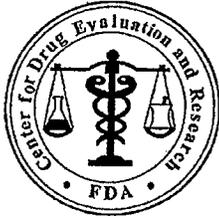


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-198

**RISK ASSESSMENT and RISK
MITIGATION REVIEW(S)**



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 27, 2008

To: Donna Griebel, M.D., Director
Division of Gastroenterology Products

Through: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Patient Labeling and Education Team
Division of Risk Management (DRISK)

Subject: Review of Patient Labeling

Drug Name(s): Sancuso (granisetron transdermal system)

Application Type/Number: NDA 22-198

Applicant/sponsor: Strakan International Limited

OSE RCM #: 2008-1577

1 INTRODUCTION

Strakan International Limited submitted an original New Drug Application, NDA 22-198 for Sancuso (granisetron transdermal system) on June 29, 2007. The 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. The proposed labeling for this submission is in PLR format and includes patient labeling in the form of a Patient Package Insert (PPI) with patient instructions for applying Sancuso.

This review is written in response to a request from the Review Division to review the patient labeling submitted for this NDA.

2 MATERIAL REVIEWED

- SANCUSO (granisetron transdermal system) Patient Package Insert (PPI) submitted June 29, 2007 and further revised by the Review Division on May 15, 2008
- SANCUSO (granisetron transdermal system) Patient Instructions for Use submitted June 29, 2007 and further revised by the Review Division on May 15, 2008
- SANCUSO (granisetron transdermal system) Prescribing Information (PI) submitted June 29, 2007 and further revised by the Review Division on May 15, 2008

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.0, and a Flesch Reading Ease score of 60.9. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the PPI, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- rearranged information to be consistent with PLR format
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The Review Division should consult with the Safety Requirements Team as soon as possible to see if this product needs a Risk Evaluation and Mitigation Strategy (REMS).
2. A PPI for Sancuso (granisetron transdermal system) is voluntary. Unless the product is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. The sponsor should state their mechanism for intended distribution of the PPI to patients.

3. The name Sancuso is very different from other formulations of granisetron, specifically Kytril. We have added a statement to the PPI section "What is SANCUSO?" in a box for emphasis:

Important: SANCUSO contains granisetron, the same medicine in Kytril. Do not take Kytril at the same time you use SANCUSO unless your healthcare provider tells you it is alright."

We also recommend that this language be added to the PI, such as in section 17 Patient Counseling Information. We note that the title of section 17 is missing in the PI.

4. The Daytrana patch has a Medication Guide with patch instructions for use that contains a description and figure showing the layers of the patch. Consider this approach for Sancuso.
5. The SANCUSO PI is in PLR format. If the Review Division determines that hypersensitivity reactions

b(4)

6. In the section "What should I avoid while using Sancuso?" the sponsor states: _____ may be affected by direct sunlight or exposure to sunlamps."

- _____
- Patients need to know the difference between photosensitivity and other skin reactions seen with SANCUSO. _____

b(4)

_____ The sponsor should clarify if tanning beds should also be added.

7. The sponsor includes language in the PPI telling patients that if the patch becomes unstuck, they can "use surgical bandages or medical adhesive tape to keep the patch in place." The sponsor should clarify whether there is data to support the use of surgical bandages or medical adhesive tape to secure the patch. Additionally, the sponsor should clarify whether the bioavailability of the drug is altered and whether the patch remains

effective if surgical bandages or medical adhesive tape must be employed to secure the patch in place.

8. We have added the statement, "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Sancuso, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

16 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Other- 1

**This is a representation of an electronic record that was signed electronically and
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/s/

Sharon Mills
5/27/2008 04:39:26 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
5/27/2008 09:19:14 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April, 14 2008

To: Donna Griebel, MD
Director, Division of Gastroenterology Products, HFD-180

Through: Kellie Taylor, Pharm D, MPH, Team Leader
Denise Toyer, Pharm D, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention, HFD-420

From: Richard Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention, HFD-420

Subject: Label and Labeling Review for Sancuso

Drug Name(s): Sancuso (Granisetron) Transdermal System

Application Type/Number: NDA # 22-198

Applicant: Straken International Limited

OSE RCM #: 2007-1573

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EXECUTIVE SUMMARY

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) Transdermal System which may lead to medication errors. Moreover, the design of this dosage form may predispose this product to be used incorrectly. A primary concern centers on the Applicant's attempt to address the potential adhesive problem inherent in the patch dosage forms with product labeling. We also question whether all of the information and statements regarding use of the patch are supported by the data collected in controlled studies. As some data provided by the Applicant is under review, we plan to further discuss our concerns during the team labeling meetings for Sancuso. The Division of Medication Error Prevention's recommendations for label and labeling modifications are found in Section 5.2.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Gastroenterology (HFD-180), to review the transdermal patch label, container labels, carton and insert labeling for Sancuso (granisetron) transdermal system. The proposed proprietary name was reviewed without objection in OSE review # 2007-1573, on March 18, 2008.

1.2 PRODUCT INFORMATION

Sancuso (granisetron) is indicated for the prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy for up to five consecutive days. The patch is a new dosage form for granisetron. The patch, applied 24 to 48 hours prior to chemotherapy, delivers — mg of granisetron per 24 hour period and may be worn for up to seven days. The patch should not be removed for at least 24 hours after chemotherapy cycle is completed.

b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Medication Error Prevention Staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the Medication Error Prevention Staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on June 29, 2007 the following labels and insert labeling for the Division of Medication Error Prevention review (see Appendix A, B, and C for images):

- Patch Label: — ng/24 hours
- Pouch Labeling
- Carton Labeling (1 Patch)
- Carton Labeling (3 Patches)
- Prescribing Information (no image)

b(4)

3 RESULTS

Upon review of the patch labels, pouch, and carton labeling, we noted the labeling indicates adhesion failures have occurred in clinical studies. In addition, the Patient Information Section of the Insert labeling contains multiple suggestions and cautions to patients to assist in the patch staying attached.

The Medication Error Prevention Staff notes the patch is _____

The Medication Error Prevention Staff notes an abbreviation — is used throughout the labels and labeling to represent the word —

b(4)

The expression of strength on the pouch label and carton labeling lacks the _____

The pouch label and carton labeling lack the warning _____ provided in the Patient Information leaflet.

b(4)

The carton labeling lacks the _____ statement.

The carton labeling lacks a bar code label.

The carton labeling lacks a _____

b(4)

The strength of the product used on the patch label, pouch and carton labeling (— mg per 24 hours) is not easily found in the Dosage Forms and Strengths sections (both Highlights and Full Prescribing Information) of the proposed Insert Labeling.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Section 3 of the Insert labeling, Dosage Forms and Strengths, uses a word, nominal, that seems unrelated to the information within this section.

The Medication Error Prevention Staff notes in the Patient Information section that steps _____ refers to removal of the patch.

b(4)

Finally, the Medication Error Prevention Staff notes the drug and adhesive are _____

b(4)

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information appears to be vulnerable to confusion that could lead to medication errors. Moreover, the design of the dosage form may predispose this product to be used incorrectly.

4.1 ADHESIVENESS OF THE PATCH

4.1.1 General Adhesion

The Medication Error Prevention Staff's primary concern with the product design is regarding the adhesion of the patch. We note this issue as the Applicant states in the Section 14 "Clinical Studies" that less than 1% of patients evaluated for patch adhesion had the patch become detached. However, the Applicant fails to specify if these detachments were partial or if the patch completely fell off of the patient. If these are complete detachments, we wonder in how many cases the patches simply began to peel off the skin prior to end of therapy and if information pertaining to partial detachments was collected.

Additionally, given the relatively long patch wear of seven days, we wonder if the sponsor collected data on the time of adhesion failures. Post-marketing surveillance indicates that patches often do not adhere to the patient for a multiple day duration and patients end up using creative ways to keep the patch adhered to the skin. The labeling indicates adhesion failures, although small in the number reported, have occurred in clinical trials. We are concerned the loss of adhesiveness will lead to an interruption of granisetron therapy and possibly medication errors if patients invent measures to improve the adhesion (e.g. use of tape or bandages).

The Applicant includes in the "Patient Information" section of the Package Insert labeling instructions on how to address a patch that begins to or becomes unstuck. The instructions state to secure the patch to the same area using "surgical bandages or medical adhesive tape to keep the patch in place." The Medication Error Prevention Staff is concerned the use of occlusive dressings to assist in maintaining adhesiveness of this patch could potentially alter the delivery of this product by increasing the temperature of the skin at the application site and/or changes in skin permeability. The Medication Error Prevention Staff wonders if studies have been completed to determine if the application of surgical bandages or medical adhesive tape affects the absorption of granisetron from the Sancuso patch. The potential effect on absorption is concerning as we note from the insert labeling the product's delivery and absorption are

variable.³ If the use of an occlusive dressing was not assessed in clinical trials, we are concerned that the labeling lists these measures as measures of ensuring patch adhesiveness.

The Medication Error Prevention Staff is also concerned about the transfer of adhesive to the skin upon patch removal. We note the active drug, granisetron, embedded in the adhesive of the product creates an adhesive drug matrix. Post-marketing surveillance demonstrates that patches, in which the drug is contained in the adhesive, have failed to completely release the patch from the liner resulting in adhesive and drug remaining on the release liner prior to applying the patch. This results in patients not receiving the intended amount of medication from the patch. The design of the patch's drug matrix reservoir and the release liner impact whether an error of improper dose resulting in under dose is likely to occur.

The Patient Information section contains information to the patient in "How do I remove and dispose of SANCUSO?" explaining the adhesive may be "left on your skin" after removing the patch. The Medication Error Prevention Staff wonders if data were collected on this phenomenon during clinical trials. We note the section does not clearly convey to the patient the adhesive contains the medication, granisetron. It is unclear from the information reviewed by the Medication Error Prevention Staff whether granisetron would continue to be absorbed if the adhesive is not removed from the skin, although we suspect this to be the case given the drug adhesive matrix patch design. Additionally, we are concerned that the adhesive residue on the skin (or measures patients invent to remove the residue) could increase the risk of adverse skin reactions. Therefore, we believe patients should clearly understand that the drug is contained in the adhesive and thus the potential may exist for the duration of the effect of granisetron to be prolonged if the adhesive is not washed from the skin after patch removal.

4.1.2 Water Exposure

The Patient Information section of the labeling also includes cautions stating, _____

b(4)

_____ The Medication Error Prevention Staff wonders whether data were collected (e.g. number of water exposures during patch wear, type of water exposures, or duration of water exposures) to demonstrate the delivery of granisetron and adhesion of the patch is not altered when the patch gets wet other than the 30 minute in vitro, single submersion test data provided to the Agency. Furthermore, we note this caution lacks specific instructions to patients on how to avoid getting the patch wet. The Medication Error Prevention Staff believes the phrase "_____" is ambiguous and thus prone to interpretation and likely to result in patients exposing the patch to water when bathing or showering longer than the Applicant intends. Although the cautions are listed in the Patient Information Leaflet, we remain concerned the patch may fall off prior to the end of desired therapy if the patient gets the product wet. We believe the Applicant should provide the patient with more explicit directions on how to avoid getting the patch wet and what is the specific amount of time the patch can get wet without losing adhesiveness.

b(4)

³ Sancuso proposed insert labeling Section 12.2 Pharmacokinetics.

4.1.3 Lotions and Creams

The Medication Error Prevention Staff notes the WARNINGS AND PRECAUTIONS section of the Insert Labeling warns about the potential for skin irritation and the risk of photosensitivity when using this product. Post-marketing surveillance of medications delivered by transdermal delivery systems or patches has shown that patients often use corticosteroid creams or other skin products on areas that become irritated by these patches. Patients who have experienced rash or irritation from a patch previously may attempt to prevent this type of reaction by applying these creams to the skin prior to applying the patch. The creams contain oils which are likely to inhibit the patch from adhering to the skin. This results in the patch falling off, and the patient going without medication.

The Applicant includes in the Patient Information section of the Insert labeling a cautionary statement within "Where do I apply the SANCUSO patch?" to address this potential problem. This statement reads, "Do not put SANCUSO on areas that have been treated with creams, oils, lotions, powders or other skin products that could keep the patch from sticking well to your skin." However, we believe this information should be provided elsewhere in the package insert labeling as the Patient Information provided by the Applicant is not likely to be read or discussed with the patient at the time the medication is prescribed or dispensed. In addition, post-marketing surveillance demonstrates that patients may not read or understand the "Patient Information" provided with the product prior to use. Although the cautions are listed in the Patient Information Leaflet, Medication Error Prevention Staff remains concerned healthcare providers unaware of this warning included in the patient section of the labeling may recommend creams or lotions to treat skin reactions related to the patch.

4.1.4 Potential Patch Related Issues

Post-marketing surveillance of medication errors involving transdermal delivery systems demonstrate several other potential issues including healthcare providers unable to find or identify patches on a patient particularly transparent patches that are poorly marked, the adhesive transfer to the release liner on application or the patient's skin upon removal, external heat sources increase the release of the drug, and crystallization of the medication in the adhesive or reservoir.

The Medication Error Prevention Staff note the proposed product will be _____ identifying the medication, granisetron, and the anticipated absorption or flux rate of _____mg per hour. Post-marketing surveillance demonstrates that when patches are _____ healthcare providers overlook them and administer a dose of unnecessary medication leading to overdoses. The Applicant has added _____ lettering to the back of the patch of the translucent patch. As the patch is not entirely _____ we believe the printing on the patch will be difficult to read. In addition, the labeling states that the site the patch is worn should be covered by clothing during therapy and for ten days post removal to avoid sun exposure to the application site. We believe the appearance of the patch is likely to increase the potential for medication errors while providing no benefit to the patient.

b(4)

b(4)

Finally, we note from post-marketing surveillance that the warming of patches by heating pads may increase the rate and extent of absorption of the medication from the patch. In addition, post-marketing surveillance demonstrates crystal formation in the adhesive decreases the ability of the patch to remain attached to the patient. Although the Initial Quality Assessment from

Chemistry noted crystal formation in early batches of this product, we were unable to determine from the Chemistry review, dated August 7, 2007, if the Applicant had implemented manufacturing specifications to reduce the risk of crystallization in future batches.

4.2 EXPRESSION OF STRENGTH

Medication Error Prevention Staff notes the use of the abbreviation — throughout the labels and labeling to represent — Although this specific abbreviation has not been identified as an “error-prone abbreviation” by the Institute of Safe Medication Practices,⁴ the Medication Error Prevention Staff identified this abbreviation in several medical abbreviation sources as having multiple meanings^{5,6} including height, hospital, heparin, human, and hundred and thus has the potential for misinterpretation. We believe there is adequate space on the labels to use the entire word — in the expression of the strength.

b(4)

b(4)

The submitted labeling expresses the strength of Sancuso as ‘ — This expression provides several opportunities for medication error or misinterpretation. Medication Error Staff reviewed the nomenclature for other patches and identified a commonality in the expression of strength between them which includes using the word “delivers” or “delivery” prior to the strength. The strength expression without the terms delivers or delivery could be misinterpreted as the patch requires changing after 24 hours when actually the product delivers medication for up to 7 days. In addition, without the word “delivers” or “delivery” in the expression of the strength, we believe ‘ — mg is likely to be interpreted as the total drug content of the patch rather than the amount of granisetron delivered in 24 hours. Therefore, the Medication Error Prevention Staff believes expressing the strength as “delivers — ; over 24 hours for 7 days” to more clearly express that the patch can be worn longer than 24 hours and provides patients with — g each day that the patch is worn.

b(4)

b(4)

b(4)

4.3 PATCH CUTTING

The Medication Error Prevention Staff notes the daily dose delivered by Sancuso Transdermal System, — mg per 24 hours, is larger than either the intravenous dose (10 mg/kg or 1 mg one time) or the oral dose (2 mg as a single daily dose or divided as 1 mg twice a day). Post-marketing surveillance demonstrates patients are likely to cut transdermal patches in an attempt to reduce the cost of the medication, improve adhesion of the patch, as well as to reduce side effects of the drug. However, the Applicant includes under “When do I apply the SANCUSO patch?” in the “Patient Information” section of the insert labeling a caution stating, “Do not cut the Sancuso patch into smaller pieces.”

b(4)

Despite the inclusion of this information in the labeling, we renew our concern that the Patient Information provided by the Applicant may not be routinely read or discussed with the patient at the time the medication is prescribed or dispensed. In addition, post-marketing surveillance demonstrates that patients may not read or understand the “Patient Information” provided with

⁴ www.ismp.org, “ISMP’s List of Error Prone Abbreviations, Symbols, and Dose Designations,” The Institute of Safe Medication Practices, 2006.

⁵ www.medilexicon.com, accessed February 26, 2008.

⁶ Davis, N, Medical Abbreviations: 26,000 Conveniences at the Expense of Communication and Safety, 12th Edition, 2005.

the product prior to use. Therefore, Medication Error Prevention Staff believes providing the caution "Do not cut patch." closer to patient application of the patch, either on the carton labeling and if space allows on the pouch labeling, may increase the possibility that this information is conveyed to the patient.

4.4 PRESENTATION OF INFORMATION

The carton label lacks the _____ statement. This statement assists pharmacy staff in identifying products as _____

b(4)

Outpatient pharmacy systems may utilize bar code scanners to verify medications prior to dispensing to reduce the potential for medication errors. We noted that the carton labeling for the Sancuso single patch and the 3 patch carton do not include a bar code label. Without a bar code label these scanning systems provide no additional benefit to reduce errors. Additionally, bar code labels are required per 21 CFR 201.25.

Our review of the insert labeling finds the display of the information in Dosage Forms and Strengths to be confusing and the strength difficult to find when compared to the strength as presented on the patch, pouch label and carton labeling (_____ ng per 24 hours). The Medication Error Prevention Staff believes the strength of the product may be missed in the current format of the total drug content of the patch and patch size first followed by the flux rate (_____ ng per hour) in both the Highlights as well as the Full Prescribing Information. The Medication Error Prevention Staff acknowledges the size and full drug content of the patch may be useful information to healthcare providers, but the strength of the product (_____ ng per 24 hours) is most likely to be utilized by prescribers when ordering or prescribing this product. Thus, we believe a healthcare provider's ability to find the strength of _____ ng per 24 hours minimizes the potential for medication errors. Furthermore, the word 'nominal' appears in this section but has an unclear meaning which adds to the potential confusion.

b(4)

b(4)

The Patient Information section provides information and recommendations patients need to use the product safely. The steps _____ included in "How to apply the SANCUSO patch?" relate to _____ applying the patch. The Medication Error Prevention Staff believes this has the potential to be misinterpreted when applying the patch or the information may be missed when removing the patch.

b(4)

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The Applicant attempts to address the inherent risks associated with transdermal delivery systems in the proposed labeling of Sancuso, and the Medication Error Prevention Staff questions whether all of these measures are supported by the data collected in controlled studies. We believe the risks we have identified should be addressed and mitigated prior to drug approval, and provide recommendations that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this

understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5.1 COMMENTS TO THE DIVISION

The Medication Error Prevention Staff noted potential medication error or misuse issues related to transdermal delivery systems in the discussion of this review. The Applicant notes in the Package Insert a detachment rate of 1%, but does not specify if these were partial or complete. However, the Applicant has attempted to address several of the known product related concerns through information included in the Patient Package Insert including using medical tape or surgical tape when the patch becomes unstuck, getting the patch wet, patients cutting the patch, and using creams prior to patch placement affect adhesion. Several of our recommendations address these information statements and where to place them to increase the likelihood the patient will read them.

However, the Medication Error Prevention Staff note several potential patch inherent issues that the information provided for this review do not address; such as healthcare providers unable to find or identify worn patches, the adhesive remaining on the release liner, the effect of heating the patch on release of the drug, and crystallization of the medication in the drug matrix reservoir affecting adhesiveness of the patch. We believe these potential issues should be evaluated prior to approval of this product.

1. The Medication Error Prevention Staff would like to actively participate in the labeling discussion in order to remedy some of the risks noted in our review.
2. Please copy Medication Error Prevention Staff on any communication to the Applicant with regard to this review.

If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

In the review of the container labels, carton and insert labeling of Sancuso, Medication Error Prevention Staff recommends implementation of the label and labeling revisions as outlined below in the interest of minimizing user error and maximizing patient safety.

5.2.1 General Comments

1. We recommend making the patch easier to find and identify on a patient (e.g. using a bolder font for the printed information on the backing).

5.2.2 Transdermal system backing (— ng/24 hour)

1. The abbreviation — can have multiple meanings and has the potential to be misinterpreted. The Medication Error Prevention Staff recommends replacing the abbreviation — with the word hours to minimize the potential for confusion.

b(4)

5.2.3 Pouch Label (3.6 mg/24 hours)

1. The abbreviation — can have multiple meanings and has the potential to be misinterpreted. The Medication Error Prevention Staff recommends replacing the abbreviation — with the word — to minimize the potential for confusion. b(4)
2. The expression of the strength as _____ suggests this patch should be changed every 24 hours and may be misinterpreted as the total drug content. The Medication Error Staff recommends expressing the strength as “delivers — mg over 24 hours for 7 days.” b(4)
3. Include an “Rx Only” statement.
4. We recommend adding the caution “Do not cut patch,” if space allows.
5. It is unclear if the proposed packaging will provide any means of child resistance. The Medication Error Prevention Staff recommends adding the statement, “Keep out of the reach of children” if no child resistance mechanism is utilized.

5.2.4 Carton Labeling (One patch)

1. The abbreviation — can have multiple meanings and has the potential to be misinterpreted. The Medication Error Prevention Staff recommends replacing the abbreviation — with the word — to minimize the potential for confusion. b(4)
2. The expression of the strength as _____ suggests this patch should be changed every 24 hours and may be misinterpreted as the total drug content. The Medication Error Prevention Staff recommends expressing the strength as “delivers — mg over 24 hours for 7 days.” b(4)
3. Include the “Rx Only” statement on the principal display panel.
4. As patients may not read the Patient Information provided by the Applicant in the Insert Labeling, the Medication Error Staff recommends adding the caution “Do not cut patch,” to the carton labeling to alert patients that only whole patches should be applied.
5. It is unclear if the proposed packaging will provide any means of child resistance. The Medication Error Prevention Staff recommends adding the statement, “Keep out of the reach of children” if no child resistance mechanism is utilized.
6. Include a bar code label per 21 CFR 201.25.

5.2.5 Carton Labeling (Three patches)

1. The abbreviation — can have multiple meanings and has the potential to be misinterpreted. The Medication Error Staff recommends replacing the abbreviation — with the word — to minimize the potential for confusion. b(4)
2. The expression of the strength as _____ suggests this patch should be changed every 24 hours and may be misinterpreted as the total drug content. The Medication Error Prevention Staff recommends expressing the strength as “delivers —mg over 24 hours for 7 days.” b(4)
3. Include the “Rx Only” statement on the principal display panel.

4. As patients may not read the Patient Information provided by the Applicant in the Insert Labeling, the Medication Error Prevention Staff recommends adding the caution "Do not cut patch," to the carton labeling to alert patients that only whole patches should be applied.
5. It is unclear if the proposed packaging will provide any means of child resistance. The Medication Error Prevention Staff recommends adding the statement, "Keep out of the reach of children" if no child resistance mechanism is utilized.
6. Include a bar code label per 21 CFR 201.25.

5.2.6 *Insert Labeling*

1. The abbreviation _____ can have multiple meanings and has the potential to be misinterpreted. The Medication Error Prevention Staff recommends replacing the abbreviation _____ with the word _____ to minimize the potential for confusion. b(4)
2. We recommend the strength of _____ mg over 24 hours should be closer to the beginning of the statement in Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling. b(4)
3. We recommend deleting the word _____ from Section 3 Dosage Forms and Strengths. b(4)
4. We recommend including the warning regarding the use of creams, oils lotions, powders or other skin products in the patient counseling section of the Insert labeling as part of 17.2 Skin Reactions.
5. We recommend including in the "What to do if the SANCUSO patch becomes unstuck?" statement of the Patient Information what not to use to keep the patch in place, such as scotch tape, masking tape or duct tape.
6. We recommend moving _____ from "How do I apply the SANCUSO patch?" in the Patient information to "How do I remove and dispose of Sancuso?" b(4)
7. We recommend changing the wording in "Can I bathe or Shower while wearing Sancuso?" from _____ to a specific amount of time patients can follow. This specified time should be reflective of the conditions the clinical trials completed by the Applicant regarding this issue. b(4)
8. We recommend noting the adhesive contains medication in step two of "How do I remove and dispose of SANCUSO?" In addition, include specific cleaning agents the patient can use to wash the adhesive off of the skin.

6 REFERENCES

1. *OSE Review #2007-1573, Proprietary Name Review for Sancuso, Abate, R.*

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

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