

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206500Orig1s000**

**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  
Office of Medication Error Prevention and Risk Management**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

|                                     |                                                                        |
|-------------------------------------|------------------------------------------------------------------------|
| Date:                               | August 25, 2015                                                        |
| Reviewer(s):                        | Felicia Duffy, RN, BSN, MSED<br>Division of Risk Management            |
| Acting Team Leader:                 | Jamie Wilkins Parker, Pharm.D.<br>Division of Risk Management          |
| Acting Deputy<br>Division Director: | Reema Mehta, Pharm.D., M.P.H.<br>Division of Risk Management           |
| Subject:                            | Evaluation to determine if a REMS is necessary                         |
| Drug Name(s):                       | rolapitant                                                             |
| Therapeutic Class:                  | selective competitive antagonist of human substance P/NK1<br>receptors |
| Dosage and Route:                   | 90 mg tablets                                                          |
| Indication:                         | chemotherapy induced nausea and vomiting                               |
| Application Type/Number:            | NDA 206500                                                             |
| Applicant/sponsor:                  | Tesaro, Inc.                                                           |
| OSE RCM #:                          | 2014-2149                                                              |

## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation to assess the need for a risk evaluation and mitigation strategy (REMS) for rolapitant hydrochloride tablets, NDA 206500. On September 5, 2014, the Agency received an original NDA from Tesaro, Inc. (Tesaro) for rolapitant. The Sponsor's proposed indication is for use in combination with other antiemetic agents in adults for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Tesaro did not include a proposed REMS or risk management plan with the submission.

### 1.1 BACKGROUND OF CONDITION<sup>1,2</sup>

Nausea and vomiting are two of the most debilitating side effects of cytotoxic chemotherapy. After administration of highly-emetogenic chemotherapy (HEC) without prophylaxis, >90% of treated patients will experience chemotherapy-induced nausea and vomiting (CINV). Agents that induce an incidence of CINV in 31% to 90% of patients are referred to as moderately-emetogenic chemotherapy (MEC). Active management of CINV reduces patient suffering and increases the likelihood that cancer patients will continue to receive potentially life-extending treatment on schedule and at appropriate doses.

There are two described phases of CINV, acute and delayed, which are mediated by neurotransmitter-driven mechanisms, primarily serotonin (5-HT) and neurokinin (NK1). The acute phase, which represents the first 24 hours following chemotherapy, is mediated in part by chemotherapy-induced increases in 5-HT release and activation of 5-HT<sub>3</sub> receptors on vagal afferent neurons in the gut. In addition to serotonin, other neurotransmitters are implicated in the etiology of acute CINV, as indicated by a further reduction in the incidence of nausea and vomiting when NK1 receptor antagonists are added to a standard antiemetic regimen that includes a 5-HT<sub>3</sub> receptor antagonist.

The etiology of the delayed phase of CINV, which occurs 2 to 5 days following the initiation of chemotherapy, involves the release of the neurokinin peptide substance P in the brain. Antiemetic therapy with a corticosteroid and 5-HT<sub>3</sub> receptor antagonist alone is minimally effective during the delayed phase of CINV. The combination of NK1 and 5-HT<sub>3</sub> receptor antagonists, together with a corticosteroid, provides the greatest preventative effect from CINV. This triplet mitigates risk for CINV across the entire 5-day period following administration of chemotherapy. For patients who cannot tolerate dexamethasone, triplet therapy may not be an option and for these patients, an NK1 receptor antagonist becomes even more important for offering protection from CINV.

A variety of treatments are used to prevent CINV. Treatment regimens differ based on the emetogenic potential of the chemotherapeutic agents (i.e., high, medium, low). Table 1 below describes the typical treatment regimens used to prevent CINV based on the emetogenic potential of the chemotherapeutic agent(s).

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<sup>1</sup> Tesaro. Clinical Overview for Varubi (rolapitant hydrochloride), received September 5, 2014. Supplement 000/Sequence 0000.

<sup>2</sup> Tesaro. Summary of Clinical Safety for Varubi (rolapitant hydrochloride), received September 5, 2014. Supplement 000/Sequence 0000.

**Table 1. Adult patients exposed to emetogenic chemotherapeutic agents are treated with the following to prevent CIN<sup>3</sup>:**

| <b>Emetic risk and effects</b>                                                                                                                                                                                                                                                                                                                                                   | <b>Therapy</b>                                                                                                                                                    | <b>Recommended dosage</b>                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Emetic risk: high</p> <p>5-HT<sub>3</sub> receptor antagonists:<br/>common side effects – constipation, headache, asthenia;<br/>serious side effects: hypersensitivity (W&amp;P); QT prolongation (adverse reactions)</p> <p>NK-1 receptor antagonists:<br/>common side effects - alopecia, anorexia, asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea</p> | <p>5-HT<sub>3</sub> receptor antagonists AND dexamethasone orally or IV AND substance P neurokinin-1 (NK-1)-receptor antagonist (aprepitant or fosaprepitant)</p> | <p>Dolasetron 100 mg orally or 100 mg IV or 1.8 mg/mg IV</p> <p>Granisetron 2 mg orally or 1 mg IV or 0.01 mg/kg IV or 34.3 mg transdermal patch</p> <p>Ondansetron 16 – 24 mg orally or 8 – 12 mg IV (maximum 32 mg)</p> <p>Palonosetron 0.25 mg IV</p> <p>Dexamethasone 12 mg orally</p> <p>Aprepitant 125 mg orally or Fosaprepitant 115 mg IV</p> <p>Netupitant/palonosetron 300mg/0.5mg orally</p> |
| Emetic risk: moderate                                                                                                                                                                                                                                                                                                                                                            | 5-HT <sub>3</sub> receptor antagonists AND dexamethasone orally or IV AND aprepitant or fosaprepitant                                                             | <p>Dolasetron 100 mg orally or 100 mg IV or 1.8 mg/mg IV</p> <p>Granisetron 2 mg orally or 1 mg IV or 0.01 mg/kg IV or 34.3 mg transdermal patch</p> <p>Ondansetron 16 – 24 mg orally or 8 – 12 mg IV (maximum 32 mg)</p> <p>Palonosetron 0.25 mg IV or Palonosetron 0.5 mg orally</p> <p>Dexamethasone 8 - 12 mg orally or IV</p> <p>Aprepitant 125 mg orally or Fosaprepitant 115 mg IV</p>           |
| Emetic risk: low                                                                                                                                                                                                                                                                                                                                                                 | Dexamethasone                                                                                                                                                     | Dexamethasone 8 - 12 mg orally or IV                                                                                                                                                                                                                                                                                                                                                                    |
| Emetic risk: minimal                                                                                                                                                                                                                                                                                                                                                             | None                                                                                                                                                              | N/A                                                                                                                                                                                                                                                                                                                                                                                                     |

NK-1 receptor antagonists are associated with alopecia, anorexia, asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea and may cause clinically significant drug-drug interactions with warfarin and oral contraceptives in light of its inhibition of the CYP3A4 isoenzyme.

<sup>3</sup> Barbara Wells, et al. Dosage Recommendations for CIN<sup>3</sup> for Adult Patients, Chapter 27, Nausea and Vomiting, Pharmacotherapy Handbook, 2012.

## 1.2 PRODUCT BACKGROUND

Rolapitant is a selective competitive antagonist of human substance P/NK<sub>1</sub> receptors. The Sponsor's proposed indication is for use in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Rolapitant will be available as 90 mg (equivalent to 100 mg rolapitant hydrochloride) oral tablets. The recommended dose is 180 mg administered 2 hours prior to the start of chemotherapy (b) (4)

(b) (4) It should be administered in combination with dexamethasone and a 5-HT<sub>3</sub> receptor antagonist. Rolapitant can be administered with or without food.

Rolapitant is a cytochrome P450 2D6 (CYP2D6) inhibitor and the effects last at least 7 days. Therefore, rolapitant is contraindicated in patients receiving thioridazine, a CYP2D6 substrate due to a potential increased risk of QT prolongation and torsades de pointes. Additionally, use of rolapitant should be avoided with pimozide, another CYP2D6 substrate, due to a potential increased risk of QT prolongation. Prescribers should monitor for adverse reactions if concomitant use of rolapitant and other CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

## 1.3 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to the evaluation to assess the need for a REMS for rolapitant:

September 5, 2014: The Agency received an original NDA submission from Tesaro for rolapitant for use in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. The Applicant did not submit a proposed REMS or risk management plan with the submission.

February 12, 2015: The Agency communicated to the Sponsor at the Mid-cycle communication meeting that, at this time, we do not believe that a REMS is necessary to ensure benefits of this product outweigh the risks.

May 14, 2015: Late-cycle meeting background package from the Agency to the Sponsor communicated that at this stage, we do not believe that a REMS is necessary to ensure the benefits of the product outweigh the risks.

June 3, 2015: The Late Cycle meeting was held between the Sponsor and the Agency. REMS was not discussed during this meeting.

## 2 MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Tesaro Inc. Clinical Overview for Rolapitant (NDA 206500), received September 5, 2014.
- Tesaro Inc. Summary of Clinical Safety for Rolapitant (NDA 206500), received September 5, 2014.

- Johnson, A. DGIEP Mid-cycle Meeting slides for Rolapitant (NDA 206500), dated February 3, 2015.
- Chung M. DGIEP Mid-cycle Communication to Tessaro Inc. for Rolapitant (NDA 206500), dated March 13, 2015.
- Johnson, A. DGIEP Clinical Review for Rolapitant (NDA 206500), dated May 5, 2015.
- Tesaro Inc., Draft Prescribing Information for Rolapitant (NDA 206500), received July 25, 2015.

### 3 RESULTS OF REVIEW

#### 3.1 OVERVIEW OF CLINICAL PROGRAM

The core development program to support efficacy of rolapitant for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy is based on three clinical studies (Study P04832, P04833, and P04834). For all 3 studies, the primary efficacy endpoint was complete response (CR) defined as having no emesis and no rescue medication use in the delayed phase (>24-120 hours) following the administration of HEC or MEC during the first cycle of chemotherapy. No emesis was defined as no vomiting, writhing or dry heaving. Additional details regarding the studies is as follows:

- Studies P04832 and P04833: These HEC studies were identical with the exception of the location of the study sites. The studies were global, multicenter, randomized, parallel-group, double-blind, and active-controlled studies. The primary objective of the studies was to determine whether administration of rolapitant with a 5-HT<sub>3</sub> receptor antagonist (granisetron) and dexamethasone improves protection from CINV in the delayed phase (>24 to 120 hours) compared to administration of placebo with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in subjects receiving HEC. All subjects received a single dose of rolapitant 200 mg or placebo 1 to 2 hours prior to administration of the first chemotherapeutic agent on Day 1.  
In Study P04832 and P04833, per DGIEP, the CR rate in the delayed phase was statistically significantly higher in the rolapitant 200 mg compared to the placebo group. The control rate seen in rolapitant patients was 72.7% and 70.1%, respectively; while the control rate seen in placebo patients was 58.4% and 61.9%, respectively.
- Study P04834: This study was a global, multicenter, randomized, parallel-group, double-blind, active-controlled study designed to determine whether administration of rolapitant with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone improves CINV in the delayed phase (>24 to 120 hours) compared with administration of placebo with 5-HT<sub>3</sub> receptor antagonist (granisetron) and dexamethasone in subjects receiving MEC. The dose and timing of receipt of rolapitant or placebo (i.e., 1-2 hours prior to the initiation of chemotherapy on Day 1) was the same in this study as in studies P04832 and P0433. Per DGIEP, the CR rate for patients taking rolapitant in the delayed phase was 71.3% compared with a 61.6% complete response rate seen in placebo patients, p<0.001.

Per the DGIEP medical reviewer: *The primary efficacy results from studies 32, 33, and 34 support the efficacy of rolapitant 200 mg for the prevention of CINV in the delayed phase (>24-120 hours) following the administration of HEC and MEC.* (b) (4)

(b) (4) *the delayed phase should be indicated. It is accepted that the 5-HT<sub>3</sub> antagonist class of medications and steroids work for the prevention of CINV (b) (4) the use of rolapitant with these products is likely to provide coverage for the prevention of CINV during the (b) (4) delayed phase (b) (4) following the administration of HEC and MEC.*<sup>4</sup>

### 3.2 SAFETY CONCERNS

Rolapitant was evaluated in 1,567 patients with cancer undergoing treatment with MEC or HEC in controlled phase 2 and 3 studies. During Study 51, a phase 2 trial, 273 patients were exposed to doses of rolapitant less than 200 mg. In Studies 32, 33, 34, and 51 there were 1,294 patients exposed to 200 mg of rolapitant.

Per DGIEP, The overall incidence of treatment emergent adverse events (TEAEs) across the 1,567 patients who received rolapitant (all doses) was 65.2%. The percentage of patients reporting TEAEs leading to study drug discontinuation was the same among control- and rolapitant-treated patients, 3.1%. Similarly, the incidence of serious adverse events and deaths was similar among control- and rolapitant-treated patients. The clinical reviewer commented that the deaths reported in the rolapitant program were expected given the patient population.

The most commonly reported adverse events in the CINV studies were gastrointestinal disturbances, reported in 43.5% and 45.3% of subjects in the 200 mg rolapitant and control groups, respectively, primarily related to reports of constipation (14.4% and 16.5%, respectively), diarrhea (12.7% and 12.3%, respectively) and nausea (11.7% and 15.4%, respectively). Other commonly reported events in the rolapitant 200 mg and control groups included: fatigue (19.8% and 19.4%, respectively), asthenia (14.1% and 14.6%, respectively), neutropenia (15.2% and 13.3%, respectively), anemia (10.5% and 8.7%, respectively), alopecia (15.8% and 17.4%, respectively) and decreased appetite (13.4% and 13.2%, respectively).

The most commonly reported SAEs in the rolapitant 200 mg group with corresponding incidence in the control group were febrile neutropenia (2.6% and 3.0%, respectively) and neutropenia (1.2% and 2.0%, respectively). The clinical reviewer indicated that it appears reasonable and not drug-related that the most commonly reported SAEs was febrile neutropenia given that the patients were receiving myelosuppressive chemotherapy.

## 4 DISCUSSION

Chemotherapy induced nausea and vomiting causes significant morbidity and decreased quality of life in the U.S. population and there is a need for more treatments for this condition, especially in light of the aging population and consequent ongoing increase in the prevalence of cancer and chemotherapy treatment.

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<sup>4</sup> Johnson, A. DGIEP Clinical Review for Rolapitant (NDA 206500), dated May 5, 2015.

In the clinical trials, rolapitant was found to be more efficacious as compared to placebo for the prevention of CINV during the delayed phase, and will be approved with the indication for use in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including but not limited to HEC.

Rolapitant was associated with a low incidence of SAEs and non-serious adverse events. Most deaths were associated with comorbidities associated with the patient's cancer diagnosis or adverse events from a patient's chemotherapy regimen. Furthermore, the observed safety profile in the clinical studies for rolapitant was consistent with the known safety profile for the drug class. Therefore, DRISK has determined that a REMS is not necessary to ensure the benefits of rolapitant outweigh the risks.

## **5 CONCLUSION**

In conclusion, risk mitigation measures beyond professional labeling are not necessary for rolapitant. Rolapitant has proven efficacy and safety for its use in combination with other antiemetic agents for the prevention of delayed nausea and vomiting associated with initial and repeat course of emetogenic cancer chemotherapy. Thus, the benefit-risk profile for rolapitant is acceptable and the risks can be adequately communicated through professional labeling.

Should DGIEP have any concerns or questions, feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/  
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JAMIE C WILKINS PARKER  
08/25/2015

REEMA J MEHTA  
08/26/2015  
I concur.