and the MTL. Required phase 4 Commitments from all disciplines are addressed in Section IV of the current review.

3. STATISTICAL

Conclusions and Recommendations formulated by Dr. Wen-Jen Chen's Statistical Review and Evaluation, dated July 1st, 2008, are that, from a statistical perspective, the single pivotal Study 392 MD/15/C does not provide substantial evidence _____ that the GTDS patch is non-inferior to oral granisetron in prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy. Dr. Chen clarifies that this conclusion does not imply the GTDS patch should be judged ineffective in the pivotal study. He comments that the lower bound for the two-sided 95% confidence interval on the proportion of complete control in the acute phase for GTDS patch is not less than 0.50, calculated using pivotal Study 392 MD/15/C. He further proposes that using this result as a reference, if the medical division deems that the complete control rate in the acute phase would

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be higher than that of placebo, then, the GTDS patch can be considered effective. From his comparison [s] to historical placebo response, the MTL concludes that granisetron, when given as a TDS formulation, is definitely active. Furthermore, in clinical practice, GTDS is not expected to be administered alone. This is because today's standard of care for patients being administered highly emetogenic chemotherapeutic regimens in whom prevention of HECINV is critical, is to administer three drugs with different mechanism of action: 1) a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist [such as granisetron]; 2) a corticosteroid [such as dexamethasone]; and an NK1 receptor antagonist [such as aprepitant].

NOTE: In a July 16, 2008 E-mail, Dr. Mike Welch commented that after examining the data [results from the pivotal trial] on the basis of Complete Response per country, the results do not show evidence of non-homogeneity across regions with regard to relative risk, so regional variation does not appear to be an issue.

Please note that included in Appendix 2 of the current review are other Sections of interest excerpted from Dr. W-J Chen's Statistical Review and Evaluation.

4. ANIMAL PHARMACOLOGY/TOXICOLOGY

Dr. S Chakder, from the Pharmacology Toxicology Division, reviewed several new toxicology studies that were conducted to address the safety of the new transdermal formulation. Also reviewed were published pharmacology, PK and toxicology studies with granisetron that were provided in the NDA submission. P/T reviewed two-week bridging toxicology studies comparing granisetron patches with i.v. and orally administered granisetron HCl conducted in rats and dogs. These studies showed that application of granisetron patches produced increased severity of edema at the application sites compared to placebo patches. In rats, lymphocytic infiltration in the heart was observed in groups receiving the patch, and oral or i.v. granisetron. Interstitial nephritis in the kidneys was observed in those rats receiving the patch and the i.v. dose. In dogs, fatty infiltrations in the liver and increased ALT levels were observed in those animals receiving all three dosage forms. Dr. Chakder concluded that sustained exposure of granisetron to rats and dogs for 2 weeks through application of granisetron patch or continuous i.v. administration of granisetron hydrochloride showed similar toxicity profiles to granisetron administered orally once daily. No new target organs of toxicity were identified following application of the patch in rats and dogs.

In addition, per the P/T review, non-clinical safety issue relevant to clinical use was that granisetron was positive in the *in vitro* chromosome aberration assay in Chinese hamster ovary cells in the presence of UV irradiation. Granisetron gave negative results in the absence of UV irradiation. Thus, patients should avoid exposure to sunlight or any artificial sunlight while wearing and for at least 10 days after removing the patch. Dr. Chakder recommends approval of the application and incorporating this information in the label. The MTL agrees with these recommendations, which should be incorporated in the labeling.

5. CHEMISTRY

Dr. Rao Puttagunta's recommendation and conclusion on approvability stipulated in his July 7, 2008 review of the evidence is that the submitted CMC information is adequate to assure identity, strength, purity and quality of the product. Therefore, from the CMC standpoint this NDA is recommended for approval. Highlights from his review are as follows. Appropriate in-process, release, and stability acceptance criteria have been established for the drug product to ensure consistency in quality. The in-process specification and the drug product specification were considered adequate as revised. Although the applicant proposed a _____ expiration date, based on the submitted drug product stability data for up to 24 months _____ in the product, a 24-month expiration date is granted. Granisetron may be affected by direct natural or artificial sunlight. A warning is included to avoid direct exposure of application site to natural or artificial sunlight by covering with clothing while wearing the patch and for 10 days after removing it.

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Dr. Puttagunta notes that the NDA original submission and amendments provided adequate CMC information for Sancuso® (granisetron TDS) and the following conclusions were made.

- The referenced DMFs for drug substance and container closure system are adequate.
- The submitted raw material controls are adequate.
- The manufacturing process and process controls are robust to ensure consistent product quality in conformance with the established specification.
- The drug product specification as revised is adequate.
- The submitted stability data is adequate to support the revised expiration dating period of 24 months.
 - The packaging information is adequate to ensure the product quality during storage, transportation, and use. The above information is sufficient for assuring identity, strength, purity, and quality of the drug product.
- The submitted labeling/labels as revised are acceptable from the CMC standpoint.
- The Office of Compliance issued an overall recommendation as "Acceptable" on 8/06/07.

The information on the composition of the pouch laminate was referenced to DMF _____. The submission included specifications for the pouch laminate and the _____ film (slip sheet). The submission included references to appropriate CFR sections (indirect food additives) for the components of the patch. [Adequate]. The proposed tests and acceptance criteria for microbial limits are adequate for a topical product. Since the formulation _____ microbial loading is not expected to be of concern. Moreover, the fact that the product is tested for microbial limits provides an added assurance. [Adequate]. It was stated that the manufacturing process will be validated prior to commercialization. The drug product does not contain any compendial excipients. The applicant developed a procedure to _____ within the patch, and proposed an acceptance criterion for the _____ (See drug product specification in Chemistry review). The proposed acceptance criterion for the _____ was found to be acceptable. [Adequate].

b(4)

b(4)

6. DDMAC LABELING COMMENTS

In a memorandum dated May 6, 2008, Dr. SM Skariah, a Regulatory review Officer from the Division of Drug Marketing, Advertising, and Communications (DDMAC) noted that DDMAC has reviewed the proposed product labeling (PI) and Medication Guide for SANCUSO® (Granisetron Transdermal System) (Sancuso) (version dated 06/2007). DDMAC offered comments under HIGHLIGHTS, PI, and PATIENT LABELING. These are incorporated into Appendix 3 of the current review.

7. LABEL and LABELING REVIEW for SANCUSO from the OFFICE of SURVEILLANCE and EPIDEMIOLOGY

From his October 1, 2007 review on the use of the proprietary name, Sancuso Dr. Richard Abate, a safety evaluator, Division of Medication Error Prevention, formulated the below listed recommendations to our Division:

1. The Division of Medication Error Prevention has no objections to the use of the proprietary name, Sancuso.
2. The Medication Error Staff will evaluate the label and labeling for Sancuso in a separate review.
3. DDMAC finds the proprietary name Sancuso acceptable from a promotional perspective.
4. The Medication Error Staff raises concerns about the potential for duplicate therapy medication errors associated with the introduction of a granisetron transdermal patch.

In a second memorandum, dated April 14, 2008 and also authored by Dr Abate, the Division of medication Error Prevention's Label and Labeling Risk Assessment identified vulnerabilities in the presentation of information in the labels and labeling of Sancuso (granisetron) TDS which may lead to medication errors. Moreover, the design of this dosage form may predispose this product to be used incorrectly. A primary concern centered on the applicant attempt to address the potential adhesive problem inherent in the patch dosage forms with product labeling. Also questioned was whether all the information and statements regarding use of the patch were supported by the data collected in controlled studies. As, at the time of this memo, some data provided by the Applicant was under review, HFD-420 planned to further discuss their concerns during the team meetings for Sancuso. They provided Comments to the Applicant in Section IV of the Consult Review.

8. DRISK: REVIEW of PATIENT LABELING

Comments, deletions, and other revisions to the Patient Information included in Ms. S R Mills memorandum dated May 27, 2008, can be found in Appendix 5 of the current review. Ms. Mills

is a patient Product Information Specialist and a member of the Patient Labeling and Education Team, DRISK.

IV. REQUIRED PHASE 4 COMMITMENTS

Characterization of the use of the granisetron TDS in the target population and in other populations that may benefit from the use of this patch is incomplete. Clinical Pharmacology has called attention to the fact that heat, either through a heating pad or other external source, has been shown to markedly increase the rate of drug absorption into the systemic circulation from transdermal dosage forms. Given that Sancuso is intended for multi-day use, CP ask the applicant to commit to the conduct of a study to determine the impact of heat on drug delivery. Such a study could be done using a validated in vitro model upon prior agreement by the Agency as to the model and protocol design. Should such a model not be available, then a trial could be done in healthy subjects. In addition, there is need for PK studies in the pediatric population to assess safety and tolerability and randomized, double-blind studies comparing granisetron TDS with granisetron I.V. in the pediatric population to assess safety and efficacy. Attention has been called to the fact that while an in vivo PKs study in healthy adults and a limited sampling study in subjects receiving chemotherapy have already been conducted, there is a lack of PK data from patients who have altered skin integrity due to advanced age or poor nutritional status related to chronic illness. In addition, available data suggest that the drug is delivered into subcutaneous fat and is released from that compartment over time. It is possible that individuals with varying nutritional status and resultant differences in subcutaneous fat would have marked differences in pharmacokinetics. The Agency has concerns that altered delivery of drug may arise in patients with altered skin integrity or extremes in subcutaneous fat. This could lead to altered efficacy in those individuals.

Based on the above-mentioned Clinical Pharmacology considerations, the applicant should commit to the following required Phase 4 Commitments:

- 1) PK studies in the pediatric population (aged 2 to 17 years) to assess safety and tolerability and randomized, double-blind studies comparing granisetron TDS with granisetron I.V. in the pediatric population (aged 2 to 17 years) to assess safety and efficacy.
- 2) An in vivo PK study in subjects with differing levels of body fat (and thus subcutaneous fat) composition ranging from lean to obese (based on generally accepted IBW tables)
- 3) An in vivo PK study in elderly individuals.
- 4) A study to determine the impact of heat on drug delivery (either a validated in vitro model or if this model is not available, then a trial in healthy subjects).

It is worth noting that should the results of these required Phase 4 studies indicate an altered delivery that could be correlated to body mass (IBW, etc) or age, this information would be important to include in the label.

Details on the design and proposed execution of these required Phase 4 commitments are under intramural discussion.

Also under discussion are considerations of possible request of a thorough QTc study. This possible request arises from findings of QTc prolongation in three patients receiving the oral formulation of granisetron, the active comparator used in the pivotal trial submitted under NDA 22-198. Although no case of QTc prolongation in apparent association with granisetron TDS was reported in the clinical trials, the patch appears to have the potential for induction of QTc prolongation and this safety concern needs to be further explored.

Hugo E Gallo-Torres, MD, PhD, PNS
Medical Team Leader
Division of Gastroenterology Products
HFD-180

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APPENDICES

APPENDIX 1

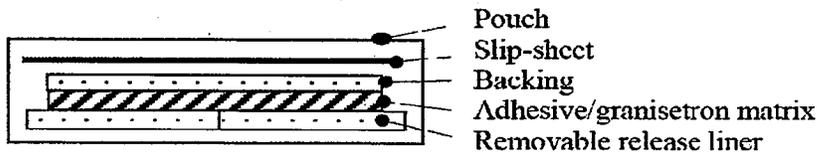
Transposed from Dr. T-M Chen Clinical Pharmacology Review dated July 3, 2008

2. Question Based Review

2.1 General Attributes

Formulation:

Granisetron base was used as the drug substance rather than granisetron hydrochloride, as the non-ionized material is the form most likely to provide acceptable skin permeation properties. Granisetron transdermal delivery system (referred to as GTDS) is a dermal patch formulation. The patch consists of a matrix of granisetron base in a commercially-available adhesive, _____ as shown below:



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Sancuso GTDS is a 52 cm² patch containing a nominal dose of 34.3 mg of granisetron. The formulation was designed to deliver granisetron for up to 7 days following dermal application in order to increase patient compliance during chemotherapy.

Mechanism of Action: In general, vomiting triggered by drugs or chemical agents is mediated through the CTZ (chemoreceptor trigger zone). The mode of action of granisetron is believed to be through binding to 5-HT₃ receptors, blocking serotonin stimulation, and thus preventing vomiting in response to emetogenic stimuli such as chemotherapy.

Indication:

Sancuso GTDS patch is indicated for the prevention of nausea and vomiting in patients receiving up to 5 consecutive days of moderately and/or highly emetogenic (ME and/or HE) chemotherapy.

Proposed Dosing Regimen:

For adults, apply a single patch to the upper outer arm 24-48 hours before chemotherapy as appropriate and remove the patch a minimum of 24 hours after completion of chemotherapy. The patch can be worn for a minimum of 24 hrs after completion of chemotherapy and up to 7 days depending on the duration of the chemotherapy regimen.

b(4)

2.2 General Clinical Pharmacology

Q1. How was the Sancuso Patch Size (52 cm²) Selected?

The patch size selection was primarily based on the Phase 1 Study 392MD/11/C. This was a four-way crossover study in 12 healthy male subjects to assess the bioavailability of three sizes of granisetron patches (15, 33 and 52 cm²) following a single 6-day application and an oral granisetron regimen (2 mg once-daily for 5 days).

The mean plasma granisetron concentration-time profiles for the 3 sizes (15 cm², 33 cm², and 52 cm²) of Sancuso GTDS after being applied on the upper outer arm for 6 days are shown in Figure 5 and the mean

granisetron PK parameters for the 3 patch sizes and for oral dosing are presented in Table 4.

Figure 5. Mean (\pm SEM) plasma granisetron concentration versus time after application of one GTDS patch (15, 33, and 52 cm²) on the upper outer arm for 6 days to healthy male subjects (n=12)

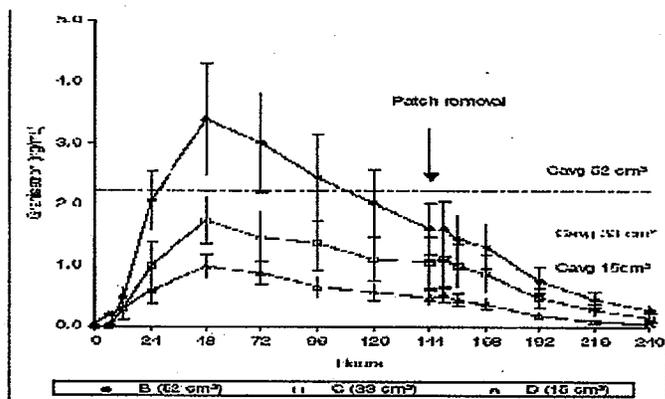


Table 4. Mean (%CV) Granisetron PK Parameters for Three Patch Sizes and Oral Granisetron Obtained from 12 Healthy Male Subjects

Parameter	Study 392MD/11/C				
	15	33	52	Oral QD Dosing x 5 days	
Patch Size, cm ²	15	33	52	Oral QD Dosing x 5 days	
Nominal Dose, mg	9.9	21.8	34.3	2 (per day)	
C _{max} , ng/mL	1.15 (73)	2.08 (110)	3.85 (77)	5.25 (42%) (Day 1)	5.50 (68%) (Day 5)
T _{max} , hr ¹	48 [48-96]	48 [24-150]	48 [24-168]	1.5 [1-4]	2 [1-4]
T _{1/2} , hr	30.9 (32)	30.9 (21)	35.9 (35)	6.4 (74%)	7.9 (74%)
AUC _{0-t} , ng-hr/mL ²	98 (83%)	179 (110%)	321 (89%)	51 (80%)	62 (110%)
C _{avg} , ng/mL ³	0.68 (83%)	1.24 (110%)	2.23 (89%)	2.14 (79%)	2.60 (108%)

¹ Median [range]

² AUC_{0-t}: AUC₀₋₁₄₄ for patch application for 6 days and AUC₀₋₂₄ for QD oral dosing.

³ C_{avg} was calculated as (AUC₀₋₁₄₄)/144 h for patch application and (AUC₀₋₂₄)/24 h for oral dosing.

After repeated 2 mg QD oral dosing, the mean C_{max} was 5.25 ng/mL on Day 1 and 5.50 ng/mL on Day 5, and mean T_{max} was around 1.5-2 hrs. Following GTDS patch application, mean plasma granisetron concentrations peaked at approximately 48 hours (T_{max}, a median) and then declined steadily thereafter even though the patch was still left on the skin. The mean C_{max} for the three patch sizes were 1.15, 2.08, and 3.85 ng/mL, respectively, which were all lower than that observed with oral granisetron 2 mg QD. The mean apparent terminal half-life (T_{1/2}) of granisetron after GTDS patch removal was estimated to be around 31-36 hrs across the patches tested, which was much longer than that observed with oral granisetron

(6.5-8.0 hrs). This is likely to be due to the continued drug release from the skin after the patch removal.

The patch size selection was based on the mean C_{avg} value (average plasma concentration). For the patches, C_{avg} was calculated as $(AUC_0-144)/0.144$ hr which were 0.68, 1.24, and 2.23 ng/mL for the 15, 33, and 52 cm² patches, respectively. For the oral 2 mg QD dosing, C_{avg} was calculated as $(AUC_0-24)/0.24$ hr and was evaluated to be 2.14 ng/mL on Day 1 and 2.60 ng/mL on Day 5 (Table 4). As shown in Table 4, C_{avg} (mean: 2.23 ng/mL) for the 52 cm² patch was similar to those obtained from the approved once-daily oral dosing of 2 mg granisetron (Day1: 2.14 ng/mL and Day5: 2.60 ng/mL). The C_{avg} for the 15 and 33 cm² patches were 0.68 and 1.24 ng/mL, respectively, which were too low compared to that for the oral dosing. The 52 cm² GTDS patch was therefore selected by the sponsor for further development.

Q2. Why Sancuso Patch is proposed to be applied 24 to 48 h prior to chemotherapy?

The 52 cm² GTDS patch was tested in a Phase 2 Study 392MD/8/C. This was a study in 173 patients undergoing a single-day regimen of chemotherapy with moderately emetogenic (ME) potential. A 5-day patch application (starting on Day -1) was compared with a single oral dose of 2 mg tablet. Post chemotherapy, blood samples were taken from all patients on Day 0 (1st hr), Day 1 (24th hr) and Day 4 (96th hr). The PK results obtained from the study are shown below:

Figure 6. Mean (\pm SEM) Plasma Granisetron Concentrations following Granisetron TDS and Oral Administration to Cancer Patients in Study 392MD/8/C (along with the fitted curve)

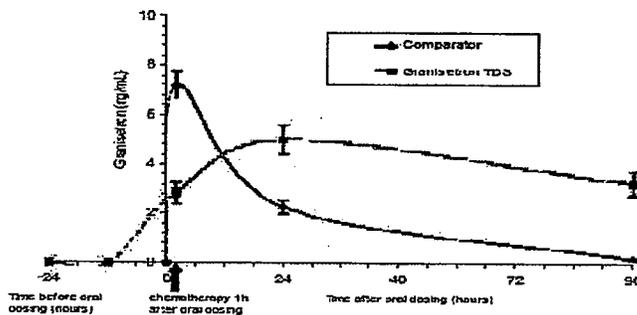


Table 5. Plasma Granisetron Concentrations (ng/mL) following Granisetron TDS and Oral Administration to Cancer Patients in Study 392MD/8/C

Parameter	Study Days				
	Day 0 (1st hr)#	Day 1 (24 h)	Day 4 (96 h)	Day 5 (120 h)	Day 6 (144 h)
Granisetron TDS 52 cmz Patch					
N	86	85	79	10*	10*
Mean ± SD	2.84 ± 3.86	5.00 ± 5.32	3.26 ± 4.35	0.98 ± 0.87	0.49 ± 0.47
Oral Granisetron 2 x 1 mg Tablets					
N	82	81	80	7*	7*
Mean ± SD	7.17 ± 4.90	2.28 ± 2.38	0.19 ± 0.44	0.04 ± 0.07	<LOQ

Blood samples taken 1 hr post chemotherapy, i.e., 2 h after granisetron oral dosing.

*From a subset of patients.

In patients treated with a single 2 mg dose of oral granisetron (given 1 hr prior to chemotherapy), the mean plasma granisetron value was 7.17 ng/mL at 2 hrs post oral dosing (near its Tmax). In patients receiving GTDS, mean concentration at this time point (equivalent to 25 hr post patch application) was 2.84 ng/mL and the concentration was higher at 24 hrs after chemotherapy, i.e., 48 hr after patch application (mean: 5.00 ng/mL). Note that high intersubject variability was observed for both the patch (>100%) and oral granisetron tablets (70% to >100%).

The efficacy outcome was measured by the percentage of patients with total control, which was defined as “no vomiting or retching, no nausea, or no rescue medication.” For the delayed CINV, the response rate for the patch was comparable with, but not superior to the oral granisetron (32.2% vs. 29.8%). For the acute CINV, the % responders was lower for the patch compared to oral granisetron (43.7% vs. 52.4%) as shown in Table 6. Since the patch had low initial (0 to 24 h) granisetron concentrations, this might explain its lower response rate for the acute CINV. As it might take 48 h to reach Cmax, the sponsor proposed to have the patch applied onto the upper outer arm 24 to 48 hrs before the start of chemotherapy in the Phase 3 trial 392MD/15/C.

Table 6: Clinical Outcome from Phase 2 Study 392MD/8/C

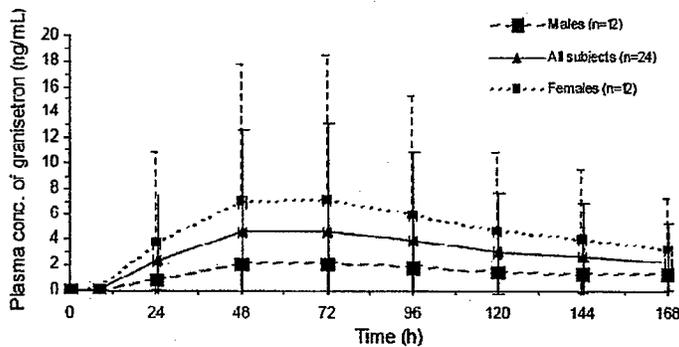
Endpoint Total Control: CINV		Number (%) of Patients (ITT)		
		GTDS (n=87)	Oral G (n=84)	Total (n=171)
1°: Delayed Phase (24-120 hr)	No	59 (67.8%)	59 (70.2%)	118 (69.0%)
	Yes	28 (32.2%)	25 (29.8%)	53 (31.0%); p=0.6288
2°: Acute Phase (0-24 hrs)	No	49 (56.3%)	40 (47.6%)	89 (52.0%)
	Yes	38 (43.7%)	44 (52.4%)	82 (48.0%); p=0.2445
2°: Overall (0-120 hrs)	No	65 (74.7%)	63 (75.0%)	128 (74.9%)
	Yes	22 (25.3%)	21 (25.0%)	43 (25.1%); p=0.9111

Q3. What are the PK Characteristics of Granisetron after GTDS Application?

The PK data presented below were obtained from Study 392MD/26/C, a study to evaluate the sensitization² and irritation of GTDS patch in healthy volunteers, because this study used the 52 cm² patch manufactured at the new site (Aveva DDS). In this study, both the active and placebo patches were simultaneously applied to the upper outer arm on opposite arms on Days 1, 8, and 15. Patches remained in place for 7 days after each application. A subset of 24 subjects (12 females & 12 males) had blood samples taken for PK analysis at predose and at 8, 24, 48, 72, 96, 120, 144, and 168 hrs after the first patch application.

The plasma concentration-time profiles following single 7-day application of GTDS 52 cm² patch are shown in Figure 7-1. The mean PK parameters for GTDS are presented in Table 7-1. Peak plasma concentrations (mean: 5.0 ng/mL) was reached approximately 72 hours following patch application. Plasma concentrations then decline with time even though the patch remained on the skin. At 168 hours following patch application, mean plasma granisetron concentration was approximately half of the mean C_{max} value. Intersubject variability in both C_{max} and AUC was very high (CV: ~170%; Table 7-1).

Figure 7-1. Mean (± SD) Granisetron Plasma Profiles in 24 Healthy Volunteers ; Table 7-1. Mean (CV%) Granisetron PK Parameters in Healthy Volunteers in Study 392MD/26/C



PK Parameters	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (ng-hr/mL)	C _{avg} (ng/mL)
All Subjects	5.0 (170)	72[24-168] ¹	527 (173)	3.1 (170)
Male (n=12)	2.5 (110)	66 [24-144]	253 (115)	1.5 (120)
Female (n=12)	7.6 (150)	78 [24-168]	802 (150)	4.8 (150)

¹Mean [Range].

Q4. Are There Gender Differences in Granisetron PK and Efficacy Outcome Following Patch Application?

Pharmacokinetics:

Gender differences for granisetron plasma data were observed in Study 392MD/26/C (Figure 7-1 & Table 7-1). Female subjects were found to have a 3-fold higher systemic exposure than male subjects. One female subject (#23) had unusually high (8-fold of female mean value) plasma granisetron levels after

GTDS application. The reason for this observation is unknown. (The sponsor verified that this female subject received only one active patch, the residual amount of granisetron after patch removal was in the same range as those observed for the other subjects (9.9 mg vs. 4.3–16.9 mg), and that the assay method was valid.) When Subject #23 is excluded from the analysis, female subjects still had 80% higher mean C_{max} and AUC compared to male subjects (Table 7-2 and Figure 7-2).

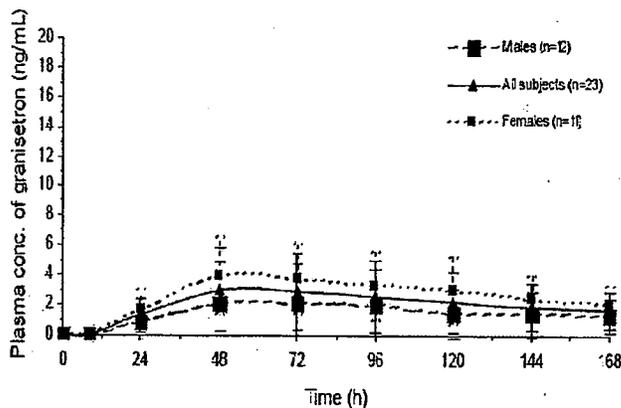
Table 7-2. Mean (CV%) Granisetron PK Parameters in Healthy Male (n=12) and Female Subjects (n = 11); Study 392MD/26/C

PK Parameters	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₁₆₈ (ng-hr/mL)	C _{avg} (ng/mL)
All Subjects ¹	3.4 (79)	72 [24-168] ²	351 (85)	2.1 (170)
Male (n=12)	2.5 (110)	66 [24-144]	253 (115)	1.5 (120)
Female (n=11)	4.4 (55)	79 [24-168]	459 (60)	2.7 (150)

¹ Excluding female subject # 23.

² Mean [Range].

Figure 7-2. Mean (± SD) Granisetron Plasma Profiles in Healthy Male (n = 12) and Female subjects (n=11, excluding Subject #23); Study



Additional

Analysis:

From the pivotal Phase 3 study, 392MD/15/C, the sponsor provided scatter plots upon our request to compare the granisetron concentrations in males (upper panel; in purple) and females (lower panel; in blue) upon our request (Figure 8 below). Although more female patients had higher concentrations, generally the concentration range was similar between males and females.

CPReviewer's Comment:

There is evidence to suggest that female subjects had higher granisetron concentrations than male subjects following patch application. Based on the Phase 3 trial results, it appears that any gender differences in PK did not translate into differences in clinical efficacy outcome.

Q5. What is the Drug Delivery Rate following Application of Granisetron Patch?

The sponsor defined a term “*in vitro* flux” which was calculated based on the residual amount of granisetron at the time of patch removal. Specifically, the released dose was calculated as the administered dose (initial patch content) minus the residual granisetron amount in the patch after removal. The *in vitro* flux is then calculated as the released dose divided by the number of days of patch application. The sponsor provided the results for several studies after dose normalization to a 52 cm² patch (Table 8). For Study 392MD/26/C, the actual assay for the clinical batch used (# 35073) was 32.7 mg and the mean residual amount after patch removal was determined to be 11.0 mg. Therefore, the patch released on average 21.7 mg of granisetron over 7 days, i.e., mean “*in vitro* flux” was estimated to be 3.10 mg/day (CV: 16.6%).

Table 8. *In Vitro* Flux, Released Amount of Granisetron Per Day, from Granisetron TDS Patch Across 3 Studies (Dose-Normalized)

Study	392MD/8/C	392MD/11/C		392MD/26/C	
Manufacturer	Aveva DDS				
Patch, cm ²	52	15	33	52	52
Days contact	5	6	6	6	7
Dose, mg	34.3	9.9	21.8	34.3	32.7 ¹
N	84	12	12	12	211
Volunteers/Patients	Patients	Volunteers			Volunteers
Male/Female	27/57	12/0	12/0	12/0	53/158
Delivered dose, mg	16.3	6.4	12.6	22.1	21.7
Mean <i>In Vitro</i> Flux, mg/day (CV%)	3.27 (25.6%) M: 3.36/F:3.26	3.68 (21.0%)	3.31 (24.5%)	3.68 (13.8%)	3.10 (16.6%) M:3.19/F:3.06

b(4)

¹ Based on the actual assay value for the clinical batch (No.35073).

Reviewer’s comment:

Using the term “*in vitro* flux” can be misleading as it implies that the value was obtained from an *in vitro* study and that the drug release rate from the patch is relatively constant over the intended time period of use (whereas after patch application, it actually varies with a time lapse). We, therefore, consider it as the average daily delivery rate. One should bear in mind that this number is for labeling purpose only and that it does not represent the actual drug delivery rate.

It appears that the drug, after permeating through the skin, can be stored in the subcutaneous adipose tissue first and subsequently released to systemic circulation.

Q6. What was the Primary Efficacy Endpoint in the Pivotal Phase 3 Study 392MD/15/C?

The primary efficacy endpoint used in the pivotal Phase 3 trial was “complete control”, which is defined as no vomiting 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 the multiday chemotherapy. The response rate for prevention of acute CINV was comparable between the patch and oral granisetron (60.2% vs. 64.8%) according to Dr. Karyn Berry, Medical Officer of HFD-180.

Q9. Is the assay methods adequately validated?

The assay performance is found to be acceptable (Tables 10-11) [Not reproduced here].

13. Detailed Labeling Recommendations

13.3 Phototoxicity

Granisetron was not phototoxic when tested *in vitro* in a mouse fibroblast cell line. When tested for potential photogenotoxicity *in vitro* in a Chinese hamster ovary (CHO) cell line, at 200 and 300 µg/ml, granisetron increased the percentage of cells with chromosome damage following photoirradiation. When tested *in vivo* in guinea-pigs, SANCUSO patches did not show any potential for photoirritation or photosensitivity.

CPReviewer's Comment:

The study results were reviewed and found acceptable.

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APPENDIX 2

Excerpts from Dr. Wen-Jen Chen's Statistical Review and Evaluation of NDA 22-198 dated July 1st, 2008

1.2 Brief Overview of Clinical Studies

The applicant submitted two studies to support the use of Granisetron TDS (GTDS) in prevention of nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy. Study 392 MD/8/C was a phase 2 supportive study and Study 392 MD/15/C was a phase 3 pivotal study. Both studies compared GTDS to oral granisetron.

The objective of Study 392MD/8/C was to assess the effect of Granisetron TDS patch based upon the primary endpoint of the total control for chemotherapy induced nausea and vomiting (CINV) for the period 24 - 120 hours (delayed phase) post single-day moderate emetogenic chemotherapy, while that of Study 392MD/15/C was to evaluate the effect of Granisetron TDS patch based upon the primary endpoint of the complete control for CINV from the first administration until 24 hours (acute phase) post moderate emetogenic (ME) or highly emetogenic (HE) chemotherapy following multi-day chemotherapy. For the supportive study, the endpoint used was total control, defined as no nausea, no vomiting, no use of rescue medication, and no withdrawal from the study; for the pivotal study, the endpoint was complete control, defined as no vomiting, no more than mild nausea, and no rescue medication. The differences in these studies are further addressed in Section 2.0.

1.3 Statistical Issues and Findings

1.3.1 Phase 2 Study 392 MD/8/C

The applicant's two studies (392 MD/15/C & 392 MD/8/C) differed in objective, inclusion/exclusion criteria, primary assessment period, duration of patch application, duration of chemotherapy application, primary endpoint, and the efficacy analysis. As a result, the supportive Study 392MD/8/C does not provide direct evidence of replication in support of the single pivotal study.

In addition, as for the primary endpoint (total control in the delayed phase) analysis, the applicant's assertion of comparability between the two treatments is based upon a non-significant result of a superiority analysis for testing the null hypothesis of no treatment effect difference is not scientifically valid. Finally, the lower bound of the two-sided 95% confidence interval for complete control in the acute phase for GTDS minus oral granisetron is -26%, much less than the -15% margin set up for the primary endpoint (CC for the acute phase) for the pivotal study. This result suggests that the efficacy of the study drug, with respect to CC, may be inferior to that of oral granisetron by more than 15%.

Consequently, it appears that no efficacy evidence is provided by Study 392MD/8/C to support the pivotal Study 392MD/15/C for GTDS patch in use of the proposed indication. The efficacy assessment of the study drug GTDS should mainly rely on the single pivotal Study 392 MD/15/C.

1.3.2 Phase 3 Study 392 MD/15/C

The following analyses and comments on the efficacy assessments are for the non-inferiority of GTDS patch versus oral granisetron based upon the primary endpoint - complete control for the first 24 hour from the first administration until 24 hours after the start of the last day's administration of the ME or HE chemotherapy regimen.

The applicant's logistic regression analysis and this reviewer's simple proportion (unadjusted) analysis show that the

lower bounds of the two-sided 95% confidence intervals for the proportion of complete control are close to the non-inferiority margin of -15% (-13.0% and -12.40% respectively for logistic regression and simple proportion analyses). In addition, since the complete control rate of GTDS patch is 5.0% less than that of oral granisetron, this result indicates that the non-inferiority conclusion is not robust.

Following the efficacy assessment criteria for the superiority analysis of a single clinical trial, a much higher level of confidence is recommended to be applied, for example, 99.75%. The lower bound of the two-sided 99.75% is -17.0%, less than the non-inferior margin of -15%; this also suggests, that the evidence for non-inferiority of the GTDS patch to oral granisetron as assessed by complete control provided by this single study is not substantial.

The applicant's analysis on the complete response (no vomiting and no rescue therapy) indicates that the lower bounds of the two-sided 95% confidence intervals for the complete response are -14.4% and -15.3% respectively, for PPS and FAS populations. Because of the two lower bounds either very close (-14.4% from PPS) to or smaller (15.3% from FAS) than the negative non-inferiority margin (-15%), the efficacy of GTDS is very likely inferior to that of oral granisetron by more than 15 percent even assessed at the regular two-sided 95% confidence interval normally used for two pivotal studies. Since the 15% non-inferiority margin selected by the applicant is mainly based upon historical data of complete response, that margin may be better suited for a complete response analysis. Thus the result for the complete response analysis does not support but perhaps diminishes the efficacy of GTDS in use of the proposed indication.

Finally, the non-inferiority margin of 15% was not determined by relevant information in accordance with ICH E10. According to the applicant's response documents, historical placebo controlled trials in similar conditions and patient populations to the current study were not conducted. In addition, the applicant admits in their response documents, the 15% margin was not selected with a formal statistical approach. The non-inferiority margin of 15% was selected based upon clinical reasoning and exploratory/descriptive type of data analysis using two IV granisetron trials roughly estimating the complete response rate of active control oral granisetron and one research paper quoting placebo effect of zero complete response. It also should be noted that the original studies for granisetron submitted under NDA 20305, the non-inferiority margin of 10% was used for the non-inferiority analysis. This reviewer believes that the non-inferiority margin of 15% selected by the applicant for the pivotal study was too large.

Based upon the above efficacy assessment on the pre-specified non-inferiority study design, one may conclude that even using this disputable and large margin of 15% selected by the applicant, the non-inferiority of GTDFS patch to oral granisetron demonstrated by the single pivotal Study 392 MD/15/C is only on the borderline and is not robust.

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APPENDIX 3

Excerpts from Dr. Sushanta Chakder's Pharmacology/toxicology Review and Evaluation dated June 11, 2008

A. Recommendation for nonclinical studies: None.

B. Recommendations on labeling: Following changes in the sponsor's proposed labeling is recommended:

8.1 Pregnancy

Evaluation:

Recommended version: The sponsor's proposed labeling is based on the approved labeling of Kytril. However some changes in the language are recommended. In addition, the comparison of doses between humans and animals should be based on daily dose of 3.1 mg/day for an average body weight of 50 kg.

13.3 Phototoxicity¹¹⁰

Granisetron was not phototoxic when tested *in vitro* in a mouse fibroblast cell line. When tested for potential photogenotoxicity *in vitro* in a Chinese hamster ovary (CHO) cell line, at 200 and 300 µg/ml, granisetron increased the percentage of cells with chromosome damage following photoirradiation. When tested *in vivo* in guinea-pigs, SANCUSO[®] patches did not show any potential for photoirritation or photosensitivity.¹¹¹

Evaluation: The comparison of doses between humans and animals should be based on 3.1 mg/day _____ and on the basis of an average body weight of 50 kg. _____
_____ Moreover, there are human data on the safety of SUNCUSO.

b(4)

Recommended version:

13.2 Phototoxicity

Granisetron was not phototoxic when tested *in vitro* in a mouse fibroblast cell line. When tested for potential photogenotoxicity *in vitro* in a Chinese hamster ovary (CHO) cell line, at 200 and 300 µg/ml, granisetron increased the percentage of cells with chromosomal aberration following photoirradiation. When tested *in vivo* in guinea-pigs, SANCUSO[®] patches did not show any potential for photoirritation or photosensitivity.

II. Summary of nonclinical findings

Published Toxicology Studies:

Toxicological Study of Granisetron Hydrochloride- Single Dose Toxicity in Mice and Rats and Repeated Dose Toxicity in Rats and Dogs. Hahansson S, Artus JA, Kelvin AS, Abdi M, Nishioka Y, Iwabuchi M. The Clinical Report 1990, 24(10): 371.

Toxicological Study of Granisetron Hydrochloride (Second Report) – Oral Repeated-Dose Toxicity in Rats. Abdi M, Hakansson S, Kelvin A and Toseland CD. *Jpn Pharmacol Ther* 1995, 23 (5); 12371247.

Toxicological Study of Granisetron Hydrochloride (Third Report) – Oral Repeated-Dose Toxicity in Dogs. Abdi M, Hakansson S, Kelvin A and Toseland CD. *Jpn Pharmacol Ther* 1995, 23 (5); 1249.

2.6.6.1 Overall toxicology summary

Two-week bridging toxicology studies comparing granisetron patches with i.v. and orally administered granisetron HCl have been conducted in rats and dogs. Application of granisetron patches produced increased severity of edema at the application sites compared to placebo patches. In rats, lymphocytic infiltration in the heart was observed in groups receiving the patch, and oral or i.v. granisetron, and interstitial nephritis in the kidneys was observed in groups receiving the patch and the i.v. dose. In dogs, fatty infiltration in the liver and increased ALT levels were observed in groups receiving all three dosage forms. Thus, sustained exposure of granisetron to rats and dogs for 2 weeks through application of granisetron patch or continuous i.v. administration of granisetron hydrochloride showed similar toxicity profiles to granisetron administered orally once daily. No new target organs of toxicity were identified following application of the patch in rats and dogs.

2.6.6.3 Genetic toxicology

The following published study on the genotoxicity of granisetron was submitted.

Toxicological Study of Granisetron Hydrochloride – Mutagenicity Study. Mitchell IG, Rees RW, Carlton JB, Nishioka Y, Ishii R. *The Clinical Report* 1990, 24(13): 261.

Genetic toxicology summary:

The genotoxic potential of granisetron was examined in five assays – the unscheduled DNA synthesis (UDS) assay in HeLa cells, the bacterial reverse mutation assay (Ames test), the gene mutation assay in mouse lymphoma L5178Y cells, the human lymphocyte chromosome aberration assay and the mouse micronucleus assay. Granisetron was not mutagenic in an *in vitro* Ames test and the mouse lymphoma cell forward mutation assay, and the *in vivo* mouse micronucleus test. 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

2.6.6.6 Reproductive and developmental toxicology

The sponsor submitted the following published studies in which the reproductive toxicity of granisetron was examined in rats and rabbits.

Toxicity study of Granisetron Hydrochloride – Intravenous Administration Study during Organogenesis in Rats and Rabbits. Baldwin JA, Davidson EJ, Goodwin J, Pritchard AL, Ridings JE, Nishioka Y, Iwabuchi M. *The Clinical Report* 1990, 24:423

Toxicology Study of Granisetron Hydrochloride – Fertility and General Reproductive Performance Study and Perinatal and Lactation Period Study in Subcutaneously Treated Rats. Baldwin JA, Davidson EJ, Goodwin J, Pritchard AL, Ridings JE, Nishioka Y, Iwabuchi M. *The Clinical Report* 1990, 24:435.

Toxicological Study of Granisetron Hydrochloride – Reproductive Toxicity in Orally Treated Rats. Baldwin JA, Davidson EJ, Goodwin J, Pritchard AL, Ohta M, Yasuda E, Nishioka Y. Jpn Pharmacol Ther. 1993, 21 (6):115.

Reproductive and Developmental Toxicology Summary:

Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m²/day) and oral doses up to 100 mg/kg/day (600 mg/m²/day) had no effect on fertility and reproductive performance of male and female rats. Teratogenicity studies with granisetron hydrochloride have been conducted in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m²/day) and oral doses up to 125 mg/kg/day (750 mg/kg/day). Teratogenicity studies have been conducted in pregnant rabbits at intravenous doses up to 3 mg/kg/day (36 mg/m²/day) and at oral doses up to 32 mg/kg/day (384 mg/m²/day). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to granisetron. It was not teratogenic in rats and rabbits. In a Segment III reproductive toxicity study in rats, there were no treatment-related effects on the body weight, water or food consumption and reproductive performance of dams, or development of offspring at oral doses up to 125 mg/kg/day.

Labeling Recommendations: None.

2.6.6.7 Local tolerance

The key findings in Study # 19136/05 were that granisetron base laminate did not produce skin irritation or sensitization in guinea pigs.

Chromosomal Aberration:

Structural aberration: Treatment of the cells with granisetron base in the absence of UV irradiation did not cause a significant increase in the frequencies of cells with structural chromosome aberrations as compared to concurrent vehicle control. The positive control caused a significant increase in the frequencies of cells with chromosome aberrations. The data for non-irradiated samples are summarized in the Table below.

Treatment of the cells with granisetron base in the presence of UV irradiation resulted in statistically significant, concentration-related increase in the frequencies of cells with structural chromosome aberrations, and these increases were higher than the historical control range at 200 and 300 µg/mL concentrations. The data for UV-irradiated samples are summarized in the Table below.

The numbers and types of aberrations are shown in the Table below.

Numerical aberration: Frequencies of cells with numerical aberrations were within historical negative control ranges for all granisetron concentrations both in the absence and presence of UV irradiation. Thus, granisetron base induced increases in the frequency of structural chromosome aberrations in Chinese hamster ovary cells in the presence of UV light, as a maximum UVA dose level of 700 mJ/cm² in the absence of metabolic activation.

Study Title: Photosensitization Test of Granisetron Transdermal Patch after Dermal Application

Key Findings: Under the condition of the experiment [Study Report No.: 21022/06] , Granisetron Transdermal Patch did not show any photosensitizing effects in guinea pigs.

2.6.6.9 Discussion and Conclusions

However, since this is a new dosage form with no previous experience, the Division recommended that “Preclinical

Bridging Studies Comparing the Transdermal (Using the Proposed Patch Formulation) to the Intravenous Route of Administration will need to be Performed in Multiple Species Because the Route, Dosage Form and Duration are Different from What has been Approved". The sponsor conducted 2-week bridging toxicity studies in rats and dogs comparing the patches with the i.v. and oral formulations. In addition, published pharmacology, PK and toxicology studies with granisetron are provided in the NDA submission. The sponsor also conducted studies to examine the irritation and photosensitization potentials of the patch, and photogenotoxicity potential of granisetron. Toxicology studies with the patch in rats and dogs did not identify any new target organs of toxicity, and the toxicological profiles were similar for the patch, and i.v. and oral formulations. However, there were irritations at the site of application in both species. Thus, the new patch formulation does not raise any serious concerns about the adverse effects of the new dosage form of the drug.

Conclusions:

Thus continuous exposure of granisetron for 2 weeks through application of granisetron patch or continuous i.v. administration of granisetron hydrochloride showed similar toxicity profiles to granisetron administered orally once daily. No new target organs of toxicity were identified following application of the patch in rats and dogs. Thus, from a nonclinical standpoint the granisetron patch does not appear to have any serious safety concerns.

Unresolved toxicology issues (if any): None

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8 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Hugo Gallo Torres
7/24/2008 10:18:42 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-198
Submission Code N000

Letter Date 02 May 2007
Stamp Date 02 May 2007
PDUFA Goal Date 02 May 2008

Reviewer Name Karyn Berry, MD, MPH
Review Completion Date 14 July 2008

Established Name Granisetron
(Proposed) Trade Name Sancuso
Therapeutic Class 5-HT3 receptor antagonist
Applicant Strakan Pharmaceuticals Ltd

Priority Designation S

Formulation Transdermal Delivery System
Dosing Regimen 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.

Indication Prevention of nausea and vomiting in persons receiving moderately and/or highly emetogenic chemotherapy.

Intended Population Adults (aged 18 years and older)

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Karyn L. Berry, MD, MPH
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Sancuso® (Granisetron transdermal system)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Sancuso (granisetron Transdermal System) 52 cm² be approved for the prevention of prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no applicable activity related to risk management for this New Drug Application (NDA).

1.2.2 Required Phase 4 Commitments

Safety and efficacy have not been established in pediatric patients. This reviewer recommends that pediatric studies in ages 0 to 23 months be waived and pediatric studies in patients between 2 to 17 years of age be deferred.

This reviewer also agrees with the Clinical pharmacology division's recommendation to require additional pharmacokinetic studies to address the potential for altered delivery of granisetron TDS in patients with altered skin integrity, extremes in subcutaneous fat and to assess the impact of heat on the patch.

The following studies are required Phase 4 commitments:

- 1) Pharmacokinetic studies in the pediatric population to assess safety and tolerability and randomized, double-blind studies comparing granisetron TDS with granisetron I.V. in the pediatric population to assess safety and efficacy.
- 2) An in vivo pharmacokinetic study in subjects with differing levels of body fat (and thus subcutaneous fat) composition ranging from lean to obese (based on generally accepted IBW tables)
- 3) An in vivo pharmacokinetic study in elderly individuals.
- 4) A study to determine the impact of heat on drug delivery (either a validated in vitro model or if this model is not available, then a trial in healthy subjects).

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

Granisetron, a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist, is currently marketed in the United States under the name of Kytril, is available in injectable, oral and oral solution formulations. It is indicated for the prevention of chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV) and post operative nausea and vomiting (PONV).

Granisetron Injection was approved for use in the United States for the prevention of CINV in pediatric and adult patients in December 1993. Granisetron Tablets were approved in March 1995 to treat adult patients with CINV.

1.3.1 Brief Overview of Clinical Program

Two studies were submitted by the Applicant to evaluate the clinical efficacy and safety of Sancuso (granisetron TDS) 52cm² for the prevention of CINV in patients receiving moderately and/or highly emetogenic (ME and/or HE) chemotherapy for up to 5 consecutive days.

One Phase 3 study conducted in cancer patients undergoing multi-day chemotherapy with either moderately or highly emetogenic regimen (392MD/15/C) is considered pivotal. One Phase 2 study conducted in cancer patients undergoing single day ME chemotherapy (392MD/8/C) is considered supportive. A total of 810 patients were enrolled in the two cancer trials (404 patients in the granisetron TDS group and 406 patients in the oral granisetron group).

Three additional Phase 1 studies (392MD/4/C, 392MD/11/C and 392MD/26/C) conducted in healthy subjects were included in the safety assessment of granisetron TDS. A total of 236 healthy subjects were enrolled in these 3 studies.

1.3.2 Efficacy

Two clinical studies were submitted by the Applicant to provide data for the efficacy review to support the CINV indication being sought. These are: Phase 3 pivotal study (392MD/15/C) and a Phase 2 supportive study (392MD/8/C).

Sudy 392/15/C (pivotal) is a randomized, active control, double-blind, double-dummy, parallel group, multi-national study that assessed the efficacy, tolerability and safety of the granisetron transdermal delivery system (TDS) in CINV associated with the administration of ME or HE multi-day chemotherapy.

The primary efficacy endpoint was the percentage of patients achieving Complete Control (CC) of CINV (CC is defined by the Applicant as no vomiting and/or retching, no more than mild

nausea and no rescue medication) from the first administration until 24 hour after the start of the last day's administration of the ME or HE chemotherapy regimen.

Of note, the Applicant used different terminology to describe the endpoint than that used by the innovator, Kytril tablets. Kytril defined no vomiting, no moderate or severe nausea and no rescue medication as "Complete Response."

Study 392/8/C is a randomized, double-blind, double-dummy, multicenter, Phase II study designed to compare the efficacy, safety and tolerability of a granisetron transdermal patch with oral granisetron in CINV following a single day administration of ME chemotherapy.

Although the phase 2 study was submitted as supportive of the Phase 3 study, there were significant differences between many aspects of the two studies that may limit the supportive role of the Phase 2 trial. These differences included: primary endpoint (total control vs. complete control); primary assessment period (delayed phase vs. acute phase); duration of patch application (5 days vs. 7 days); duration of chemotherapy treatment (single day vs. multiple days); type of chemotherapy (moderately emetogenic vs. moderately/highly emetogenic) and efficacy analysis (superiority vs. non-inferiority). Differences also existed in characteristics of the study population (the inclusion/exclusion criteria, chemotherapy naivety versus non-naïve and concomitant use of dexamethasone).

In pivotal study, 392MD/15/C, treatment success rates at 0 to 24 hours after chemotherapy administration were 60.2% in the granisetron TDS group and 64.8% in the oral granisetron comparator group. The treatment difference (95% CI [-12.91, 3.13]) was within the predefined non-inferiority margin of 15%. The primary efficacy endpoint analysis (complete control [no emesis, no more than mild nausea and no use of rescue medication] during the acute phase of HEC/MEC chemotherapy) demonstrated non-inferiority between granisetron TDS 52 cm² and daily oral granisetron 2 mg.

Supportive study 392MD/8/C had a different primary efficacy endpoint than study 392MD/15/C. The results of the secondary endpoint analysis of complete control during the acute phase demonstrated no significant statistical difference between granisetron TDS 52 cm² and daily oral granisetron 2mg.

From a clinical standpoint, this reviewer concludes that granisetron TDS treatment success rates were similar to oral granisetron 2 mg daily in the prevention of CINV in moderately and/or highly emetogenic chemotherapy over a 5-day period.

1.3.3 Safety

Adverse events in the granisetron TDS clinical development program were similar to those attributable to other formulations of granisetron, with the exception of dermal tolerance. The majority of adverse events were gastrointestinal related. The most common related adverse event reported was constipation, which occurred in 5.4% of the granisetron TDS group and 3.0% in the oral granisetron group.

Sixteen deaths occurred during the 5 studies. All deaths were in the cancer group. Only one of the deaths (toxic megacolon) was reported by the sponsor as related to oral granisetron.

Of the 36 serious adverse events (SAE) seen in the cancer patient studies, the sponsor reported that four events were drug related. These 4 SAE were 3 QTc prolongations in the oral granisetron group and one constipation in the granisetron TDS group.

While overall, the patches were well tolerated, the results of the dermal tolerance studies in both healthy subjects and cancer patients suggest that the patches have the potential of mild irritation. Study 392MD/26/C also suggest that hypersensitivity reactions are possible with the granisetron patch, since one subject had a sensitivity reaction.

1.3.4 Dosing Regimen and Administration

The dose of granisetron TDS selected for both the Phase 2 and Phase 3 studies was based on results of the Phase 1 (healthy subjects) dose ranging study (392MD/11/C) which compared 15 cm², 33 cm² and 52 cm² patches with 2 mg oral granisetron.

The proposed 52 cm² patch is approximately equivalent to the 2 mg oral granisetron dose.

The dosing regimen and administration is to apply a single patch to the upper outer arm a minimum of 24 hours before chemotherapy administration. 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.

1.3.5 Drug-Drug Interactions

The Applicant reports that no studies were conducted to specifically investigate the potential for granisetron TDS to cause or result in drug-drug interactions. Granisetron is not known to induce or inhibit CYP-450 drug metabolizing enzyme systems in vitro.

1.3.6 Special Populations

Although granisetron I.V. has been studied, the safety and effectiveness of granisetron TDS has not been adequately assessed in sufficient numbers of patients with renal insufficiency, hepatic insufficiency, age ≥ 65 years, age < 18 years, Blacks or in women who are pregnant or nursing.

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

Clinical Review
Karyn L. Berry, MD, MPH
NDA 22198
Sancuso® (Granisetron transdermal system)

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trade name: Sancuso Transdermal System (Granisetron base)

Proposed Indication: Sancuso's proposed indication is for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.

Proposed Age Group: Adults (18 years of age and older)

Pharmacologic Class: Granisetron is a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist with little or no affinity for other serotonin receptors.

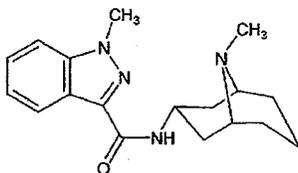
Route of Administration, Description, and Formulation: Sancuso is a 52cm² patch containing 34.3 mg of granisetron. The patch releases a mean of 3.1 mg of granisetron per 24 hours for up to 7 days. Sancuso is a thin, translucent, matrix-type transdermal patch that is rectangular in shape with rounded corners, consisting of a backing, the drug matrix and a release liner.

Proposed Treatment Regimen: The applicant proposes the following treatment regimen for the age group studied (ages 18 years and older): 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.

Chemical name of the main ingredient in Sancuso (granisetron):
1-methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide

Molecular formula: C₁₈H₂₄N₄O

Structural formula:



2.2 Currently Available Treatment for Indications

The American Society of Clinical Oncology's (ASCO) 2006 updated guidelines for antiemetics in oncology recommends the use of a 3-drug combination consisting of 1) a 5-HT₃ serotonin receptor antagonist, 2) dexamethasone, and 3) a NK-1 antagonist. This 3-drug regimen is to be administered before chemotherapy of high emetic risk. The 3-drug combination of a 5-HT₃ serotonin receptor antagonist, dexamethasone, and NK-1 antagonist is also recommended for patients receiving an anthracycline and cyclophosphamide "AC" regimen. For patients receiving chemotherapy of moderate emetic risk other than "AC" the ASCO recommends the 2-drug combination of a 5-HT₃ serotonin receptor antagonist and dexamethasone.

There are currently four (4) 5-HT₃ antagonist drugs that are FDA approved for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy. These are: Ondansetron, Granisetron, Dolasetron and Palonosetron. All four of these 5-HT₃ receptor antagonists are available in injectable (Intravenous) formulations and all except palonosetron are available in oral formulations.

Ondansetron hydrochloride (Zofran) was approved in January 1991. Its label states that efficacy of the single dose beyond 24 hours in these patients has not been established. Granisetron hydrochloride (Kytril) was approved in December 1993. It is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy. Dolasetron mesylate monohydrate (Anzemet) was approved in September 1997. It is currently indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. Palonosetron (Aloxi) was approved in July 2003. It is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Palonosetron is also indicated for the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

2.3 Availability of Proposed Active Ingredient in the United States

Granisetron, currently marketed in the United States under the name of Kytril, is available in injectable, oral and oral solution formulations. It is indicated for the prevention of chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV) and post operative nausea and vomiting (PONV).

Granisetron Injection (10 µg/kg) was approved for use in the United States for the prevention of CINV in pediatric and adult patients in December 1993. Granisetron Tablets were then approved in March 1995 to treat adult patients with CINV, and in July 1999 received approval for prevention of adult radiation-induced nausea and vomiting (RINV). In June 2001, Granisetron

Oral Solution was approved for the treatment of adult patients with CINV or RINV. In August 2002, Granisetron Injection was approved for the prevention and treatment of post operative nausea and vomiting in adult patients.

**Table 1: Granisetron
 Approved Indications**

Granisetron	Chemotherapy Induced Nausea and Vomiting	Radiation Therapy Induced Nausea and Vomiting	Post Operative Nausea and Vomiting (adults only)	Dose	Approved Age
Injection	December 1993	-	August 2002	10 mcg/kg (1 mg/ml)	Pediatric & Adult
Tablets	March 1995	July 1999		2 mg tab PO QD or 1 mg tab PO BID	Adult
Oral Solution	June 2001	June 2001		(2 mg/10 ml) 10 ml QD or 5 ml BID	Adult

2.4 Important Issues With Pharmacologically Related Products

As previously discussed, there are currently four 5-HT₃ receptor antagonist that are FDA approved for the prevention of CINV. As a class, 5-HT₃ receptor antagonists are generally perceived as safe. They have though been infrequently associated with cardiovascular adverse events, mainly hypertension, QT prolongation and rarely arrhythmias, such as atrial fibrillation.

However, the European Medicines Agency (EMA) has contraindicated the use of dolasetron in pediatric patients because of serious cardiovascular events associated with its use.

2.5 Presubmission Regulatory Activity

Summary of Key Applicant and Agency interactions related to IND 70,582 (Phase 3) and NDA 22-198

Table 2: Regulatory History

Date	Activity
January 11, 2005	Pre-IND meeting
January 31, 2005	Submission of sponsor pre-IND meeting minutes
December 30, 2005	IND submission including Phase 3 protocol
January 23, 2006	FDA response to IND submission

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January 25, 2006	SN002: sponsor's proposal for addressing FDA request for additional safety monitoring (ECGs and vital signs)
January 27, 2006	SN003: Protocol amendment
June 6, 2006	FDA comments on Phase 3 protocol
December 14, 2006	CMC Type B meeting
February 22, 2007	Type B – Face to Face meeting; pre-NDA

Source: Applicant's table

A pre-IND meeting was held with the applicant in January 2005 and a pre-NDA was held with the Applicant in February 2007. During the pre-IND meeting the Agency recommended changes to the Phase 3 study design and clinical protocols to include assessment for vital signs and 12 lead ECGs (measuring QTc). During the pre-NDA meeting held on February 22, 2007, the Agency denied the applicant's request for a full pediatric waiver and instead agreed to waive studies in patient birth to 12 years of age and defer studies on patients 13 to 17 years of age, citing a potential need in this patient population. Also during that meeting, the Agency agreed to a waiver from performing phototoxic and photoallergenicity studies in humans since the applicant intended to include in the label instructions to avoid direct exposure to sunlight.

2.6 Other Relevant Background Information

Granisetron is currently approved for use in the prevention of chemotherapy induced nausea and vomiting in Europe.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC Division stated that adequate information was provided for their review and this information was sufficient for assuring identity, strength, purity and quality of the drug product.

3.2 Animal Pharmacology/Toxicology

The Pharmacology Toxicology Division reviewed several new toxicology studies that were conducted to address the safety of the new transdermal formulation. In addition, published pharmacology, PK and toxicology studies with granisetron were provided in the NDA submission.

Pharmacology Toxicology reviewed two-week bridging toxicology studies comparing granisetron patches with i.v. and orally administered granisetron HCl conducted in rats and dogs. They found that application of granisetron patches produced increased severity of edema at the application sites compared to placebo patches. In rats, lymphocytic infiltration in the heart was observed in groups receiving the patch, and oral or i.v. granisetron, and interstitial nephritis in

the kidneys was observed in groups receiving the patch and the i.v. dose. In dogs, fatty infiltration in the liver and increased ALT levels were observed in groups receiving all three dosage forms. Pharmacology Toxicology concluded that sustained exposure of granisetron to rats and dogs for 2 weeks through application of granisetron patch or continuous i.v. administration of granisetron hydrochloride showed similar toxicity profiles to granisetron administered orally once daily. No new target organs of toxicity were identified following application of the patch in rats and dogs.

Per the Pharmacology Toxicology review, non-clinical safety issue relevant to clinical use was that granisetron was positive in the *in vitro* chromosome aberration assay in Chinese hamster ovary cells in the presence of UV irradiation. It was negative in the absence of UV irradiation. Thus, patients should avoid exposure to sunlight or any artificial sunlight while wearing and for at least 10 days after removing the patch.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data used in this review are the results of the submitted clinical trials with NDA 22-198 supporting granisetron transdermal system as indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 days. Other sources of clinical data consulted in this review include:

- Labeling for Kytril tablets and Kytril injection
- Electronic submission of the medical section of the NDA (including narratives and case report forms)
- Electronic submitted data sets
- Physicians Desk Reference
- Electronic orange book

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Table 34: Patch reaction during the induction phase – frequency of irritation scores

Parameters %	Baseline (N =201)	Day 8 (N = 201)	Day 15 (N =201)	Day 22 (N =201)
GTDS				
0: No reaction	100.00	45.27	51.74	47.76
1: Slight erythema	0	41.29	37.31	39.80
2: Moderate erythema	0	12.94	10.95	12.44
3: Severe erythema	0	0.50	0	0
4: Erythema with vesicles, erosion or bullae	0	0	0	0
Total N	100.00	100.00	100.00	100.00
Placebo				
0: No reaction	100.00	32.84	32.34	22.39
1: Slight erythema	0	44.78	47.26	49.75
2: Moderate erythema	0	19.40	15.42	22.39
3: Severe erythema	0	2.99	3.48	2.99
4: Erythema with vesicles erosion or bullae	0	0	1.49	2.49
Total N	100.00	100.00	100.00	100.00

Applicant's table study 392MD/26/C

Table 35: Patch adhesivity during the Induction Phase

Frequency n (%)	Day	Patch adhered >90%	Patch adhered 75-90%	Patch adhered 50-74%	Patch adhered <50%	Total
Granisetron	8	119 (59.20)	71 (35.32)	11 (5.47)	0 (0.00)	201
	15	168 (83.58)	31 (15.42)	2 (1.00)	0 (0.00)	201
	22	159 (79.10)	34 (16.92)	7 (3.48)	1 (0.50)	201
Placebo	8	139 (69.15)	55 (27.36)	7 (3.48)	0 (0.00)	201
	15	187 (93.50)	12 (6.00)	1 (0.50)	0 (0.00)	200 (*)
	22	181 (90.50)	16 (8.00)	3 (1.50)	0 (0.00)	200 (*)

(*) One missing data at Day 15 and Day 22 for the placebo patch
 Applicant's table 392MD/26/C

Table 36: Subjective symptoms during the Induction Phase on patch removal
Days

n (%)	Granisetron			Placebo		
	Days			Days		
	8	15	22	8	15	22

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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)

Applicant's table study 392MD/26/C

Table 37: Sensitization potential of GTDS and placebo

Sensitization reaction (N= 200)	n (%)
Negative	199 (99.5)
Equivocal	0
Positive	1 (0.50)

Applicant's table study 392MD/26/C

Table 38: Patch reaction during the challenge phase – frequency of irritation scores

Parameters %	30 min (N=200)	24 h (N=200)	48 h (N=200)	72 h (N=200)
GTDS				
0: No reaction	51.5	63.5	80	92
1: Erythema without edema	45.5	34.5	18	7
2: Erythema with edema or small papules	3	2	2	0.5
3: Erythema with individual vesicles	0	0	0	0.5
4: Erythema and swelling with blisters	0	0	0	0
Total N	100.00	100.00	100.00	100.00
Placebo				
0: No reaction				
1: Erythema without edema				
2: Erythema with edema or small papules				
3: Erythema with individual vesicles	0	0	0	0
4: Erythema and swelling with blisters	0	0	0	0
Total N	100.00	100.00	100.00	100.00

Applicant's table study 392MD/26/C

Medical Reviewer's comments: The active patch appeared to be less irritant than the placebo patch at all time points. The Applicant notes that this probably reflects the suppression of

cutaneous flare reactions by 5-HT₃ receptor antagonists. This seems like a plausible explanation of the finding. The active patch induced one positive contact allergic reaction, while no reaction was reported with the placebo. This finding suggests that hypersensitivity reactions are possible with the granisetron patch. The most common subjective symptom during the induction phase for both active and placebo patches was pruritis, followed by stinging.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

The Applicant did not collect data to look at the effects of withdrawal/rebound or drug abuse potential during the clinical development program. No withdrawal/rebound effects or abuse potential have been reported with other granisetron formulations.

7.1.13 Human Reproduction and Pregnancy Data

The Applicant reports that no information is currently available on the use of granisetron in pregnancy and no new information was collected as a result of the granisetron TDS development program. Precautions were enforced in all clinical trials to ensure that women of childbearing potential were not pregnant or nursing at the time of the study.

7.1.14 Assessment of Effect on Growth

Granisetron's effect on growth has not been studied.

7.1.15 Overdose Experience

The Applicant reports that no new information was collected during the granisetron TDS clinical development program about safety in overdose. There is no specific treatment for granisetron overdose and in the case of an overdose, the patch should be removed and symptomatic treatment should be given. The sponsor reports that overdose of up to 38.5mg of granisetron hydrochloride injection has been reported without symptoms or only the occurrence of a slight headache.

7.1.16 Postmarketing Experience

Granisetron TDS has not been approved in any country to date.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Safety data that were available as of 14 May 2007 were included in the integrated analysis of safety to provide a comprehensive safety profile for granisetron TDS in healthy subjects and

cancer patients. The safety data relate to deaths, serious adverse events, withdrawals, adverse events and skin tolerability. A total of 5 clinical trials were completed during the granisetron TDS clinical development program. These consisted of 2 pharmacokinetic studies, 1 skin irritation and sensitization study and 2 efficacy studies. All of these studies were included in the integrated safety database.

7.2.1.1 Study type and design/patient enumeration

Table 39: Studies contributing safety information to the granisetron integrated safety database

Study Location	Design	Indication	Primary Endpoints	Total (safety set)	Granisetron TDS			Comparator	Duration Of patch Exposure (days)	M/F Mean Age (range) B/W/O
					15 cm ² patch	33 cm ² patch	52 cm ² patch			
Healthy Subject Studies										
392MD/4/C Germany	Randomized, placebo controlled	BA/PK	Safety (AEs, labs, ECG), PK	12 (12)	12	-	-	Placebo patch (12)	5	50% M 50% F 31 (23-39) All W
392MD/11/C Germany	Dose ranging, 4 - arm, randomized, crossover	BA	Dose ranging, Safety (AEs, labs, ECG), PK	12 (12)	12	12	12	Oral granisetron 2 mg (12)	6	100%M 37(25-42) All W
392MD/26/C France	Randomized, placebo controlled sensitization & irritation study	S&I	S&I, safety (AEs, labs, ECG), PK	212 (212)	-	-	212	Placebo patch (212)	Induction phase: 21 (3 sequential patches, 7d each) Challenge phase: 2	25%M 75%F 37 (19-64) 97%W 3%O
Cancer Patient Studies										
392MD/8/C Germany	Phase 2 (supportive) Randomized, active control double-blind, double dummy	CINV Single day chem.	TC of nausea & vomiting, Safety (AEs, labs, ECG)	179 (173)	-	-	88	Oral granisetron 2 mg (85)	5	36.8% M 63.2%F 60.6 (33-83) 99%W 1%O
392MD/15/C Multi-national	Phase 3 (pivotal) Randomized, active control, double blind, double dummy, parallel-group	CINV Multi day chemo	CC of nausea & vomiting, Safety (AEs, labs, ECG)	641 (637)	-	-	316	Oral granisetron 2 mg (321)	7	49%M 51%F 54.4 (16-86) 77%W 23%O

Source: Modified applicant's table from integrated summary of safety
 BA= Bioavailability, PK=Pharmacokinetics, n=number of subjects, S & I=sensitization and irritation, CINV=Chemotherapy induced nausea and vomiting, AEs=Adverse events, TC=Total control, CC=Complete control, M=Male, F=Female, B=Black, W=White, O=Other

7.2.1.2 Demographics

Table 40: Demographic data – healthy population

Variable	15 cm2 patch (N = 24)	33 cm2 patch (N = 12)	52 cm2 patch (N = 224)	Granisetron TDS all sizes (N = 236)
Gender (N [%])				
Male	18 (75%)	12 (100%)	66 (29.5%)	72 (30.5%)
Female	6 (25%)		158 (70.5%)	164 (69.5%)
Age (years)				
Mean ± SD	34.3 ± 5.8	37.1 ± 4.8	36.9 ± 10.6	36.6 ± 10.4
Median	34.5	38.0	36.5	36.0
Range	23.0-42.0	25.0-42.0	19.0-63.0	19.0-63.0
Ethnic group (N [%])				
Caucasian	24 (100%)	12 (100%)	217 (96.9%)	299 (97%)
Other			7 (3.1%)	7 (3%)
Weight (kg)				
Mean ± SD	72.5 ± 11.7	76.8 ± 9.0	65.3 ± 12.1	65.4 ± 12.1
Median	72.5	75.5	63.0	63.0
Range	46.0-92.2	64.1-92.2	44.0-104.0	44.0-104.0
BMI (kg/m²)				
Mean ± SD	23.6 ± 2.6	24.2 ± 2.8	23.3 ± 3.8	23.2 ± 3.8
Median	23.0	24.1	22.5	22.5
Range	20.0-27.9	20.0-27.9	17.6-39.1	17.6-39.1

Source: Modified from Applicant's table in Integrated Summary of Safety
 BMI = Body Mass Index

Table 41: Demographic data - cancer patients

	Granisetron TDS 52 cm ² (N = 404)				Oral Granisetron (N = 406)			
	Mean	SD	Median	Range	Mean	SD	Median	Range
Age (years)	55.1	12.5	56.0	17-83	56.2	13.2	57.0	16-86
Weight (kg) ^{1,2}	68.0	15.1	66.3	31-139	68.7	15.4	67.5	36-134
Height (cm) ²	165.3	9.9	165.0	139-195	165.3	10.3	165.0	106-193
BMI (kg/m ²) ^{1,2}	24.8	5.0	24.4	14.3-51.9	25.2	6.4	24.5	14.2-106.8
	Number (n)		Percentage %		Number (n)		Percentage %	
Age Group								
<65 years	306		75.7		278		68.5	
65-74 years	78		19.3		104		25.6	
75+ years	20		5.0		24		5.9	
Gender								
Male	185		45.8		192		47.3	
Female	219		54.2		214		52.7	
Ethnic Origin³								
White	328		81.2		335		82.5	
Asian	46		11.4		35		8.6	
Hispanic/Latino	30		7.4		32		7.9	

Black/African American	-	-	1	0.2
Other	-	-	2	0.5
Non-Disclosure	-	-	1	0.2

Source: Applicant's table Integrated Summary of Safety

7.2.1.3 Extent of exposure (dose/duration)

Overall, 640 persons were exposed to granisetron TDS. The majority of healthy subjects wore the 52 cm² patch for a minimum of 6 days (range from 1 to 23 days). 202 healthy subjects wore the 52 cm² patch for 23 days. All the cancer patients were exposed to the 52 cm² patch. The majority of cancer patients wore the patch for 7 days (range from 1 to 11 days). The majority of cancer patients exposed to oral granisetron received it for 3 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Postmarketing experience

Granisetron TDS is not approved in any country.

7.2.2.2 Literature

The Applicant's literature search was adequate.

7.2.3 Adequacy of Overall Clinical Experience

The database is sufficiently large to allow for adequate assessment of the safety profile of granisetron TDS, although events that occur rarely may not have been detected.

In general the demographics of patients treated with granisetron TDS are adequate for the purposes of analyzing the safety of granisetron TDS for the prevention of CINV. The number of non-Caucasian patients exposed to granisetron TDS was small. It is not known whether granisetron TDS would be appreciably different in non-Caucasian populations. The experience with granisetron TDS in the pediatric and geriatric populations is incomplete, therefore the safety data currently available can not necessarily be extrapolated to children, adolescents and older patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The animal and/or in vitro testing data submitted by the Applicant as a part of the application was considered adequate by the Pharmacology/Toxicology Review Team.

7.2.5 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate. The methods for obtaining laboratory, vital signs, and adverse event data in the development program are described in the relevant sections (7.1.5 Common Adverse Events, 7.1.7 Laboratory Finding, 7.1.8 Vital Signs).

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The clinical pharmacology data submitted by the Applicant as a part of the application was considered adequate by the Clinical Pharmacology Review Team (see section 5).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The database is sufficiently large to allow for adequate assessment of the safety profile of granisetron TDS. Although the assessment for these events has been adequate, there is limited data to allow for detection of adverse events that are rare. Adverse events that require a long duration exposure to occur are unlikely to be captured since the patch is intended for use for at most of seven days.

Adverse events of particular concern for granisetron TDS include the following: 1) constipation and 2) dermal tolerance (irritation and hypersensitivity). Other than the dermal tolerance concerns, which are inherent to the new formulation, the adverse event profile of granisetron TDS is similar to Kytril oral tablets as per the label.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of adequate quality.

7.2.9 Additional Submissions, Including Safety Update

N/A

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Across the studies 1,056 healthy subjects and cancer patients were included in the database, and 1,046 healthy subjects and patients were included in the safety summary. Two hundred and

thirty-six (236) healthy subjects received granisetron TDS and 12 subjects received oral granisetron. Four hundred and four (404) cancer patients received granisetron TDS and 406 patients received oral granisetron.

Overall, the healthy subjects had a higher incidence of Treatment Emergent Adverse Events (TEAEs) with granisetron TDS (80%) compared to cancer patients (42%). In cancer patients the overall incidence of TEAEs similar between granisetron TDS and oral granisetron. The most common adverse event reported (> 1%) in both groups of cancer patients involved the gastrointestinal system.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Applicant's primary safety data presentations were based on pooled data from all studies (healthy subjects and cancer patients).

7.4.1.2 Combining data

This review pools studies by simple combination of numerators and denominators and does not employ other pooling procedures.

7.4.2 Explorations for Predictive Factors

7.4.3 Causality Determination

Dermal tolerance (irritation and sensitivity) and constipation were observed by the Applicant to have occurred close to the time of granisetron TDS administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The DOSAGE AND ADMINISTRATION section of the proposed label describes the following:

b(4)

8.2 Drug-Drug Interactions

The sponsor reports that no studies were conducted to specifically investigate the potential for granisetron TDS to cause or result in drug-drug interactions. Granisetron is not known to induce or inhibit CYP-450 drug metabolizing enzyme systems in vitro.

8.3 Special Populations

Although granisetron I.V. has been studied, the safety and effectiveness of granisetron TDS has not been adequately assessed in sufficient numbers of patients with renal insufficiency, hepatic insufficiency, age ≥ 65 years, age < 18 years, Blacks or in women who are pregnant or nursing.

8.4 Pediatrics

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

The sponsor has been granted a deferral for studies in children aged 2 to 17 years of age.

8.5 Advisory Committee Meeting

There was no Advisory Committee meeting required for this NDA because there is considerable experience with other granisetron formulations, such as I.V., tablets and oral solution and because there are no new concerns related to the safety or efficacy of granisetron TDS that would require recommendations from an Advisory Committee.

8.6 Literature Review

A brief review of the scientific literature was conducted.

8.7 Postmarketing Risk Management Plan

In this NDA, there are no applicable issues related to risk management.

8.8 Other Relevant Materials

The review of this application included consultation from the Division of Drug Marketing, Advertising and Communication, and the Office of Surveillance and Epidemiology

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant submitted the results of 5 clinical studies (2 pharmacokinetic studies, 1 skin irritation and sensitization study and 2 efficacy studies) to support the indication of granisetron TDS for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.

Efficacy

This reviewer concludes that in Study 392MD/15/C (pivotal study), the primary efficacy analysis (complete control [no emesis, no more than mild nausea and no use of rescue medication] during the acute phase of HEC/MEC chemotherapy) demonstrated non-inferiority between granisetron TDS 52 cm² and daily oral granisetron 2mg. Treatment success rates were 60.2% in the granisetron TDS group and 64.8% in the oral granisetron group. The treatment difference (95% CI [-12.91, 3.13]) was within the predefined non-inferiority margin of 15%.

The reviewer concludes that though the supportive study 392MD/8/C had a different primary efficacy endpoint, the secondary endpoint of complete control during the acute phase demonstrated no significant statistical difference between granisetron TDS 52 cm² and daily oral granisetron 2mg.

Safety

Across the two cancer studies (392MD/8/C and 392MD/15/C), 404 patients received granisetron TDS and 406 patients received oral granisetron for approximately 6 to 7 days.

Adverse events were similar to those attributable to other formulations of granisetron, with the exception of dermal tolerance. The majority of adverse events were gastrointestinal related. The most common adverse event reported was constipation. This occurred in 5.4% of the granisetron TDS group and 3.0% in the oral granisetron group.

Sixteen deaths occurred during the 5 studies. All deaths were in the cancer group. Only one of the deaths (toxic megacolon) was reported as the sponsor as drug related oral granisetron.

Thirty-six (36) serious adverse events seen in the cancer patient studies, the sponsor reported that four events were drug related. Three (3) QTc prolongations in the oral granisetron group and one constipation in the granisetron TDS group.

In the safety population, 3 adverse events were recorded for application site pruritis and one case of edema. Of these, 2 of the pruritis cases and the edema were reported to be related to the study medication. While overall, the patches were well tolerated, the results of the dermal tolerance studies in both healthy subjects and cancer patients suggest that the patches have the potential of

mild irritation. Study 392MD/26/C also suggest that hypersensitivity reactions are possible with the granisetron patch, since one subject had a sensitivity reactions.

9.2 Recommendation on Regulatory Action

This reviewer recommends that granisetron TDS 52 cm² be approved for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days. The information in this submission provides the evidence to support the proposed indication and there are data to provide adequate directions for use.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no applicable activity related to risk management for this NDA.

9.3.2 Required Phase 4 Commitments

The Applicant should commit to undertake the following studies related to 1) pediatric safety and effectiveness and 2) efficacy and PK data needed to assess the potential for altered drug delivery and efficacy in patients with altered skin integrity due to advanced age or poor nutritional status related to chronic illness.

Safety and efficacy have not been established in pediatric patients. A deferral was granted for patients aged 2 to 17 years of age and a waiver for patients 0 to 23 months of age. The Applicant has agreed to conduct studies in patients aged 2 to 17 years of age.

The Clinical Pharmacology division requires additional pharmacokinetic studies to address the potential for altered delivery of the granisetron TDS in patients with altered skin integrity or extremes in subcutaneous fat and the impact of heat on drug delivery. These issues could possibly lead to altered drug efficacy in these patients.

While an in vivo pharmacokinetics study in healthy adults and a limited sampling study in patients receiving chemotherapy have already been conducted, there is a lack of PK data from patients who have altered skin integrity due to advanced age or poor nutritional status related to chronic illness. Heat, either through a heating pad or other external source, is another factor that has been demonstrated to markedly increase the rate of drug absorption into the systemic circulation from transdermal dosage forms.

The following studies are required Phase 4 commitments:

- 1) Pharmacokinetic studies in the pediatric population (aged 2 to 17 years) to assess safety and tolerability and randomized, double-blind studies comparing granisetron TDS with granisetron I.V. in the pediatric population (aged 2 to 17 years) to assess safety and efficacy.
- 2) An in vivo pharmacokinetic study in subjects with differing levels of body fat (and thus subcutaneous fat) composition ranging from lean to obese (based on generally accepted IBW tables)
- 3) An in vivo pharmacokinetic study in elderly individuals.
- 4) A study to determine the impact of heat on drug delivery (either a validated in vitro model or if this model is not available, then a trial in healthy subjects).

9.3.3 Other Phase 4 Requests

N/A

9.4 Labeling Review

Discussions between the Applicant and CDER have resolved major issues with regard to the label. Several significant changes have been made to the Applicant's proposed label.

9.5 Comments to Applicant

The Phase 4 commitment studies should be conveyed to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Not attached

10.2 Line-by-Line Labeling Review

Not attached

REFERENCES

Clark RA, Grall RJ. Delayed emesis: a dilemma in anti-emetic control. Support Care Cancer 1993; 4:182-185.

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