

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-145**

**PROPRIETARY NAME REVIEW(S)**

**Division of Medication Errors and Technical Support (DMETS)  
Office of Surveillance and Epidemiology  
White Oak Bldg #22, Mailstop 4447  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME, LABEL, AND LABELING REVIEW**

**DATE OF REVIEW:** March 26, 2007

**IND#** 69,928  
**NDA #:** 22-145

**NAME OF DRUG:** Isentress  
(Raltegravir Potassium) Tablets  
400 mg

**NDA HOLDER:** Merck & Co., Inc.

**I. INTRODUCTION:**

This review was written in response to a request from the Division of Antiviral Products (HFD-530), for an assessment of the proprietary name "Isentress" regarding potential name confusion with other proprietary or established drug names. Container and insert labeling were provided for review and comment at this time. The sponsor has also submitted a RiskMAP to address the risks of Immune Reconstitution Inflammatory Syndrome (IRIS), drug resistance, malignancies and drug interaction with rifampin, phenobarbital, phenytoin, and other strong UGT1A1 inducers. Comments on the RiskMAP will be forwarded under separate cover from the Office of Surveillance and Epidemiology.

**PRODUCT INFORMATION**

Isentress (raltegravir potassium) is indicated in combination with other anti-retroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Isentress will be available in 400 mg tablets. The recommended dose is 400 mg twice daily. Isentress will be supplied in \_\_\_\_\_

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3,4</sup> for existing drug names which sound-alike or look-alike to “Isentress” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted<sup>5</sup>. The Saegis<sup>6</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Isentress. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Isentress, acceptable from a promotional perspective.
2. The Expert Panel identified thirteen proprietary names that were thought to have the potential for confusion with Isentress. The names are as follows: Invirase, Iressa, Astelin, Asendin, Pitressin, Vi-Stress, Estrovis, Centrax, Lucentis, Enpresse-28, Centex PSE, and Imitrex. In addition, one panel member commented that Isentress could look like “1 Centrum”.

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<sup>1</sup> MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

<sup>4</sup> Phonetic and Orthographic Computer Analysis (POCA)

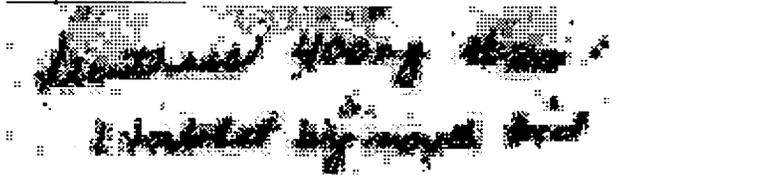
<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

B. PRESCRIPTION STUDY ANALYSIS

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Isentress with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Isentress (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	Isentress 400 mg Dispense #30 1 tablet by mouth bid
<u>Inpatient RX:</u> 	

3. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A (page 8) for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Isentress, thirteen proprietary names were identified as having a similar appearance or sound to Isentress. These names are: Invirase, Iressa, Astelin, Asendin, Pitressin, Vi-Stress, Estrovis, Centrax, Lucentis, Enpresse-28, Centex PSE, 1 Centrum and Imitrex.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Isentress.

Upon further analysis, six of the twelve names were not considered further due to the lack of significant look-alike and/or sound alike similarities to Isentress in addition to differentiating product characteristics that may include: indication for use, product strength, usual dosage, route of administration, frequency of administration, dosage form, prescriber population, patient population, product unavailability and/or area of marketing. These five names include: Astelin, Asendin, Centrax, Lucentis, Centex PSE and 1 Centrum.

The remaining seven products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Isentress	Raltegravir potassium Tablets 400 mg	400 mg twice a day	NA
Invirase	Saquinavir Mesylate Capsules: 200 mg Tablets : 500 mg	1000 mg twice a day in combination with zidovudine 100 mg twice a day; should be taken within 2 hours after a meal	LA
Iressa	Gefitinib Tablets: 250 mg	250 mg tablet daily with or without food	LA
Enpresse-28	Ethinyl estradiol; levonorgestrel Tablets: 0.03 mg , 0.04 mg, 0.03 mg; 0.05 mg, 0.075 mg, 0.125 mg	<i>Adult and adolescent females:</i> 1 tablet PO once daily for 21 days in the order indicated in the pack, followed by a period of 7 days without drug. Your pill pack contains 21 pills with active medication. It may also contain 7 reminder pills with no medication. Take one active pill (with hormones) once daily for 21 days in a row. If you are using a product with 28 tablets, take an inactive pill once daily for 7 days in a row after you have taken the last active pill unless otherwise directed by your doctor.	LA/SA
Imitrex	Sumatriptan Injection: 4 mg, 6 mg prefilled syringe; single dose vial: 6 mg Tablets: 25, 50, 100 mg Nasal spray: 5 mg, 20 mg	Injection: 6 mg injected subcutaneously at the onset of headache; maximum dose that can be given in 24 hours is two 6 mg injections separated by at least one hour. Tablets: 25-100 mg by mouth Intranasal: 5 mg, 10 mg or 20 mg spray in one nostril as a single dose	LA/SA
Pitressin	Vasopressin Injection: 20 units/mL	<i>Adults:</i> 5-10 units IM or SC, 2-4 times per day as needed <i>Children:</i> 2.5-10 units IM or SC, 2-4 times per day as needed	LA
Vi-Stress	Nutritional Supplement Tablets	One tablet once daily	LA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
ISENTRESS	Raltegravir potassium Tablets 400 mg	400 mg twice a day	NA
Estrovis (Discontinued)	Quinestrol Tablets: 0.1 mg, 0.2 mg	No information found	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

In review of the aforementioned names Iressa, Pitressin, Estrovis, Enpresse-28 and Imitrex, were determined to have minimal potential for confusion for the following reasons:

- Iressa is indicated for the treatment of non-small lung cancer after failure of both platinum-based and docetaxel chemotherapies. Although Iressa looks slightly similar to Isentress, the products differ in therapeutic class, indication for use, strength and usual dose.
- Pitressin is used for the treatment of central diabetes insipidus and only shares an overlapping frequency of administration of twice a day with Isentress.
- Estrovis (quinestrol) is a medication used to replace estrogen that has been discontinued and does not have a generic equivalent and has minimal sound and look-alike similarity.
- Enpresse-28 is an oral contraceptive which only slightly looks or sounds similar to Isentress. Although both are oral tablets, their differentiating product characteristics include indication for use, therapeutic class, strength and frequency of administration. In addition, the modifier of 28 helps to differentiate the name pair.
- Imitrex is used as needed at the onset of migraines and only shares a weak orthographic similarity to Isentress. Although the products share an overlapping dosage form of tablets, the products differ in strength, usual dose, indication for use, and therapeutic class. Imitrex is also available as an injection and intranasally.

Although the remaining names Vi-Stress and Invirase, may share either an increased orthographic similarity or overlapping drug characteristics with Isentress compared to the above five names, they were also determined not to pose significant potential for confusion with Isentress for the following reasons listed below.

1. Vi-Stress was identified as a name with similar appearance to Isentress. Vi-Stress is an over-the-counter (OTC) dietary supplement containing vitamin E, Vitamin C and a vitamin B complex for nutritional supplementation. The recommended dose is one tablet by mouth daily.

Vi-Stress may look similar to Isentress because both names have the same suffix (-tress) and contain "is" in similar positions at the beginning of their names (see example below). However, the beginning letters "V" vs. "I" helps to differentiate the product names as well as the extra letters "en" in the middle of Isentress.

*Vi-stress  
Isentress*

Vi-Stress and Isentress have overlapping product characteristics such as route of administration (oral) and dosage form (tablets). Additionally, both products can be ordered without the specification of a strength (e.g., 1 tablet) since both products are available in one strength. However, they differ in indication of use (nutritional supplementation vs. treatment of HIV-1), frequency of administration (once daily vs. twice daily), usual dose (1 tablet daily vs. 400 mg twice a day), and prescription status (OTC vs. prescription) which may help to differentiate the names. Although there is an orthographic similarity between the names Vi-Stress and Isentress, the potential to confuse the names is minimal because of the different product characteristics.

2. Invirase was identified as a name with similar appearance to Isentress. Invirase is indicated for the treatment of HIV infection and is used in combination with ritonavir and other antiretroviral agents. The recommended dose of Invirase is 1000 mg twice a day in combination with retonavir 100 mg twice a day.

Invirase and Isentress may look similar because they are similar in length and both begin with the letter "I". Additionally, the letter "r" and the letter "s" share the same position at the end of the drug product's names (see example below). However, the letters in the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup>, positions help to differentiate the names ("-nvi-" vs. "-sen-"), as well as the upstroke letter "t" in the middle of Isentress.

*Invirase*  
*Isentress*

Both drugs share an overlapping therapeutic class (anti-viral), indication for use (treatment of HIV), route of administration (oral), dosage form (capsules and tablets vs. tablets) and frequency of administration (twice a day). However, Invirase and Isentress differ in strength (200 mg capsules or 500 mg tablets vs. 400 mg) and usual dose (1000 mg twice a day vs. 400 mg twice a day) which may help to differentiate the names. In addition an order for Invirase must be accompanied with an order for Retonavir 100 mg, as these medications must be given concomitantly. Although Invirase and Isentress share some overlapping product characteristics, the lack of convincing orthographic similarities minimize the potential for confusion between these two drug products.

## II. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

In the review of the container label and insert labeling of Isentress, DMETS focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement, which may minimize potential user error and maximize patient safety.

### 1. CONTAINER LABEL

a.



b.



1   Page(s) Withheld

       Trade Secret / Confidential

  X   Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative-  7

Appendix A: Prescription Study Results for Isentress

<b>Inpatient</b>	<b>Outpatient</b>	<b>Verbal</b>
Bentress	Isentress	ACENTRUS
isentress	Isentress	Ascentris
Isentress	Isentress	ASETRAS
Isentress	Isentress	Asentris
Isentress	Isentress	Assentres
Isentress	Isentress	Assentrus
Isentress	Isentress	Icentra
Isentress	Isentress	Icentris
Isentress	Isentress	Icentrus
Isentress	isentress	Ifentra
Isentress	Sentress	Isentra
Isentress		Isentris
Osentress		Isentris
		Isentris
		Isentrus

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