

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-198

CHEMISTRY REVIEW(S)

NDA 22-198

Sancuso (Granisetron Transdermal System), 3.1 mg/24 hours

Strakan International Ltd.

Rao Puttagunta, Ph.D.

**Branch III/Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research**

**Reviewed for
The Division of Gastroenterology Products, HFD-180**

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Chemistry Review Data Sheet

1. NDA #: 22-198
2. REVIEW #: 1
3. REVIEW DATE: 30-JUN-2008
4. REVIEWER: Rao Puttagunta, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	29-JUN-2007
Amendment (BC)	23-JUL-2007
Amendment (BC)	16-APR-2008
Amendment (BC)	25-APR-2008
Amendment (BC)	13-MAY-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Strakan International Ltd.
Address: Galabank Business Park
Galashiels, TD1 1QH
UK
Representative: Mary Ellen Norvitch, Ph.D.
Vice President, US Regulatory Affairs
Prostrakan, Inc. (A subsidiary of Strakan International Ltd.)
1430 State Highway 206, Suite 110
Bedminster, NJ 07921
Telephone: 908-234-1096 x203

8. DRUG PRODUCT NAME/CODE/TYPE:
- a) Proprietary Name: SANCUSO®
 - b) Non-Proprietary Name (USAN): Granisetron Transdermal System
 - c) Code Name/# (ONDQA only): N/A
 - d) Chem. Type/Submission Priority (ONDQA only):

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

RLD: Kytril (Granisetron HCl), Roche, NDA 20-239 (Injection), NDA 20-305 (Tablet), and NDA 21-238 (Oral Solution)

10. PHARMACOL. CATEGORY: 5-HT₃ Receptor Antagonist

11. DOSAGE FORM: Patch

12. STRENGTH/POTENCY: 3.1 mg/24 h (34.3 mg/patch)

13. ROUTE OF ADMINISTRATION: Transdermal

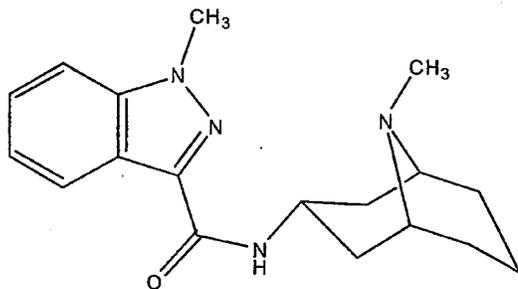
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name: 1-Methyl-N-(9-methyl-endo-9-azabicyclo[3.3.1]non-3-yl)-1H-indazole-3-carboxamide

Molecular Formula: C₁₈H₂₄N₄O

Molecular Weight: 312.4

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II		Granisetron	1	Adequate	4/04/08 (R. Puttagunta)	---
	IV			3	Adequate	2/25/02	---
	IV			4	---	---	21 CFR §177.1630, §174.5
	III				---	---	21 CFR §175.300, §175.320 §176.170, §176.180
	IV			4	---	---	21 CFR §73.1, §73.312, §73.1, §73.575, §73.1575, §175.105, §175.300
	IV			4	---	---	21 CFR §177.1630, §177.1315, §175.300
	IV				---	---	21 CFR §176.170, §177.1520, §175.105

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,582	Granisetron Transdermal Patch

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	8/06/07	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A per new ONDQA policy		
DMETS (DMEP)	Acceptable	5/02/08	Richard Abate,
DDMAC	Acceptable	5/02/08	Review of Richard Abate
EA	Categorical Exclusion		Rao Puttagunta
Microbiology	N/A		

The Chemistry Review for NDA 22-198

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

Granisetron is manufactured by _____ The CMC information on granisetron base was referenced to DMF _____. The DMF has been reviewed and found to be adequate. The drug substance specification was stated to be based on the Ph. Eur. Monograph for granisetron HCl. This is adequate because the manufacturing process is the same as that used for granisetron HCl except for the absence of the _____ The supplier also tests the drug substance for residual solvents.

b(4)

b(4)

2. Drug Product:

The drug product Sancuso® (granisetron transdermal system) is a thin, translucent, matrix-type transdermal patch that is rectangular-shaped with rounded corners consisting of a backing, the drug matrix and a release liner. Sancuso® is a 52 cm² patch containing 34.3 mg of granisetron. The patch releases 3.1 mg of granisetron per 24 hours for up to 7 days.

Each patch is printed on one side with the words "Granisetron 3.1 mg/24 h." Each patch is packaged in a separate sealed foil-lined plastic pouch. The sealed patches are supplied in cartons in 1 and 3 patch counts.

CHEMISTRY REVIEW

Executive Summary Section

The drug product is labeled for storage at controlled room temperature of 20-25°C (68-77°F).

The only inactive ingredient in the adhesive blend is: _____ . This is not a compendial ingredient. However, this adhesive is used in currently approved products of the same dosage form. Other components in the drug patch are the: _____
_____ Release Liner. Appropriate DMF references were provided for these components, but references were provided in the application to appropriate CFR section to support their suitability. The specifications for these components were included.

b(4)

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.

The drug product container closure system (pouch) material was referenced to DMF _____. However, CFR references were provided to the appropriate CFR sections for suitability the pouch material.

b(4)

Although the applicant proposed a _____ expiration date, based on the submitted drug product stability data for up to 24 months, _____
_____ a 24-month expiration date is granted.

b(4)

Sancuso (Granisetron Transdermal System) is packaged as a single patch with a slip-sheet, within a sealed foil-lined pouch. The pouch is packaged in a cardboard carton.

Granisetron Transdermal System is supplied in a individually sealed pouches, and a single pouch packaged in a carton.

B. Description of How the Drug Product is Intended to be Used

Sancuso® (granisetron trans dermal delivery system), 3.1 mg/24 hr, is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 days. A single transdermal system (patch) is applied 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. The patch is removed 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.

The patch is should be applied directly after the pouch has been opened. The 52 cm² patch contains 34.3 mg of granisetron delivering 3.1 mg per 24 hours. The patch should not be cut into pieces.

Executive Summary Section

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.

C. Basis for Approvability or Not-Approval Recommendation

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.

Therefore, the NDA 22-198 is recommended for approval from the CMC perspective.

III. Administrative

A. Reviewer’s Signature

Rao Puttagunta {electronic signature}

B. Endorsement Block

Moo-Jhong Rhee {electronic signature}
Branch Chief, DPAIL, ONDQA

C. CC Block

N/A

40 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Rao Puttagunta
7/7/2008 05:22:28 PM
CHEMIST

Moo-Jhong Rhee
7/7/2008 05:30:13 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 22-198
Applicant: STRAKAN
Stamp Date: 6/29/2007
Received by PAL: 7/9/2007
Review Date: 7/27/2007
PDUFA Date: 5/2/2008
Filing Meeting: 8/23/07
Proposed Trademark: SANCUSO®
Established Name: granisetron
Dosage Form: patch
Route of Administration: transdermal
Indication: nausea and vomiting with chemotherapy

P.A.L.: Marie Kowblansky, PhD

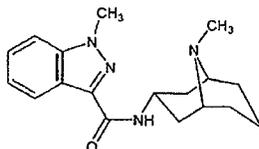
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

A. Summary

The SANCUSO® Granisetron Transdermal Delivery System (granisetron TDS), or patch, is intended for the prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy. This product, which was studied under IND 70,582, is being filed as a 505(b)(2) application. The 52 cm² patch, with a granisetron content of 34.3 mg per patch and a flux of —mg/24 h, is intended for application to the upper arm between 24 and 48 hours before chemotherapy and removal 24 hours after completion of chemotherapy. It can be worn for up to 7 days, depending on the duration of the chemotherapy regimen. Since granisetron may be degraded by light, the patch application site must be covered (e.g. with clothing) throughout the period of wear and for 10 days following its removal. The label recommendation is not to store the product above 25°C

Drug Substance

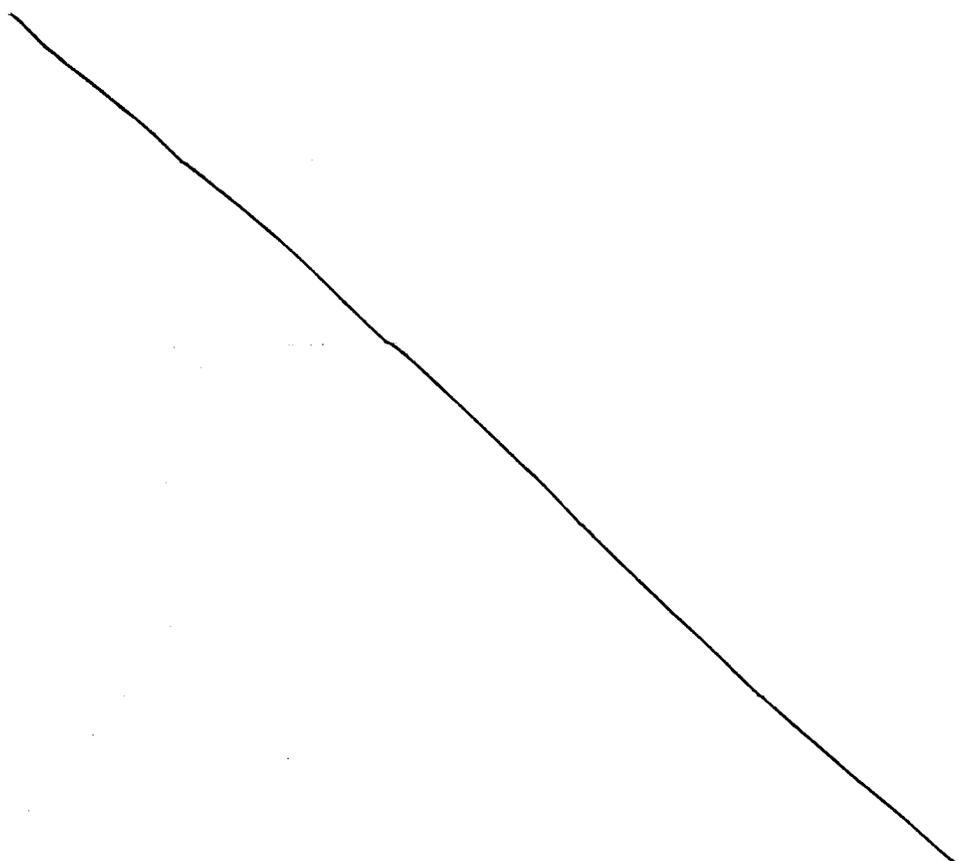
The active drug substance in the patch is granisetron



Although all currently approved oral and I.V. products containing granisetron use the _____ their formulations, the current product uses _____

_____ The granisetron base will be manufactured by _____ Only limited

b(4)



b(4)

b(4)

Initial patches for Phase 1 and 2 clinical trials were manufactured at _____ For Phase 3 trials, manufacture of the product was transferred to Aveva DDS, where the proposed commercial product will be manufactured. According to the applicant, the formulation and the basic process have not changed from the start of the Phase 1 clinical program, although some process scale-up and technology transfer was required prior to initiating the Phase 3 study. The _____ ng/24 h flux which is claimed for the commercial product was determined on healthy subjects using Aveva-produced product.

b(4)

The finished product specification includes testing for appearance, identification, potency, content uniformity, related substances, dissolution (testing at 6, 24, 48, 72, and 96 hours), microbial limits, peel force, adhesion, and residual solvents _____
Dissolution acceptance limits are in accord with USP recommendations for modified release dosage forms. _____

b(4)

_____ Limits of _____ are set for individual known and unknown impurities at release and at _____ at expiry. For a drug product with a daily dose of _____ mg per day, the proposed limit of _____ for unidentified impurities at release conforms to ICH guidance, but the proposed _____ limit at expiry exceeds ICH recommendations.

b(4)

Up to 12 months of real time (25°C) and accelerated stability data are supplied for three primary batches of the product manufactured at Aveva DDS. Although the data for these batches do not

show trends indicative of instability, it should be noted that stability data for product manufactured at _____ (which was used in Phase 1 and 2 trials) and early batches of product manufactured at Aveva (used for supporting stability data, but not used in clinical trials) _____

b(4)

The proposed product name is SANCUSO® (Granisetron Transdermal System)

Strakan International Ltd. appropriately claims categorical exclusion from the requirement for submitting an environmental assessment on the basis that the estimated concentration of granisetron at the point of entry into the aquatic environment will be below 1 part per billion (ppb).

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

B. Critical issues for review

For the drug substance:

-- The proposed acceptance criteria for residual solvents meet ICH requirements (ICH Q3C), but greatly exceed the levels observed in any of the batches for which data have been provided. Also, many of the solvents for which limits are proposed are not observed in any of the batches. The need for such a large list of residual solvents and such liberal acceptance criteria should be closely evaluated.

b(4)

For the drug product:

b(4)

-- The acceptance criterion for unidentified impurities should be lowered to _____ to conform to ICH requirements. All impurities exceeding this limit will need to be identified.

-- The backing material for the commercial product is different from what was used in clinical and stability batches. Although the applicant argues that the new backing material _____ and the previously used material _____ are very similar, the differences need to be closely assessed to determine if additional stability studies will be required.

b(4)

b(4)

-- Label recommendations are not to store the product above 25°C (with excursions permitted to 30°C). This statement implies that storage at refrigerated conditions would be acceptable. The storage recommendation should be closely scrutinized, since it does not appear that any stability studies were conducted below 25°C.

-- Since the flux was determined from clinical data, the reviewer should determine in consultation with the Biopharmaceutics reviewer if the labeled value of ~~—~~mg/24 h is correct and in accord with labeling conventions for this type of product.

b(4)

-- The proposed product name should be evaluated for conformance to FDA conventions for this type of delivery system.

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

8/6/2007
Date

Moo-Jhong Rhee, PhD
Branch Chief

8/6/2007
Date

NDA 22-198

Manufacturing Sites

Drug substance (DMF) _____

b(4)

Drug product

Aveva Drug Delivery Systems, Inc
3250 Commerce Parkway,
Miramar, Florida 33025 USA

APPEARS THIS WAY ON ORIGINAL

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

/s/

Marie Kowblansky
8/7/2007 05:35:42 PM
CHEMIST

Moo-Jhong Rhee
8/8/2007 03:39:37 PM
CHEMIST
Chief, Branch III