CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205677Orig1s000

PROPRIETARY NAME 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
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	September 16, 2013
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Hetlioz (Tasimelteon) Capsules, 20 mg
Application Type/Number:	NDA 205677
Applicant/sponsor:	Vanda Pharmaceuticals, Inc.
OSE RCM #:	2013-1434

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This memorandum is in response to a June 17, 2013 request from Vanda Pharmaceuticals to reconsider the proposed proprietary name, Hetlioz for Tasimelteon Capsules.

On December 13 2012, FDA notified Vanda that the proposed proprietary name was unacceptable because of orthographic and overlapping product characteristics with Haltran (Ibuprofen).

2 MATERIALS REVIEWED

In our review of the request for reconsideration, I considered the Safety Evaluator's and Team Leader's draft reconsideration review (attached), the findings of our previous name review[1], an analysis conducted by (b) (4) submitted by Vanda in support of the name, and drug use information related to the prescribing of Haltran[2].

3 DISCUSSION

The Safety Evaluator and Team Leader recommended that we maintain the position that Hetlioz is unacceptable based the orthographic similarity of the proposed name Hetlioz to Haltran, along with similarities in product characteristics. They considered Vanda's arguments that 1) Haltran is a prescription product that has been discontinued 2) Hetlioz will be dispensed using specialty pharmacies 3) Physicians will most likely write Hetlioz as "QHS" or "before bedtime" thus distinguishing Hetlioz for Haltran in prescribing and 4) no misinterpretations occurred in (b) (4) name simulation study.

I agree with the review team's position on arguments 2, 3, and 4 in their entirety. The review team's position is well supported by post-marketing errors that have occurred with similarly situated drug products and other scientific information in the literature and published FDA guidance documents.

However, I disagree with the review team's position on argument 1, that the discontinuation of Haltran would not prevent confusion between this name pair. The review team's position is that the name Haltran continues to be used in prescribing at "a low volume," and that the USPTO has an active trademark filed by Doctor's Affiliates in 2013 for the use of the name Haltran with Ibuprofen. Given the recent filing of the trademark for Haltran by Doctor's Affiliates with USPTO, I attempted to locate further information about the patent holder and the distribution of Haltran in the market and could find none. I reviewed the drug use data and find that Haltran is indeed prescribed at a very, very low volume (i.e. less than a dozen prescriptions in each of the past three years). Moreover, our drug use database shows there were no prescriptions issued for the drug in 2009 or 2008. Although, I agree with the review team that literature shows that proprietary names are used after product discontinuation, I find in this particular case that the use is virtually nonexistent. I suspect this may be related to the fact that other proprietary names for ibuprofen, such as Motrin and Advil, have enjoyed greater

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[1] Neshiewat J. Hetlioz: proprietary name review (IND 054776; RCM 2012-1422). Silver Spring (MD): Food and Drug Administration, Division of Medication Errors and Prevention (US); 2012 Dec 13.

[2] (b) (4) Vector One®: National (VONA).Year 2008 to 2012. Extracted June 27, 2013.

popularity and recognition than Haltran ever achieved, although I have no data to support this hypothesis. Based on these factors, it is plausible to me that in this case the discontinuation of Haltran marketing in 2004 does alleviate the potential for this name to cause confusion in the current marketplace.

Lastly, although Vanda does not raise the point, I re-evaluated the orthographic similarity of this name pair given the recent trademark filing by Doctor's Affiliates. I find the names do in fact have sufficient differentiation. Hetlioz and Haltran have some similarity in length and the position of the upstroke letters, but the letters l and t are transposed in the names, and the endings appear different in the handwriting samples I reviewed, and no misinterpretation in the name studies (FDA's and (b) (4)) suggest that –ioz appears similar to –ran. POCA assigns an orthographic similarity to this name pair of only 44%. Although name pairs with similar orthographic similarity values have been confused (e.g. Coumadin and Avandia), in those cases the overlap in unusual strengths (4 mg) was likely a contributing factor. There is some numerical similarity in the strengths (20 mg versus 200 mg), but I do not believe this numerical similarity would lead to confusion given the modest visual similarity of the names themselves. Therefore, even if Doctor's Affiliates were to achieve a significant volume of prescribing for the name Haltran, it seems possible to me that these names could safely co-exist in the marketplace.

4 CONCLUSION

My evaluation finds there is sufficient reason to reconsider the original finding, and I recommend that we approve the proposed proprietary name, Hetlioz. Section 5 provides comments for the applicant.

5 COMMENTS TO THE APPLICANT

We have completed our review of the external report conducted by the (b) (4) submitted as part of your request for reconsideration of the proposed proprietary name Hetlioz and have the following comments:

5.1 HETLIOZ WILL BE DISPENSED USING SPECIALTY PHARMACIES

You noted that Hetlioz will be dispensed in specialty pharmacies, and products such as Haltran and over the counter (OTC) ibuprofen would not be typically dispensed in a specialty pharmacy. Although specialty pharmacies may not typically dispense OTC products, if a patient took a prescription for Hetlioz to a retail pharmacy, the pharmacist may misinterpret Hetlioz as Haltran, and OTC ibuprofen could be dispensed. Furthermore, although a patient does not need a prescription to obtain OTC ibuprofen, health care practitioners issue prescriptions for OTC products.

We note that you intend physicians to fax a patient enrollment form to a specialty pharmacy to obtain Hetlioz. However, there is still potential for a physician to give a hard copy prescription for Hetlioz to a patient. Since Hetlioz is a capsule and does not have special administration instructions and does not require limited distribution under a Risk Evaluation and Mitigation Strategy (REMS), the potential for patients to take a hard copy prescription for Hetlioz to a retail pharmacy still exists. In addition, since your proposed limited distribution plan is voluntary and not enforceable, as it is not part of a REMS, we are concerned that the limited distribution plan may change at any time

without prior approval by the Agency. We do not have any means of enforcing or monitoring this plan and cannot rely on the limited distribution plan as a mechanism to prevent confusion. Furthermore, we have reports of name confusion with other products marketed under limited distribution systems and therefore our safety concern is not diminished with your product.

5.2 HETLIOZ WILL BE PRESCRIBED QHS OR (b) (4) BEFORE BEDTIME

We acknowledge that Hetlioz is intended to be prescribed once daily (b) (4) prior to bedtime; however, health care practitioners may not always write Hetlioz QHS or Hetlioz 1 PO (b) (4) before bedtime. (b) (4) data based on physician survey shows that the marketed melatonin receptor agonist, Rozarem (Ramelteon), which is in the same pharmacologic and therapeutic category as Hetlioz, can be prescribed "once a day (QD)."[3] Additionally, (b) (4) data based on physician survey shows that Ibuprofen OTC 200 mg has been prescribed "four times daily (QID)"[4]. The similarity between "QD" for Hetlioz and "QID" for Haltran increases the risk for confusion between these products[5].

5.3 NO MISINTERPRETATIONS OF HETLIOZ WITH HALTRAN IN THE NAME STUDY CONDUCTED BY (b) (4)

You provided handwriting samples to demonstrate lack of similarity between Hetlioz and Haltran. This technique of comparing the orthographic similarities of Hetlioz and Haltran is limited because you only compared scripted samples side by side from the same provider, whereas prescriptions presented to a (b) (4) armacy are likely to have a single drug written in isolation that can be misinterpreted.

You note a multifaceted name safety research study was conducted and none of the prescription interpretations resulted in the identification of Haltran or any other marketed drug products. This study included handwriting and verbal prescriptions for Hetlioz, in which 27 U.S. based healthcare practitioners interpreted the prescriptions in a simulation study. A name simulation study of this size does not provide conclusive evidence that a proposed name does not pose a risk of confusion given the small sample size used. A simulation study designed to detect close to a zero percentage error rate with statistical significance would require an extremely large sample size (e.g. a sample of approximately 26,000 would be required to detect an error rate of 0.001 at the 0.05 significance level)[6].

In summary, none of the information provided by (b) (4) was adequate to support the reconsideration of the proposed name Hetlioz. However, based on our independent review of the name pair, drug use information, and the simulation studies, we conclude

(b) (4)

[5] Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dosage Designations. 2013.

[6] This calculation was made to determine whether the error rate differs from 0.001 at a 0.05 significance level and 80% power, assuming the medication error rate of the sample is 0.0005. (published in FDA's PDUFA Pilot Project Proprietary Name Review Concept Paper)

that the name Hetlioz does not appear to be vulnerable to confusion with Haltran. This conclusion is based primarily upon the orthographic differences between these names, in conjunction with drug use data that shows that the discontinuation of the Haltran product did eliminate the prescribing of that name despite the fact that ibuprofen generics are available.

APPEARS THIS WAY ON ORIGINAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Reconsideration review

Date:	September 16, 2013
Reviewer:	Julie Neshiewat, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Hetlioz (Tasimelteon) Capsules, 20 mg
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1 INTRODUCTION

This review responds to a request from Vanda Pharmaceuticals to reconsider their proposed proprietary name, Hetlioz (Tasimelteon).[7]

On December 13, 2012, FDA notified Vanda Pharmaceuticals that the proposed proprietary name, Hetlioz, was unacceptable because of orthographic similarity and overlapping product characteristics with Haltran (Ibuprofen)[8].

2 MATERIALS REVIEWED

In our review of the request for reconsideration, we considered the information described in our previous review of the proposed proprietary name, Hetlioz, as well as the analysis submitted by Vanda Pharmaceuticals that was performed by the (b) (4) The Applicant identified four key points in the request for reconsideration cover letter:

- Use of Haltran as a prescription product has been discontinued
- Hetlioz will be dispensed using specialty pharmacies
- Physicians will most likely write the prescription as Hetlioz 1 PO QHS or Hetlioz 1 PO (b) (4) before bedtime instead of 1 PO QD
- No misinterpretations of Hetlioz with Haltran was identified in the name safety research study conducted by (b) (4)

3 CONCLUSIONS

The data reviewed is insufficient to support approval of the proposed proprietary name, Hetlioz. Section 4 provides comments to the Applicant. If you have further questions or need clarifications, please contact Ermias Zerislassie, OSE project manager, at 301-796-0097.

4 COMMENTS TO THE APPLICANT

We completed our review of your request for reconsideration of the proposed proprietary name Hetlioz. We determined that the data does not convince us that the proposed proprietary name, Hetlioz, will not pose a risk for confusion with Haltran, and we maintain our original position that Hetlioz and Haltran are vulnerable to name confusion which can lead to medication errors.

We provide the following response regarding the key points identified in your request for reconsideration cover letter.

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[7] Baroldi, P. Request for reconsideration of the proprietary name, Hetlioz (Tasimelteon), NDA 205677. Washington (DC): Vanda Pharmaceuticals, Inc. 2013 June 17.

[8] Holquist, C. Hetlioz (IND 054776): Proprietary name unacceptable (RCM 2012-1422; Reference ID 3230383). Silver Spring (MD): Food and Drug Administration, Division of Medication Error and Prevention Analysis (US); 2012 Dec 13.

4.1 HALTRAN IS A DISCONTINUED PRODUCT

You noted that SAEGIS PharmaIn-Use data indicated the last year of recorded sales for Haltran was 2004. Although the recorded sales for Haltran has discontinued, it does not indicate that health care practitioners are no longer using the name Haltran to prescribe. A search of usage data shows a low volume of health care practitioners have continued to write prescriptions for the name Haltran over the past three years[9]. We are concerned that some health care practitioners may continue to write prescriptions for Haltran despite the product discontinuation[10].

You noted that Haltran no longer appears in ChemIndex; however, when we typed Haltran into a few commonly used pharmaceutical databases, such as Clinical Pharmacology, Facts and Comparisons, and Micromedex, the monograph for Ibuprofen is retrieved. We are concerned that if a pharmacist misinterpreted a prescription for Hetlioz as Haltran and could not find Haltran in the pharmacy computer system and referred to one of those databases, the pharmacist would see that Haltran is ibuprofen and a generic ibuprofen could be dispensed to the patient.

You noted that Haltran was a trademark filed by Upjohn in 1983 and was cancelled in 2005. However, a search of the United States Patent and Trademark Office: Trademark Electronic Search System website on July 17, 2013 indicates the trademark Haltran was filed by Doctor's Affiliates, Inc. for Ibuprofen. The filing date of Haltran was May 15, 2013 with a first use in commerce date of May 1, 2013. We are concerned that the name Haltran may continue to be used and associated with Ibuprofen.

4.2 HETLIOZ WILL BE DISPENSED USING SPECIALTY PHARMACIES

You noted that Hetlioz will be dispensed in specialty pharmacies, and products such as Haltran and over the counter (OTC) ibuprofen would not be typically dispensed in a specialty pharmacy. Although specialty pharmacies may not typically dispense OTC products, if a patient took a prescription for Hetlioz to a retail pharmacy, the pharmacist may misinterpret Hetlioz as Haltran, and OTC ibuprofen could be dispensed. Furthermore, although a patient does not need a prescription to obtain OTC ibuprofen, health care practitioners issue prescriptions for OTC products.

We note that you intend physicians to fax a patient enrollment form to a specialty pharmacy to obtain Hetlioz. However, there is still potential for a physician to give a hard copy prescription for Hetlioz to a patient. Since Hetlioz is a capsule and does not have special administration instructions and does not require limited distribution under a Risk Evaluation and Mitigation Strategy (REMS), the potential for patients to take a hard copy prescription for Hetlioz to a retail pharmacy still exists. In addition, since your proposed limited distribution plan is voluntary and not enforceable, as it is not part of a REMS, we are concerned that the limited distribution plan may change at any time without prior approval by the Agency. We do not have any means of enforcing or

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[9] (b) (4) Vector One®: National (VONA).Year 2008 to 2012. Extracted June 27, 2013.

[10] Tu C, Taylor K, and Chai G. Use of Proprietary Names by Prescribers for Discontinued Brand Drug Products with Existing Generic Equivalents. Drug Information Journal. <http://dij.sagepub.com/content/early/2012/08/21/0092861512456282>

monitoring this plan and cannot rely on the limited distribution plan as a mechanism to prevent confusion. Furthermore, we have reports of name confusion with other products marketed under limited distribution systems and therefore our safety concern is not diminished with your product.

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You provided handwriting samples to demonstrate lack of similarity between Hetlioz and Haltran. This technique of comparing the orthographic similarities of Hetlioz and Haltran is limited because you only compared scripted samples side by side from the same provider, whereas prescriptions presented to a pharmacy are likely to have a single drug written in isolation that can be misinterpreted.

You further point out the ending 'ioz' in Hetlioz looks different from the ending letters 'ran' in Haltran. We disagree as the letter 'i' and 'r' can appear as a similar narrow letter, followed by similar rounded vowels of 'o' and 'a,' and if not scripted with a prominent down stroke, the 'z' and 'n' can look similar.

You note a multifaceted name safety research study was conducted and none of the prescription interpretations resulted in the identification of Haltran or any other marketed drug products. This study included handwriting and verbal prescriptions for Hetlioz, in which 27 U.S. based healthcare practitioners interpreted the prescriptions in a simulation study. A name simulation study of this size does not provide conclusive evidence that a proposed name does not pose a risk of confusion given the small sample size used. A simulation study designed to detect close to a zero percentage error rate with statistical significance would require an extremely large sample size (e.g. a sample of approximately 26,000 would be required to detect an error rate of 0.001 at the 0.05 significance level)[14].

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[13] Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dosage Designations. 2013.

[14] This calculation was made to determine whether the error rate differs from 0.001 at a 0.05 significance level and 80% power, assuming the medication error rate of the sample is 0.0005. (published in FDA's PDUFA Pilot Project Proprietary Name Review Concept Paper)

In summary, based on the above information, we do not agree that there are sufficient differences between Hetlioz and Haltran that will help minimize the risk for confusion and error.

APPEARS THIS WAY ON ORIGINAL

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

/s/

JULIE V NESHIEWAT
09/16/2013

IRENE Z CHAN
09/16/2013

CAROL A HOLQUIST on behalf of KELLIE A TAYLOR
09/16/2013
Signing on behalf of Kellie Taylor

CAROL A HOLQUIST
09/16/2013