

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-217**

**OTHER REVIEW(S)**

**RHPM Overview**  
**NDA 22-217**  
**Valturna (aliskiren/valsartan) Tablets**

Sponsor:	Novartis
Classification:	Standard
Submission Date:	November 25, 2008
Receipt Date:	November 26, 2006
User Fee Goal Date:	September 26, 2009

**Background**

Valturna is a fixed-dose combination antihypertensive product of aliskiren hemifumarate and valsartan. This supplement provides data to support a proposed indication for Valturna as treatment for hypertension. Each of the two components has been approved for treatment of hypertension used either as monotherapy or in combination with other antihypertensive agents.

Aliskiren is a renin angiotensin agonist (direct rennin inhibitor) approved under for the treatment of hypertension (Tekturna; NDA 21-985). Valsartan is an angiotensin II receptor blocker/antagonist (ARB) approved for the treatment of hypertension and New York Heart Association class II-IV heart failure patients who are intolerant of angiotensin converting enzyme inhibitors (Diovan; NDA 20-665 and 21-283).

This NDA was submitted pursuant to section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act, and contains full reports of safety and effectiveness of the combination drug.

In support of approval, the submission includes quality, pre-clinical, clinical pharmacology, and clinical/statistical data. The clinical development program included four clinical studies, including one pivotal efficacy trial (CSPP100A2327), two efficacy studies (CSPP100A2203, 2331), and a long-term safety trial (CSPV100A2310). The following dosage strengths are proposed: 150/160 mg and 300/320 mg.

The clinical development of Valsartan was conducted under IND 62,976 (SPP100A – aliskiren monotherapy) and IND 76,045 (SPV100A – aliskiren/valsartan combination). The pivotal trial (Study CSPP100A2327) was a double-blind, randomized, parallel group, placebo-controlled dose escalation study in patients with essential hypertension. It was an international, four-arm (two monotherapies, the combination, and placebo) study with forced doubling of initial doses at four weeks and evaluations at four and eight weeks.

**User Fee**

The user fee for this application was paid in full prior to the submission of the application. User Fee ID 3008833.

**Correspondence and meetings**

1. April 30, 2009 An Information Request Letter issued by CMC
2. June 16, 2009 An Information Request Letter issued by CMC regarding the dissolution specifications

### **Cross-Discipline Team Leader Review**

In his July 28, 2009 review, Dr. Marciniak stated that he recommended Valtorna be approved for the treatment of hypertension in adults contingent upon satisfactory resolution of the CMC issues. This dual combination produced greater reductions in blood pressure than the monotherapies. The adverse event profile is similar to those of the monotherapies. The combination does appear to produce more hyperkalemia than the monotherapies but discontinuations for hyperkalemia were still rare and the hyperkalemia can be managed with monitoring and dosage reduction if needed.

### **Medical Review**

In his review dated July 10, 2009, Dr. Xiao stated that Valtorna demonstrated clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in one randomized, double-blind, placebo-controlled trial and one long-term open-label trial (one year) and should be approved for the treatment of hypertension.

The antihypertensive effect was generally attained after 2 weeks of therapy. With the estimates of the probability of reaching a BP goal (systolic BP <140 or 130 mmHg and diastolic BP <90 or 80 mmHg), a greater probability of achieving systolic or diastolic goal with the combination over monotherapies was observed. Therefore, this combination should be also approved for the first-line therapy, which means that aliskiren/valsartan can be indicated for the initial treatment of hypertensive patients who are likely to need multiple drugs to achieve their blood pressure goals.

### **Statistical Review**

In her review dated July 10, 2009, Dr. Liu summarized the model diagnostic assessments:

The goodness-of-fit assessment indicates that the logistic regression models (with and without treatment-by-baseline interaction) fit the data of blood pressure control rates reasonably well.

In general, the predicted probabilities of achieving blood pressure control based on the logistic regression model and LOESS were reasonably close, except for the two tails of the curves with relatively low and high baseline blood pressures. The LOESS curves were generally more sensitive to a small number of observations with relatively low and high baseline blood pressures. In general, the predicted probabilities of achieving blood pressure control at the tails of both logistic regression and LOESS curves may be less robust due to a relatively small number of observations available.

The Pearson residuals for predicted probabilities of achieving blood pressure control appeared to be relatively random without particular patterns. The standardized values of the Pearson residuals were generally within  $\pm 3$  except a small number of points. Overall, there was no systematic departure of model assumption or indication of poor model fitting. The small number of extreme values has little impact on the predicted probabilities based on the logistic regression model fitting.

Overall, the predicted probabilities of achieving blood pressure control obtained from the logistic regression modeling (without treatment-by-baseline interaction) with inclusion of all available data appeared to be adequate.

Dr. Liu recommended approval.

### **Clinical Pharmacology Review**

In her May 27, 2009 review, Dr. Divya Menon-Anderson stated, the results of the bioequivalence study submitted in the application established an adequate link between the results of the pivotal efficacy trial conducted with the free combination, and the final market image tablet (to-be-marketed formulation). Further, it was shown that there was no clinically significant pharmacokinetic or pharmacodynamic drug interaction between the components of the FDC. Administration of the FDC with a high fat meal decreased systemic exposure to aliskiren by > 70%. This is in agreement with the prior knowledge regarding aliskiren disposition, and no dose adjustments are warranted.

The NDA is considered acceptable from a clinical pharmacology perspective.

### **Pharmacology Review**

In his April 21, 2009 review, Dr. Jagadeesh recommended that the NDA was approvable.

### **Quality Review**

Dr. Shiromani completed two reviews dated April 8, 2009 and August 25, 2009. In his review dated August 25, Dr. Shiromani stated, The applicant has provided adequate responses to the FDA IR letter sent on 30- Mar-2009 and provided an additional six months stability data; accordingly, this NDA is recommended for approval from a CMC perspective.

### **Note:**

(b) (4)

### **Environmental Assessment**

The sponsor submitted an Environmental Assessment (EA) pursuant to 21 CFR part 25. Drs. Bloom and Clark reviewed the submitted environmental assessment and found it acceptable. See Office of Pharmaceutical Science review dated July 18, 2009 for EA and FONSI.

### **EES Report**

The Office of Compliance provided an overall recommendation of “Acceptable” for the manufacturing sites inspected.

### **Financial Disclosure**

In his July 10, 2009 financial disclosure review, Dr. Xiao wrote, “Since only three investigators have the potential conflicts of interest, these should not prejudice the results greatly even if there were overt manipulation”.

### **Division of Scientific Investigations**

It was agreed by the medical officer and the statistician after the NDA Filing Meeting that no clinical site inspections were needed.

### **Pediatrics**

The sponsor requested a waiver from the pediatric requirement. The Division agreed that a pediatric waiver should be granted because the drug product is a combination antihypertensive drug.

A PeRC Committee meeting was held on July 29, 2009 and the PeRC agreed with the Division to grant a full pediatric waiver for the following reasons:

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

**Justification:** Valsartan is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by **The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**, *Pediatrics* 2004;114;555-576).

### **Labeling**

The Sponsor submitted annotated proposed labeling that was reviewed by DDMAC on June 25, 2009. Comments were provided.

### **CSO Summary**

An approval letter was drafted for Dr. Stockbridge's signature.

Lori Anne Wachter, RN, BSN  
Regulatory Health Project Manager

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22217

-----  
ORIG-1

-----  
NOVARTIS  
PHARMACEUTICA  
LS CORP

-----  
ALISKIREN & VALSARTAN

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

/s/  
-----

Lori A WACHTER  
09/14/2009

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** July 22, 2009

**To:** **Lori Wachter**  
**Regulatory Project Manager**  
**Division of Cardiovascular and Renal Products**

**From:** Michael Sauers, Regulatory Review Officer  
Zarna Patel, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** **NDA 22-217**  
**DDMAC labeling comments for Valturna (aliskiren/valsartan)**

---

DDMAC has reviewed the proposed product labeling (Package Insert (PI), Patient Package Insert (PPI)), and proposed carton and container labeling submitted for consult to DDMAC on June 10, 2009, for Valturna® (aliskiren/valsartan) Tablets.

Our comments are based on the proposed labeling circulated to the review team on July 9, 2009.

We have no comments on the proposed carton and container labeling at this time.

### Highlights

The boxed warning section includes the statement, “When used in pregnancy during the second and third trimester,…” DDMAC notes that this statement is inconsistent with the boxed warning language of other similar products that act on the renin-angiotensin system (e.g., Diovan, Tekturna), and may minimize the risk of Valturna use during the first trimester of pregnancy. DDMAC recommends deleting this statement.

The Indications and Usage section states, “May be substituted for titrated components.” While this information is included in the Indications and Usage section of the full PI, this is not important contextual information for the Highlights section and is inconsistent with competitor product labeling (Diovan HCT, Tekturna HCT). Please consider deleting.

The Warnings and Precautions section states, “Hypotension in volume- or salt-depleted Patients: Correct imbalances before initiating therapy with Valtorna.” This statement may minimize the risks of hypotension in patients with heart failure or recent myocardial infarction. DDMAC suggests revising this statement to adequately communicate the risk of hypotension in this population.

The Warnings and Precautions section states, [REDACTED] (b) (4)

Additionally, this section states, “Patients with hepatic impairment: Slower clearance may occur.” These statements minimize the risk of Valtorna therapy in patients with renal and hepatic impairment by failing to suggest caution in these patients. We note that competitor labels (Diovan/Tektorna in renal patients) suggest that caution be used in patients with impaired renal and hepatic function. Please consider revising this statement to incorporate this important risk concept.

DDMAC notes that the most common adverse reactions listed in the Highlights section are presented with a threshold incidence of  $\geq 1.5\%$  and more common than placebo. However, the Adverse Reactions section of the proposed label presents [REDACTED] (b) (4)

[REDACTED] Is there a specific reason for this inconsistency? If not, please consider revising this section to include the most [REDACTED] (b) (4)

DDMAC notes that the Drug Interactions section fails to include information regarding concomitant use of potassium sparing diuretics, potassium supplements or salt substitutes containing potassium. This information is included in the Drug Interactions section of the proposed PI as well as the Highlights section of other valsartan products (Diovan). Please consider including the following: “Potassium sparing diuretics, potassium supplements or salt substitutes may lead to increases in serum potassium, and in heart failure patients, to increases in serum creatinine.”

### **Boxed Warning**

See comment above related to boxed warning in Highlights section.

### **2.1 Dose Selection**

This section states, “Patients switched from monotherapy to Valtorna on average experience greater blood pressure reductions with use of the combination product.” DDMAC considers this statement promotional in tone and not appropriate for this section. We recommend deletion.

This section states, “The recommended once-daily dose of Valtorna is 150/160mg or 300/320mg.” However, the Highlights section of the label states,

“Add-on therapy OR Initial therapy: Initiate with 150/160mg. Titrate as needed up to a maximum of 300/320 mg.” These statements are inconsistent and should be revised to reflect the appropriate dosing recommendations.

## 2.2 Dose Titration

This section states, [REDACTED] (b) (4)

[REDACTED] This statement is misleading because it overstates and guarantees the efficacy of Valtorna by suggesting that the drug will be effective in all patients within 2 weeks. We recommend revising this language to be consistent with the Highlights section of the label (e.g., “The **majority of** the antihypertensive effect is attained within 2 weeks.”)

## 2.4 Replacement Therapy

This section states, “For convenience, patients receiving aliskiren and valsartan from separate tablets may instead wish to receive a single tablet of Valtorna containing the same component doses.” DDMAC considers this statement promotional in tone and recommends deletion. Alternative language for consideration includes “Valtorna may be substituted for the individually titrated components,” which is consistent with the Tektorna HCT and Diovan HCT labels.

## 2.5 Initial Therapy

DDMAC notes that reference to the Warnings and Precautions section is incorrect. Please revise to “[See Warnings and Precautions, Hypotension (5.3)].”

## 6.1 Clinical Studies Experience

This sections states, “Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.” DDMAC notes that this statement is in the Tektorna HCT label; however; the claim may minimize the risk of diarrhea and other gastrointestinal adverse events to Valtorna patients. Please consider deleting this statement.

## 6.2 Clinical Laboratory Test Abnormalities

This section states, “**Small** mean decreases from baseline were seen in RBC count, hemoglobin and hematocrit. . . .**These changes were small**, but were slightly more pronounced with the combination therapy...” (emphasis added). These statements minimize the risks of changes in RBC count, hemoglobin, and hematocrit, and are unnecessary given the context that follows in the sentence. We recommend deleting these statements.

## 12.1 Mechanism of Action

This section states the following:

Since aliskiren and valsartan block the RAAS at different sites (inhibition of plasma activity and antagonism of the AT1 receptor), their combination provides a complementary mechanism to achieve a pharmacologic inhibition of the RAAS. Such RAAS inhibition with Valtorna is associated with significant reductions in PRA, Ang I, Ang II and aldosterone.

Please consider deleting this statement as it is promotional in tone and provides no further information regarding the mechanism of action of Valtorna than that described previously.

## 12.2 Pharmacodynamics

This section states, "Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change." DDMAC considers inappropriate for communication in the Pharmacodynamics section and recommends moving to the Clinical Studies section of the PI.

Additionally, this section states, "In combination, 150 mg of aliskiren **neutralized** the 160 mg valsartan-induced increase in PRA, plasma angiotensin I and angiotensin II for 48 hours." (emphasis added) The term "neutralized" is promotional in tone; therefore, we recommend deletion.

## 12.3 Pharmacokinetics

This section states, "In clinical trials of Valtorna, it was administered without requiring a fixed relation of administration to meals." While we understand that this information is accurate, it is inconsistent with dosing recommendations in other sections of the label and may be used in promotion. We recommend deleting this statement.

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

This section states, "Valtorna has been studied in 2- and 13-week toxicity studies and was **generally well-tolerated**" (emphasis added). This statement minimizes the risks of Valtorna therapy and is promotional in tone. We recommend deleting this statement.

## 14.1 Clinical Studies

This section states, [REDACTED] (b) (4)

(emphasis added). Please consider specifying the difference in effect between black and Caucasian patients for context.

## **PPI**

### **What Should I tell my doctor before taking Tekturna HCT?**

Please consider presenting the following risk information as the first bullet in this section to prevent minimization of this risk:

- “are pregnant or planning to become pregnant. See IMPORTANT WARNING.

According to the PI, “Coadministration of irbesartan reduced aliskiren Cmax up to 50% after multiple dosing”, and “Coadministration of atorvastatin resulted in about a 50% increase in aliskiren Cmax and AUC after multiple dosing”. Please consider adding irbesartan and atorvastatin under “**Tell your doctor about all the medicines you take...**” to ensure that patients are made aware of these important drug interactions.

### **What are the possible side effects of Valturna?**

The following common side effects are not in consumer-friendly language, (b) (4) Please consider revising them into consumer-friendly language.

Thank you for the opportunity to comment on these proposed materials.

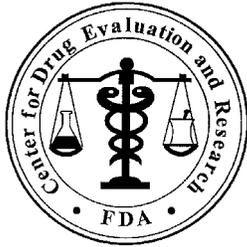
If you have any questions on the comments for the PPI, please contact Zarna Patel at 301.796.3822 or [zarna.patel@fda.hhs.gov](mailto:zarna.patel@fda.hhs.gov).

If you have any questions on the comments for the PI or carton and container labels, please contact Mike Sauers at 301.796.1035 or [michael.sauers@fda.hhs.gov](mailto:michael.sauers@fda.hhs.gov).

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

/s/

-----  
Michael A Sauers  
7/22/2009 01:37:16 PM  
DDMAC PROFESSIONAL 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: June 25, 2009

To: Norman Stockbridge, MD, Director  
Division of Cardiovascular and Renal Products

Through: Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis

From: Melina Griffis, R.Ph., Acting Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Valturna (Aliskiren and Valsartan) Tablets 150 mg/160 mg and  
300 mg/320 mg

Application Type/Number: NDA 22-217

Applicant: Novartis

OSE RCM #: 2008-1953

# CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND .....	3
1.1 Introduction .....	3
1.2 Regulatory History .....	3
1.3 Product Information .....	3
2 METHODS AND MATERIALS .....	3
2.1 Label and Labeling Risk Assessment .....	3
3 RESULTS.....	4
3.1 Label and Labeling Risk Assessment .....	4
4 DISCUSSION .....	4
4.1 Use of two colors in the proprietary name .....	4
4.2 Overlapping colors incorporated in the labeling of 300 mg/320 mg strength .....	5
5 CONCLUSIONS and RECOMMENDATIONS .....	5
5.1 Comments to the Applicant.....	5

## **EXECUTIVE SUMMARY**

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels and carton labeling for Valturna is vulnerable to confusion that could lead to medication errors. Specifically, we note the use of two colors in the proprietary name incorporates similar principles as TallMan lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since Valturna is not a name that has been involved in name confusion the differentiating color of the letter 'VAL' is inappropriately applied. In addition, we note the use of similar colors (blue versus purple and teal) for the labels and labeling of the 300 mg/320 mg product strength of Valturna. The use of similar color schemes on this label does not aid in distinguishing the strength. The Applicant should revise their labels and labeling prior to approval. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to a request for a proprietary name review dated November 26, 2008 submitted by the Applicant, Novartis, which also contained container labels, carton and insert labeling requiring our review. This review focuses on the evaluation of the labels and labeling from a medication error perspective.

### **1.2 REGULATORY HISTORY**

Valturna (aliskiren/valsartan) is a pending NDA application with an anticipated action date of September 26, 2009. A previous OSE review (2008-1952) found the proprietary name Valturna acceptable.

### **1.3 PRODUCT INFORMATION**

Valturna is indicated for the treatment of hypertension in patients not adequately controlled with monotherapy or as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. Valturna is comprised of aliskiren and valsartan and is available in two tablet strengths, 150 mg/160 mg and 300 mg/320 mg. The recommended adult daily dose is initiation at 150 mg/160mg and titrate as needed to a maximum of 300 mg/320 mg. Valturna is to be taken once daily with a routine pattern with regard to meals.

Both aliskiren and valsartan are marketed individually and in combination with HCTZ.

## **2 METHODS AND MATERIALS**

This section describes the methods and materials used by DMEPA 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 and Analysis 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.<sup>1</sup>

### **2.1 LABEL AND LABELING RISK ASSESSMENT**

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

---

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

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.<sup>2</sup>

Because DMEPA staff analyze reported misuse of drugs, our staff 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.

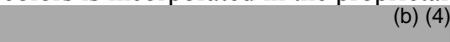
For this product the Applicant submitted the following labels and packaging for our review (see Appendices A, B, and C for images).

- Container Labels (30 and 90 count trade)
- Blister Pack Carton Labeling and Blister Card Labels (10 x 10 count)
-  (b) (4)

### **3 RESULTS**

#### **3.1 LABEL AND LABELING RISK ASSESSMENT**

Review of the Valturna container labels and carton labeling identified areas of vulnerability that could lead to medication error.

The use of two colors is incorporated in the proprietary name (30 & 90 trade container, blister pack carton labeling  (b) (4) These labels depict the ‘Val’ in Valturna with the use of a different color (teal) than the remainder of the name ‘turna’ (purple).

The use of overlapping colors is incorporated in the labeling of the 300 mg/320 mg strength (30 & 90 trade container, blister pack carton labeling  (b) (4) Similar colors (blue versus purple and teal) are utilized on labels and labeling of the 300 mg/320 mg strengths.

The dosage form is not presented on the container labels (30 and 90 count).

There is a large graphic symbol directly preceding the proprietary name.

### **4 DISCUSSION**

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

#### **4.1 USE OF TWO COLORS IN THE PROPRIETARY NAME**

The proprietary name as presented incorporates the use of two colors, teal for the “Val’ portion and purple for the ‘turna’ portion. Consequently, the use of two colors highlights and may bring prominence to only a portion of the name. The use of two colors in the proprietary name incorporates similar principles as TallMan lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since Valturna is not a name that has been involved in name confusion the differentiating color of the letter ‘Val’ or ‘turna’ is inappropriately applied.

---

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

## 4.2 OVERLAPPING COLORS INCOPORATED IN THE LABELING OF 300 MG/320 MG STRENGTH

The Applicant utilizes two colors in an attempt to differentiate the 150 mg/160 mg (blue) and 300 mg/320 mg (yellow/brown) strengths. However they also use similar colors (purple and teal) for the trade dress for both strengths of Valturna. The use of purple and teal colors for the trade dress is similar to the blue color used for the 300 mg/320 mg strength. This minimizes the differentiation of the two strengths. Since Valturna is available as two strengths, it is crucial the color chosen to identify the strength does not overlap with the colors used in the trade dress.

## 4.3 PRESENTATION OF GRAPHIC SYMBOL

The graphic symbol directly preceding the proprietary name should be decreased in size or relocated to a less prominent area on all labels and labeling.

## 5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sean Bradley, OSE Project Manager, at 301-796-1332.

### 5.1 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis has identified the following areas of needed improvement:

A. Container Labels (30 and 90 Count) and Carton Labeling [Trade (b) (4) Sample]

1. Revise the proprietary name to incorporate the use of one unique color. Ideally, the color selected should not overlap with the color utilized for the strength differentiation. The use of two colors in the proprietary name incorporates similar principles as TallMan lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since Valturna is not a name that has been involved in name confusion the differentiating color of the letter 'VAL' is inappropriately applied.
2. Revise your labels and labeling of the 300 mg/320 mg strength to utilize a color that is not similar to the purple and teal incorporated in your trade dress. As currently presented, the blue color used to designate this strength is similar to the teal and purple colors in the trade dress which minimizes the strength differentiation.
3. The graphic symbol directly preceding the proprietary name should be decreased in size or relocated to a less prominent area on all labels and labeling.

B. Container Labels (30 and 90 count for both strengths)

The dosage form statement on the container labels should be included and be displayed in a similar manner as presented on the blister carton labeling.

3 pp withheld in full immed. after this page as (b)(4) draft labeling.

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

/s/

-----  
Melina Griffis  
6/25/2009 12:19:25 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
6/25/2009 04:10:56 PM  
DRUG SAFETY OFFICE REVIEWER