DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-198 **NDA APPROVAL**

Strakan International, Ltd.
Attention: Mary Ellen Norvich, Ph.D.
Vice President, US Regulatory Affairs
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norvich:

Please refer to your new drug application (NDA) dated June 29, 2007, received July 2, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sancuso (granisetron) transdermal system.

We acknowledge receipt of your submissions dated July 23, August 23, October 8, October 12, November 21, and December 7, 2007; and January 23, March 5, March 6, March 20, April 1, April 16, April 25, May 5, May 13, May 28, May 29, June 19, July 15, August 14, and September 10, 2008.

This new drug application provides for the use of Sancuso (granisetron) transdermal system for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 2 years because necessary studies are impossible or highly impracticable. This is because many childhood cancers are uncommon and it is difficult to standardize a multi-center study or conduct a single center protocol in a sufficient number of patients.

We are deferring submission of your pediatric studies for ages 2 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

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.

Protocol Submission:	February 28, 2010
Study Start:	June 30, 2010
Final Report Submission:	February 29, 2012

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.

Protocol Submission:	February 28, 2010
Study Start:	June 30, 2011
Final Report Submission:	January 31, 2013

Submit final study reports to your NDA 22-198. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of QT prolongation observed in the cardiac safety evaluations included in your study 392MD/15/C. The pharmacokinetic profile associated with this new transdermal formulation of granisetron may pose unanticipated cardiac risks. In addition, some published reports have suggested that some 5-HT_3 receptor antagonists, including granisetron, are associated with ECG abnormalities.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess a serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of QT prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial:

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

The timetable you submitted on August 14, 2008 states you will conduct this trial according to the following timetable:

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

Submit the protocol to your IND 70,582 with a cross-reference letter to this NDA 22-198. Submit the final report to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We acknowledge your written commitment to conduct the following postmarketing studies as described in your submission dated September 10, 2008, as outlined below:

4. 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

5. 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

6. 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

Submit clinical protocols to your IND 70,582. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the submitted labeling (package insert submitted August 14, 2008, patient package insert submitted July 15, 2008). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-198."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels (submitted July 15, 2008) as soon as they are available, but no more than 30 days after they are printed. It is acceptable to change "h" to "hours" at the next printing of the patch backing. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA22-198**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, call Thomas Moreno, Regulatory Project Manager, at (301) 796-2247.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donna Griebel

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