

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-192

**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: March 25, 2009

To: Thomas Laughren, MD, Director
Division of Psychiatry Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Diane C. Smith, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Fanapt (Iloperidone) Tablets
1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg

Application Type/Number: NDA 22-192

Applicant: Vanda Pharmaceuticals

OSE RCM #: 2009-70

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review of the labels and labeling for Fanapt (Iloperidone) in OSE Review# 2009-70 dated March 4, 2009, in which we made recommendations regarding the proposed container labels, carton labeling, and insert labeling. Revised labels and labeling were submitted on March 10, 2009. We held a teleconference with the Applicant on March 16, 2009, to address some additional concerns involving three outstanding issues from the revised labels and labeling: the use of similar colors for the 1 mg and 6 mg tablets, the use of the name "FANAPTpack" for the titration packaging configuration, and use of the abbreviations "am" and "pm" in the inside cover of the titration pack. Subsequently, the Applicant submitted their revisions addressing DMEPA's requested changes on March 17, 2009. This memorandum is written in response to these revisions.

2 MATERIAL REVIEWED

DMEPA reviewed our labeling review for Fanapt signed on March 4, 2009 (OSE Review# 2009-70). We also reviewed revised labels and labeling submitted on March 10, 2009 and March 17, 2009 (see Appendices A through E for images of the labels and labeling).

- Trade Container Labels
- Professional Sample Container Labels (14 count tablet)
- Professional Sample Carton Labeling
- Commercial Titration Package Configuration
- Professional Sample Titration Package Configuration
- Package Insert Labeling (no image)

3 DISCUSSION

The Applicant has revised the labels and labeling according to our recommendations and we have no further comments.

4 CONCLUSION

The Applicant has satisfactorily revised the labels and labeling per our March 16, 2009, teleconference.

If you have questions or need clarifications, please contact Abolade Adeolu, OSE Project Manager, at (301) 796-4264.

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X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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**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: March 4, 2009

To: Thomas Laughren, MD, Director
Division of Psychiatry Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Diane C. Smith, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Fanapt (Iloperidone) Tablets
1 mg, 2 mg, 4 mg 6 mg, 8 mg, 10 mg and 12 mg

Application Type/Number: NDA # 22-192

Applicant/Applicant: Vanda Pharmaceuticals

OSE RCM #: 2009-70

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EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels for Fanapt Tablets is vulnerable to confusion that could lead to medication errors. Specifically, we note the following issues on the container labels: the lack of color differentiation between the 4 mg and 10 mg tablets as well as the 6 mg and 12 mg product strengths, the lack of color contrast of the 2 mg product strength and the presentation of the established name. Additionally, on the professional sample container labels the presentation of the "Professional Sample" statement and the size of the product strength. We also note the inappropriate use of the term "Starter" on the professional titration packs as well as the titration schedule, the utilization of graphics in the instructions for use and the net quantity contained in the pack.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated, and provides recommendations in Section 6.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Psychiatry Products for assessment of the container label, carton and insert labeling for Fanapt (Iloperidone). DMEPA completed a review of the proprietary name under a separate consult (OSE# 2009-69).

1.2 PRODUCT INFORMATION

Fanapt is an atypical antipsychotic indicated for the acute treatment of schizophrenia in adults.

The recommended dose is 12 mg to 24 mg per day administered twice daily (BID) based on clinical response. This target dose range should be achieved through the following daily dosage adjustments until the desired maintenance dose is achieved: 1 mg BID, 2 mg BID, 4 mg BID, 6 mg BID, 8 mg BID, 10 mg BID and 12 mg BID on days 1, 2, 3, 4, 5, 6 and 7, respectively.

Fanapt will be supplied as follows:

	Professional Sample Bottle of 14 tablets	Trade Container of 60 tablets	Professional Blister Cards
Tablet Strength			
1 mg		X	X
2 mg		X	X
4 mg	X	X	X
6 mg	X	X	X
8 mg	X	X	X
10 mg	X	X	X
12 mg	X	X	X

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy

potential sources of medication error prior to drug approval. DMEPA defines 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 label and carton labeling communicate critical information including proprietary and established name, strength, dosage 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.

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 United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on November 19, 2008 for our review (see Appendices A through D).

- Professional Sample Container Labels (14 count tablet)
- Titration Package Configuration
- Trade Container Labeling
- Package Insert Labeling (no image)

3 RESULTS

3.1 ALL LABELS AND LABELING

The "F" that appears above the proprietary name, Fanapt, is large in size and uses too much room on the label.

The established name is less than half the size of the proprietary name.

3.2 TRADE CONTAINER LABELS

The lavender color on the 4 mg product strength is too similar to the light grey color used for the 10 mg product. Additionally, there are similar concerns involving the colors used for the 6 mg and 12 mg product strengths.

The light yellow color font used for the 2 mg product strength is difficult to read on the white background.

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

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

3.3 PROFESSIONAL SAMPLE CONTAINER LABELS

As currently presented, the product strength (i.e., 6 mg) may not appear on the principal display panel.

The statement "Professional sample" is small and difficult to read.

3.4 TITRATION PACKAGE CONFIGURATION

The term _____ is inappropriately used on the professional sample.

The current insert labeling recommends that all patients are _____

b(4)

The dosing instructions utilize graphics of the "sun and moon" to depict that patients should take in the morning and evening.

The front cover does not adequately convey to healthcare practitioners the specific contents of each titration pack.

The November 19, 2008, submission references the inclusion of a commercial titration pack, however, the electronic file depicts a professional sample pack.

The white text font on the green background is difficult to read (i.e., white lettering on green background).

3.5 PACKAGE INSERT LABELING

The Applicant uses the abbreviation BID throughout the labels and labeling.

4 DISCUSSION

Our review of the proposed labels and labeling identified several areas of needed improvement. These areas are outlined below.

4.1 INFORMATION ON LABELS AND LABELING LACKS PROMINENCE

4.1.1 *Established Name*

The established name is less than half the size of the proprietary name and does not have the prominence commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). This makes the established name less prominent. The established name is an important feature on the labels and labeling and should be prominently displayed on the principal display panel.

4.1.2 *Professional Sample*

The statement "Professional sample" on the container labels is small and difficult to read. Increasing the size of this statement will allow healthcare practitioners to clearly identify professional samples.

4.2 STRENGTH DIFFERENTIATION

The colors used to differentiate the product strengths are too similar in appearance. The lavender color on the 4 mg product strength is too similar to the light grey color used for the 10 mg product strength. Additionally, we have similar concerns involving the colors utilized for the 6 mg and 12 mg strengths. Using similar colors increases the risk of selection errors especially when these bottles will be stored side-by-side on a pharmacy shelf. Selection errors may not be caught prior to administration which can lead to overdose and potentially result in adverse events.

4.3 DECREASED READABILITY OF PRODUCT STRENGTH DUE TO LACK OF CONTRAST

The light yellow text used for the 2 mg product strength is difficult to read adjacent to the white background. This color combination does not provide sufficient contrast to one another. The text font color used should maximize the contrast between the text and the background to ensure readability.

4.4 LOCATION OF STRENGTH

Although, the strength is prominently displayed on the professional sample container labels, it does not appear immediately following the established name but appears in the lower right hand corner. This container configuration will be likely be small and when the container label is placed on the container the current presentation of the product strength may not be visible when looking at the front panel of the container label (i.e., the portion of the label containing the product strength may wrap around to the side panel). Practitioners are accustomed to seeing the proprietary and established names and strength clearly displayed on the front panel, without having to turn the container. If the product strength does not immediately follow the established name, or when such items appear in different locations, it takes longer to locate the information or information in its place can be confused. It would be best if the strength appeared on the principal display panel underneath the established name.

4.5 TITRATION PACKAGE CONFIGURATION

4.5.1 *Proposed Titration Regimen*

The current insert labeling recommends that _____
_____. However, some patients may require further titration up to maximum daily dose of 12 mg two times a day. The proposed titration package configuration includes additional doses of _____ DMEPA believes that the titration package should stop after day four to eliminate potential confusion in patients who require additional increases in the dose.

b(4)

4.5.2 *Starter Pack Terminology*

The Applicant uses the term _____ on the titration package configuration. This is not in accordance with _____ which states a drug product which is to be given to a patient by a physician as a sample cannot use the term _____

b(4)

4.5.3 *Inappropriate Graphics*

The applicant utilizes a "sun" and "moon" graphic to depict the tablets should be taken in the morning and evening. The use of these graphics can be a source of confusion because patients can misinterpret exactly when the tablets should be taken. If prominently displayed, the wording ("Take 1 mg tablet in the morning and 1 mg tablet in the evening") is sufficient for patient understanding.

4.5.4 Decreased Readability Due to Font Size

The white font on the green background is hard to read. This may be due to the font size since this color combination is used on other Fanapt labels and labeling. Increasing the font size will increase readability of important information such as the statement "Take 1 mg tablet in the morning and 1 mg tablet in the evening" and the contents of the titration pack.

4.5.5 Inappropriate Presentation of Net Quantity

The front cover does not adequately convey to healthcare practitioners the specific contents of each titration pack. This information should be clearly stated on the front cover to ensure that healthcare practitioners understand the exact strengths and quantities contained in each pack.

4.6 INSERT LABELING

The Applicant uses the abbreviation "BID" throughout the labeling. Though it is unlikely that medication errors may occur from the abbreviation 'BID', we recommend avoiding the use of any abbreviation or acronym (e.g., BID) in the labels and labeling.

4.7 GRAPHIC PROMINENCE

The "F" that appears above the proprietary name may draw attention away from important information on the principal display panel. The most prominent information on the principal display panel should be the proprietary and established names and the product strength. Decreasing the prominence will allow healthcare practitioners to clearly recognize the products name and product strength.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the presentation of the established name, strength differentiation, lack of contrast of Fanapt 2 mg, location of strength, titration package configuration information, graphic prominence and the use of abbreviations in the insert labeling. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.1.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Bola Adeolu, OSE project manager, at 301-796-4264.

5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, DMEPA identified the following areas of needed improvement.

All Labels and Labeling:

1. Decrease the prominence of the "F" that appears above the proprietary name, Fanapt, ensuring it is not more prominent than the proprietary name or the established name.
2. Increase the size of the established name, ensuring it is 1/2 the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing feature in accordance with 21 CFR 201.10(g)(2).

Trade Container Labels

1. The lavender color on the 4 mg product strength is too similar to the light grey color used for the 10 mg product strength. There are similar concerns involving the colors utilized for the 6 mg and 12 mg strengths. Revise the colors used for these strengths to provide better differentiation.
2. The light yellow color used for the 2 mg product strength is difficult to read on the white background. Revise the color for the 2 mg product strength to increase the color contrast between the yellow text and the white background color. Ensure that the revised color is not similar to the appearance of any other product strength. (See previous comment)

Professional Sample Container Labels

1. The container configuration will likely be small and when the container label is placed on the container the current presentation of the product strength may not be visible when looking at the front panel of the container label (i.e., the portion of the label containing the product strength may wrap around to the side panel) Relocate the strength to immediately follow the established name ensuring it appears on the principal display panel (i.e., as presented on the trade size container labels).
2. The statement "Professional sample" is small and difficult to read. Increase the size of this statement.

Titration Package Configuration

1. The use of the term _____ on the professional samples is not in accordance with _____ drug product which is to be given to a patient by a physician as a sample cannot not use the term _____. Delete the term _____ from the professional samples. b(4)
2. The current insert labeling recommends that _____
_____ However, some patients may require further titration up to maximum daily dose of 12 mg two times a day. The proposed titration package configuration includes additional _____ DMEPA believes that the titration package should stop after day four to eliminate potential confusion in patients who require additional increases in the dose. Revise the titration package configuration so that the package configuration only contains a four day supply which is congruent with the recommended starting titration dose schedule. b(4)
3. The white text font on the green background is difficult to read (i.e., white lettering on green background). Increase the size of the font size to improve readability of important information such as the instructions for use and the contents of the package.
4. We note the utilization of the "sun" and "moon" graphic to depict when the tablets should be taken in the morning and evening. The use of these graphics can be a source of confusion because patients can misinterpret exactly when the tablets should be taken. Remove the "sun and moon" graphics.
5. The front cover does not adequately convey to healthcare practitioners the specific contents of each titration pack. Revise the product strength statement so healthcare practitioners and patients understand the exact strengths and quantities contained in the titration carton. Revise to read:

This package contains:

Two 1 mg tablets

Two 2 mg tablets

Two 4 mg tablets

Two 6 mg tablets

5. We note your November 19, 2008, submission references the inclusion of a commercial titration pack. However, upon review of the file, we note that the carton labeling is for a professional sample titration pack. Please clarify whether or not you plan to market a commercial titration pack.

Insert Labeling

We note the use of the abbreviation BID throughout the labels and labeling. We recommend avoiding the use of any abbreviations and acronyms (e.g., BID) in the labeling. Eliminate the use of the abbreviation "BID" throughout the package insert labeling. Revise all references to read "two times a day".

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3/4/2009 01:55:58 PM
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SEALD LABELING REVIEW

Template version: November, 2008

APPLICATION NUMBER	NDA 22-192
APPLICANT	Vanda Pharmaceuticals
DRUG NAME	Iloperidone
SUBMISSION DATE	
SEALD REVIEW DATE	1-29-09
SEALD REVIEWER(S)	Kim Shiley, BSN and Laurie Burke, RPh, MPH

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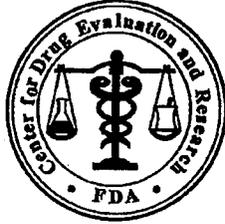
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SEALD Comments sent to Review Division on 1-29-09

Laurie Burke
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**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: June 26, 2008

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD., Deputy Director
Division of Medication Error Prevention

From: Diane C. Smith, PharmD, Safety Evaluator
Division of Medication Error Prevention

Subject: Labeling Review for Fanapta

Drug Name(s): Fanapta (Iloperidone) Tablets 1 mg, 2 mg, 4 mg, 6 mg, 8 mg
10 mg and 12 mg

Application Type/Number: NDA 22-192

Applicant/sponsor: Vanda Pharmaceuticals Inc.

OSE RCM #: 2007-538

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention's Label and Labeling Risk Assessment found that the proposed container label, carton labeling and insert labeling introduce vulnerability to confusion that could lead to medication errors. If titration is variable depending upon patient, the proposed blister titration carton packaging configuration is not appropriate and increases the risk of medication errors because it requires removal of tablets or supplemental tablets to accommodate each individual patient/schedule.

We believe the remaining risks we have identified can be addressed and mitigated prior to approval with revisions to the labels and labeling. Such improvements include elimination of error-prone abbreviations in the package insert and improvements to the design of the titration pack. We provide recommendations in Section 5.1 and request these revisions be made prior to approval in order to minimize the risk of dispensing and administration errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Psychiatry Products to evaluate the container label, carton and insert labeling for Fanapta (iloperidone) 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets.

1.2 PRODUCT LABELING

Fanapta a dopamine D(2) and serotonin 5-HT₂ antagonist, is a psychotropic agent indicated for the treatment of schizophrenia. The recommended target dose range is 12 mg to 24 mg/day administered twice daily during the acute phase. Titration to target dosage range should be achieved in daily dosage adjustment, for example 1, 2, 3, and 4 days respectively, to reach the target 12 mg/day dose. Alternatively, the starting dose can begin at 2 mg twice a daily. During the maintenance phase the target dose of _____ can be administered once daily or twice daily. Fanapta available as a 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets. Fanapta will be supplied as followed:

b(4)

Package Configuration

Tablet Strength	Bottle of 14	Bottle of 60	Blister Cards
1 mg		X	X
2 mg		X	X
4 mg		X	X
6 mg	X	X	X
8 mg	X	X	X
10 mg	X	X	X
12 mg	X	X	X

2 METHODS AND MATERIALS

This section describes the methods and materials used by 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. The Division of Medication Error Prevention defines 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.

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 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 review division forwarded on April 18, 2008 the following labels and labeling for our review (see Appendix A, B, C and D for images):

- Container Label: (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg) 60 tablet count
- Professional Sample Container Label: (4 mg, 6 mg, 8 mg, 10 mg and 12 mg) 14 tablet count
- Blister Cards 14 tablet count
- Professional Sample Blister Card
- Professional Sample Carton Labeling 14 tablet count
- Package Insert Labeling (no image)

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

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

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the container label and carton labeling identified several areas of vulnerability that could lead to potential medication error, specifically with respect to the presentation of the blister card labeling and the instructions in the dosage and administration section of the package insert labeling.

3.1.1 All Labels and Labeling

The graphic “F” above the proprietary name is distracting.

The letter “p” in the proprietary name bisects the established name and dosage form.

The established name appears to be smaller than half the size of the trade name due to the font type, color, and presentation of the trade name.

3.1.2 Trade Container Labels

The strength colors for the 4 mg and 10 mg tablets look almost identical.

The yellow font color scheme for the 2 mg is difficult to read.

3.1.3 Professional Sample Bulk Container Labels

The 14-count bottle as currently presented may not include the product strength on the principal display panel.

The statement “Professional sample” is small and difficult to read.

3.1.4 Professional Sample Carton Bulk Labeling

The white lettering on green background is difficult to read.

3.1.5 Blister Titration Carton (Retail and Professional Sample)

3.1.5.1 Front Cover

The current presentation of the strength is confusing.

The statement, i.e., “_____s” is ambiguous.

The actual number tablets with the specific strengths are not defined.

The statement “Professional sample” is small and difficult to read.

3.1.5.2 Inside Page

The white lettering on green background is difficult to read.

Directions for use do not appear on each blister label.

In the dosing instructions the applicant uses the symbols for “a sun and moon” adjacent to the product strength to convey when the tablets should be taken.

The titration schedule is over 7 days, however the “Dosage and Administration” section of the package insert states titration occurs over _____

b(4)

b(4)

3.1.6 Package Insert Labeling

In reviewing the proposed insert labeling we noted it included abbreviations QD and BID.

In the Dosage and Administration section the titration schedule is unclear and confusing.

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed labels and labeling appears to be vulnerable to confusion that could lead to medication errors.

4.1.1 All Labels and Labeling

The most important information for the safe and proper use of the drug product is the proprietary name, established name and product strength. This information should be the most prominent information on the labels and labeling. Although the applicant has prominently displayed the proprietary name; the use of the letter "F" in the graphic above the proprietary name is too prominent and distracting. Additionally, the "P" in the proprietary name bisects the established name and dosage form. We also note, due to the color scheme and font type the established name appears to be smaller than half the size of the trade name. The current colors and font weight make the established name appear less than half the size of the proprietary name as required by 21 CFR 201.10(g)(2) when taking all pertinent factors, including, typography, layout, contrast, and other printing features into account.

4.1.2 Trade Container Labels

Because of the yellow font color of the 2 mg product strength on the white background the strength is difficult to read which may lead to confusion.

We are concerned with the similar strength colors of the 4 mg and 10 mg tablets since they are presented in similar shades i.e., lavender and grey. The minimal differences in the strength color may not afford adequate differentiation of the product strengths. The visual similarities of these strengths can lead to product selection errors because all the strengths are usually stocked side-by-side on a pharmacy shelf.

4.1.3 Professional Sample Bulk Container Labels

Although, the strength is prominently displayed on the professional container labels, it does not immediately follow the established name but appears in the lower right hand corner. This container configuration will be likely be small and when the container label is placed on the container the current presentation of the product strength may not be visible when looking at the front panel of the container label (i.e., the portion of the label containing the product strength may wrap around to the side panel). Practitioners are accustomed to seeing the proprietary and established names and strength clearly displayed on the front panel, without having to turn the container. If the product strength does not immediately follow the established name, or when such items appear in different locations, it takes longer to locate the information or information in its place can be confused.

Increasing the size of the statement "Professional Sample" will allow practitioners to clearly identify samples.

4.1.4 Professional Sample Bulk Carton Labelling

The use of the white lettering on the green background on the labels and labeling is hard to read. The colors chosen don't provide sufficient contrast to one another and decrease the readability of this information.

4.1.5 Blister Titration Carton (Trade and Professional Sample)

With the proposed configuration the Applicant is trying to accommodate many different titration schedules. If the titration is variable depending upon patient then a standardized titration pack is not optimal and increases the risk of medication errors because it requires removal of tablets or supplemental tablets to accommodate each individual patient/schedule. Therefore, our final comments will be dependent upon the final titration schedule.

4.1.5.1 Front Cover

The titration blister pack does not contain the specific strength of each tablet and the total number of tablets per strength. The front cover should list the actual strengths and quantities of the various tablets contained within to prevent confusion.

The net quantity statement ' _____ ' is confusing because the inside of the titration pack has a specific titration period however, the _____ statement implies that patients may only be required to take less than 7 days worth of drug (See Section 4.1.5).

b(4)

Increasing the size of the statement "Professional Sample" will allow practitioners to clearly identify samples.

4.1.5.2 Inside Page

The use of the white lettering on the green background on the labels and labeling is hard to read. The colors chosen don't provide sufficient contrast to one another and decrease the readability of this information.

Additionally, the directions for use do not appear on each blister. Lack of adequate instructions of use can lead to confusion and increased risk of medication errors if each blister is not properly labeled with the appropriate directions for administration. Although the directions for use appear on the top portion of the blister card, we believe patients may become confused as to how to take the tablets in the lower portion of the blister since the directions are not clearly provided in that section. Also, the applicant utilizes a "sun" and "moon" graphic to depict the tablets should be taken in the morning and evening. The use of these graphics can be a source of confusion because patients can misinterpret exactly when the tablets should be taken. Lastly, the proposed titration package configuration is for 7 days, however, the "Dosage and Administration" section of the package insert states titration occurs over _____ is package configuration is inconsistent with the insert information and is could cause confusion and lead to medication errors.

4.1.6 Package Insert Labeling

We note the use of abbreviations which can be prone to misinterpretation. We recommend avoiding the use of any abbreviations and acronyms (e.g., QD, BID) in the labeling. The abbreviation "QD" specifically appears on the Institute for Safe Medication Practices (ISMP) list of "Error-Prone Abbreviations, Symbols and Dose Designations". FDA launched a campaign on June 14, 2006, warning healthcare providers and consumers not to use error-prone abbreviations, acronyms, or symbols in their prescribing. As part of this campaign, FDA agreed not to include

such abbreviations in our approved labeling because these abbreviations and acronyms are carried over to prescribing practices.

In the "Dosage and Administration" section; the titration schedule is over a 4 day period. However the Titration package contains dosing for a 7 day period. The current packaging configuration is inconsistent with the insert information which is a source of confusion that could lead to medication errors. Additionally, the insert does not clearly explain the titration schedule to the maximum target daily dose of 24 mg daily. The overall ambiguity in the titration schedule can lead to confusion and potentially medication errors with healthcare practitioners and patients.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that presentation of information on the proposed labels and labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risk we have identified can be addressed and mitigated prior to approval with simple revisions to the labels and labeling. We provide the following recommendations in Section 5.2 and request these revisions be made prior to approval in order to minimize the risk of dispensing and administration errors.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

5.1 COMMENTS TO THE APPLICANT

5.1.1 All Labels and Labeling

To improve the readability, the font color utilized on the labels and labeling should maximize the contrast between the text and the background.

Delete the graphic above the proprietary name as it distracts away from important information.

Adjust the size and/or placement of the proprietary name so that the letter 'p' does not bisect the established name on the principal display panel as it is intervening matter and thus not permitted by 21 CFR 201.10(a).

Increase the prominence of the established name taking into account typography, layout, contrast, and other printing features (e.g., font size and type), revise the established name in accordance with CFR 201.10(g)(2) so the it has a prominence commensurate with the proprietary name.

5.1.2 Trade Container Labels

Revise the color scheme for the Fanapta 4 mg or the Fanapta 10 mg container labels to ensure they are adequately differentiated and the color scheme(s) are not similar in appearance to one another or other strengths.

Revise the color scheme for Fanapta 2 mg container label to increase the color contrast between the text background and the background color. Ensure the revised color scheme is not similar in appearance to the other Fanapta container labels.

5.1.3 Professional Sample Bulk Container Labels

If the 14-count bottle size is small and the strength is not visible when reading the proprietary and established names, relocate the product strength to appear after or directly beneath the established name to ensure the strength appears on the principal display panel.

Increase the prominence of the statement "Professional Sample".

5.1.4 Professional Sample Bulk Carton Labeling

To improve the readability, revise the color font of the text utilized; to ensure adequate contrast between the text and the background.

5.1.5 Blister Titration Carton (Trade and Professional Sample)

With the proposed configuration you are trying to accommodate many different titration schedules. If the titration is variable depending upon patient then a standardized titration pack is not optimal and increases the risk of medication errors because it requires removal of tablets or supplemental tablets to accommodate each individual patient/schedule. Therefore, if the titration schedule is variable per the Dosage and Administration section, we do not recommend the use of a titration pack.

5.1.5.1 Front Cover

Revise the product strength statement so that healthcare practitioners and patients understand the exact strengths contained in the blister. For example:

This blister contains:

Two Fanapta XX mg tablets

Six Fanapta XX mg tablets..... etc.

Revise the net quantity statement to specifically state the period of time the titration pack covers.

Increase the prominence of the statement "Professional Use" only.

5.1.5.2 Inside Page

To improve the readability, revise the color font of the text utilized; to ensure adequate contrast between the text and the background.

Revise to include the directions of use on each blister label. Divide the directions for use on the blister card so that the directions read: top blister: Day 1 "Take one tablet in the morning" lower blister: "Take 1 tablet in the evening" ensuring the proprietary name and strength of each tablet is properly labeled.

Remove the "sun and moon" graphics.

Revise the packaging configuration, ensuring consistency with the "Dosing and Administration" section of the package insert.

5.1.6 Package Insert Labeling

Eliminate the use of abbreviations “QD” and “BID” throughout the package insert labeling. Revise all references to read “once daily” and “twice daily”.

Clearly explain how patients should be titrated upon initiation of therapy and when increasing the dose from 12 mg to 24 mg.

APPEARS THIS WAY ON ORIGINAL

4 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

Todd Bridges
6/27/2008 11:55:00 AM
DRUG SAFETY OFFICE REVIEWER

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