

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206500Orig1s000**

**OFFICE DIRECTOR MEMO**

Office Deputy Director Decisional Memo

|                                                       |                                                                                                                                                                                                                                                      |
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| <b>Date</b>                                           | August 31, 2015                                                                                                                                                                                                                                      |
| <b>From</b>                                           | Amy G. Egan, MD, MPH                                                                                                                                                                                                                                 |
| <b>Subject</b>                                        | Office Deputy Director Decisional Memo                                                                                                                                                                                                               |
| <b>NDA/BLA #</b>                                      | NDA 206500                                                                                                                                                                                                                                           |
| <b>Applicant Name</b>                                 | Tesaro Inc.                                                                                                                                                                                                                                          |
| <b>Date of Submission</b>                             | September 5, 2014                                                                                                                                                                                                                                    |
| <b>PDUFA Goal Date</b>                                | September 5, 2015                                                                                                                                                                                                                                    |
| <b>Proprietary Name /<br/>Established (USAN) Name</b> | Varubi/<br>rolapitant                                                                                                                                                                                                                                |
| <b>Dosage Forms / Strength</b>                        | Tablets/90 mg (equivalent to 100 mg rolapitant hydrochloride)                                                                                                                                                                                        |
| <b>Applicant Proposed Indication(s)</b>               | In adults in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.                                                        |
| <b>Action:</b>                                        | Approval                                                                                                                                                                                                                                             |
| <b>Approved<br/>Indication(s)/Populations</b>         | 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. |

| <b>Material Reviewed/Consulted</b> | <b>Names of discipline reviewers</b>                               |
|------------------------------------|--------------------------------------------------------------------|
| Medical Officer Review             | Aisha Peterson Johnson, MD                                         |
| Statistical Review                 | Wen-Jen Chen, PhD                                                  |
| Pharmacology Toxicology Review     | Tracy Behrsing, PhD                                                |
| CMC Review/OBP Review              | Danuta Gromek-Woods, PhD                                           |
| Microbiology Review                | Bryan Riley, PhD                                                   |
| Clinical Pharmacology Review       | Insook Kim, PhD                                                    |
| DPMH                               | Erica Radden MD (pediatric); Miriam Dinatale, DO (maternal health) |
| CSS                                | Katherine Bonson, PhD                                              |
| SEALD                              | Michelle Campbell, PhD                                             |
| DMPP                               | Karen Dowdy, RN, BSN                                               |
| OPDP                               | Adewale Adeleye, PharmD                                            |
| OSI                                | Susan Leibenhaut, MD                                               |
| CDTL Review                        | Donna Griebel, MD                                                  |
| OSE/DMEPA                          | Sherly Abraham, RPh                                                |

CMC=Chemistry Manufacturing and Controls  
 OBP=Office of Biotechnology Products  
 DPMH=Division of Pediatric and Maternal Health  
 CSS=Controlled Substances Staff  
 SEALD=Study Endpoints and Labeling Development  
 DMPP=Division of Medical Policy Programs  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis

### Benefit-Risk Summary and Assessment

Varubi (rolapitant) is an orally administered human substance P/NK<sub>1</sub> receptor antagonist. This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Products' approval recommendation for NDA 206500 for Varubi (rolapitant) tablets to be used in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC).

Efficacy was assessed in two double-blind, placebo-controlled trials in 1070 subjects receiving HEC randomized to a single oral dose of Varubi 180 mg plus intravenous (IV) granisetron (10 mcg/kg) or IV granisetron (10 mcg/kg) alone (Trials 1 and 2), and in one double-blind, placebo-controlled trial in 1332 subjects receiving moderately emetogenic chemotherapy (MEC), at least 50% of subjects receiving anthracycline-cyclophosphamide (AC) based chemotherapy, randomized to a single oral dose of Varubi 180 mg administered with oral granisetron (2 mg) or oral granisetron (2 mg) alone (Trial 3). The key efficacy endpoint in all trials was complete response (CR), defined as no emesis and no use of rescue medication, in the delayed phase (25-120 hours) of chemotherapy-induced nausea and vomiting (CINV) following initiation of Cycle 1 of chemotherapy. The key secondary endpoints were the CR rates for the acute (0-24 hours) and overall phases (0-120 hours) of CINV following initiation of Cycle 1 of chemotherapy. Efficacy was demonstrated in the delayed phase of CINV in all 3 trials, (b) (4)

The safety of Varubi was assessed in 1,567 cancer patients, including 781 subjects exposed to Varubi for at least 4 cycles of chemotherapy and 367 subjects exposed for at least 6 cycles. All subjects received a single oral dose of Varubi 1 to 2 hours prior to the start of chemotherapy, including 1,294 subjects who received the 180 mg dose and 273 subjects who received doses less than 180 mg. In all trials, dexamethasone and a 5-HT<sub>3</sub> receptor antagonist were co-administered. In subjects receiving cisplatin-based chemotherapy, the most common adverse reactions reported with Varubi treatment in Cycle 1 were: neutropenia, hiccups, and abdominal pain. In subjects receiving MEC, including AC based chemotherapy, the most common adverse reactions reported in association with Varubi treatment in Cycle 1 were: decreased appetite, neutropenia, dizziness, dyspepsia, urinary tract infection, stomatitis, and anemia. The safety profile in subsequent chemotherapy cycles was similar to that observed in Cycle 1. There were no serious safety issues identified in the clinical development program; however, rolapitant is a moderate inhibitor of CYP2D6, an inhibitor of Breast-Cancer-Resistance Protein (BCRP), an inhibitor of P-

glycoprotein (P-gp), and a substrate for CYP3A4. Additionally, rolapitant has a long half-life and its inhibitory properties on CYP2D6 last at least 7 days or longer after a single dose of Varubi. Therefore, there is a potential for serious adverse reactions related to drug-drug interactions.

In the NDA, the applicant proposed an indication in (b) (4) delayed phases of CINV. The major review issue was whether the NDA provided substantial evidence of Varubi's (b) (4). Given that the delayed phase of chemotherapy-induced emesis is largely associated with the activation of tachykinin family NK<sub>1</sub> receptors in the central and peripheral nervous systems, it is expected that NK<sub>1</sub> receptor inhibition should provide its greatest benefit in the delayed phase. (b) (4) (b) (4) (b) (4)

Due to methodological issues with the conduct and analysis of the Phase 2 trial (an unblinded interim analysis), the (b) (4) and the small sample size, the Agency concluded that the Phase 2 trial did not constitute an adequate and well-controlled trial. (b) (4) (b) (4) (b) (4) (b) (4)

Another review issue was the adequacy of the Phase 3 data to support the indication “for use in repeat courses” of chemotherapy. The methodology used to assess efficacy in repeat chemotherapy cycles relied on subject recall. Subjects were asked at Visit 2 (Day 6 to 8) whether, since the start of the chemotherapy cycle, they had any episode of vomiting or retching or any nausea that interfered with their normal daily life. This endpoint was not the same endpoint as was employed in Cycle 1, i.e., CR in the delayed phase. According to the SAP, “subject response of no emesis or nausea by cycle for the MITT populations was assessed to evaluate whether repeat dosing demonstrated sustained benefit of the use of rolapitant over multiple cycles.” Presumably, “no emesis or nausea” was used as a surrogate for CR (no emesis and no use of rescue medication). There were numerically more Varubi-treated subjects than placebo-treated subjects who had no emesis/retching or nausea that interfered with normal daily life in most of the repeat cycles. While the applicant did not employ a particularly rigorous approach to the collection or analysis of the repeat cycle data, this approach is not inconsistent with another member of the class for whom an indication for use in repeat courses of chemotherapy was granted. Therefore,

the indication will include “initial and repeat courses of emetogenic cancer chemotherapy”. The Clinical Studies section of labeling will include a description of how the data were collected, as well as a graphical presentation of the data, consistent with other members of the class. Since there is a tendency for CINV symptoms to become progressively more severe with subsequent cycles of chemotherapy administration, future trials of drugs for the prevention of CINV should provide a more scientifically rigorous assessment of the drug’s efficacy in repeat cycles

There were no major safety issues. Issues related to the long half-life of Varubi and its inhibitory properties on CYP2D6 substrates, and the potential for drug-drug interactions well beyond the dosing period, i.e., for at least 7 days or longer, will be addressed in labeling and will be further assessed in a post-marketing required trial.

Discussions regarding product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval. The benefit-risk analysis of Varubi is favorable and supports approval. Varubi adds to the armamentarium of drugs available for adult patients for use in the prevention of the delayed phase of CINV.

| Dimension                             | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                             |
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| <a href="#">Analysis of Condition</a> | Chemotherapeutic agents produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT <sub>3</sub> receptors located on vagal afferents to initiate the vomiting reflex. The development of acute emesis <sup>1</sup> is known to depend on serotonin activation of 5-HT <sub>3</sub> receptors, while delayed emesis <sup>2</sup> has been largely associated with the activation of tachykinin family NK <sub>1</sub> receptors in the central and peripheral nervous systems by substance P. | CINV affects a significant proportion of cancer patients undergoing chemotherapy. CINV is characterized by both an acute phase, defined as nausea and vomiting occurring 0-24 hours after the start of chemotherapy, and a delayed phase, defined as nausea and vomiting occurring 25-120 hours after the start of chemotherapy. The two phases are associated with |

<sup>1</sup> Acute emesis refers to nausea and vomiting occurring 0-24 hours after the start of chemotherapy.

<sup>2</sup> Delayed emesis refers to nausea and vomiting occurring 25-120 hours after the start of chemotherapy.

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|                                         | <p>CINV has a significant impact on a patient's quality of life and can impair the ability to administer intensive chemotherapy regimens. CINV is estimated to afflict over 70% of cancer patients undergoing chemotherapy.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>activation of different receptors, 5-HT<sub>3</sub> for the acute phase, and NK<sub>1</sub> for the delayed phase.</p> <p>CINV has an enormous impact on the cancer patient's quality of life and can impair the ability to administer intensive chemotherapy regimens.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><u>Current Treatment Options</u></p> | <p>The American Society of Clinical Oncologists (ASCO) recommends the use of a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone and a substance P/NK<sub>1</sub> receptor antagonist for the prevention of CINV in patients at high emetic risk, i.e., patients receiving HEC. Evidence to support the ASCO recommendation is derived from review of clinical trials in the published literature.</p> <p>Currently approved 5-HT<sub>3</sub> receptor antagonists include ondansetron (oral and IV; approved for acute phase CINV associated with HEC and MEC), granisetron (oral and IV; approved for acute phase CINV associated with HEC and MEC), palonosetron (oral [approved for acute phase of CINV associated with MEC] and IV [approved for acute phase of CINV associated with HEC and acute and delayed phases of CINV associated with MEC]), and dolasetron (oral [approved for acute phase of CINV associated with MEC] and IV [approved for acute phase of CINV associated with HEC and MEC]). Studies have shown that the efficacy of 5-HT<sub>3</sub> antagonists generally is reduced during the delayed phase of CINV.</p> | <p>ASCO's recommendation for the prevention of CINV in patients at high emetic risk includes a 3-drug regimen: a 5-HT<sub>3</sub> receptor antagonist, dexamethasone, and a substance P/NK<sub>1</sub> receptor antagonist.</p> <p>The 5-HT<sub>3</sub> receptor antagonists largely exhibit their greatest efficacy during the acute phase of CINV, with waning efficacy during the delayed phase. Mechanistically, the substance P/NK<sub>1</sub> receptor antagonists should exhibit their greatest efficacy during the delayed phase of CINV.</p> <p>There are approved 5-HT<sub>3</sub> receptor antagonists - both oral and IV formulations - and approved substance P/NK<sub>1</sub> receptor antagonists – both oral and IV formulations. The 5-HT<sub>3</sub> receptor antagonists are all approved</p> |

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|                | <p>Currently approved substance P/NK<sub>1</sub> receptor antagonist products include Emend, which is available in two formulations – oral (aprepitant) and solution for injection (fosaprepitant) – and Akynzeo (an oral fixed dose combination [FDC] of netupitant and palonosetron). Both the oral and IV formulation of Emend are approved for the acute and delayed phases of CINV associated with HEC, and for the overall phase of CINV associated with MEC. The netupitant component of the Akynzeo FDC is approved for the acute and delayed phases of CINV associated with cancer chemotherapy including HEC.</p>                                                                                                                                                                                                                                                                                                                                                                    | <p>for the acute phase of CINV only, with the exception of the IV formulation of palonosetron which is approved in both the acute and delayed phases in MEC. The oral and IV formulations of the substance P/NK<sub>1</sub> receptor antagonist, Emend, is approved for the acute and delayed phases in HEC, and the oral netupitant component of the Akynzeo FDC product is approved for the acute and delayed phases of “cancer chemotherapy including HEC”.</p>                                                                         |
| <u>Benefit</u> | <p>The subject of this NDA, Varubi (rolapitant), is an orally administered human substance P/NK<sub>1</sub> receptor antagonist. In radioligand binding assays, rolapitant and its major metabolite, M19, bind with high affinity to the human NK<sub>1</sub> receptor, with no significant affinities for other receptors, transporters, enzymes, and channels tested.</p> <p>Efficacy was assessed in two double-blind, placebo-controlled trials in 1070 subjects receiving HEC (≥60 mg/m<sup>2</sup> cis-platin based chemotherapy) randomized to a single oral dose of Varubi 180 mg plus IV granisetron (10 mcg/kg) or IV granisetron (10 mcg/kg) alone (Trials 1 and 2), and in one double-blind, placebo-controlled trial in 1332 subjects receiving MEC (at least 50% of subjects receiving AC based chemotherapy) randomized to a single oral dose of Varubi 180 mg administered with oral granisetron (2 mg) or oral granisetron (2 mg) alone (Trial 3). In the two HEC trials,</p> | <p>Relative to placebo, Varubi achieved statistically significant improvement in CR rates in the delayed phase of CINV in three double-blind, placebo-controlled trials, two of which were conducted in subjects receiving HEC and one in subjects receiving MEC. Relative to placebo, Varubi achieved statistically significant improvement in (b) (4)</p> <p>placebo-controlled trials, a HEC trial.</p> <p>(b) (4) the applicant has provided adequate data to support the efficacy of Varubi in the delayed phase of CINV, (b) (4)</p> |

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|  | <p>subjects also received dexamethasone 20 mg 30 minutes prior to initiation of chemotherapy on Day 1, followed by 8 mg twice daily on Days 2 through 4. In the MEC trial, subjects received dexamethasone 20 mg 30 minutes prior to initiation of chemotherapy on Day 1, followed by oral granisetron (2 mg) on Days 2 and 3.</p> <p>The key efficacy endpoint in all trials was CR, defined as no emesis and no use of rescue medication, in the delayed phase (25-120 hours) of CINV following initiation of Cycle 1 of chemotherapy. The key secondary endpoints were the CR rates for the acute (0-24 hours) and overall phases (0-120 hours) of CINV following initiation of Cycle 1 of chemotherapy. FDA and the applicant had reached agreement on these endpoints.</p> <p>In Trial 1, 42% of participants were women, 67% were Caucasian, and the mean age was 57 years. In Trial 2, 32% of participants were women, 81% were Caucasian, and the mean age was 58 years. In Trial 3, 80% of participants were women, 77% were Caucasian, and the mean age was 57 years.</p> <p>In Trial 1, a significantly greater proportion of subjects responded to the combination of Varubi plus IV granisetron than to IV granisetron alone <u>in each of the emesis phases of CINV</u>. In the delayed phase, 72.7% of Varubi plus IV granisetron-treated subjects experienced a CR as compared to 58.4% of subjects receiving IV granisetron alone (<math>p&lt;0.001</math>).</p> | <div data-bbox="1348 191 1810 464">(b) (4)</div> <div data-bbox="1348 464 1810 1166">(b) (4) the statistical review team had significant concerns with the Phase 2 data, including the performance of an unblinded interim analysis without a formal independent data monitoring committee, the sensitivity of the statistical significance of the delayed phase results to the removal and/or imputation value for a single subject, the applicant's deviation from the accepted definition of the modified intent-to-treat population, and the imputation method used for missing data in the responder analysis. (b) (4)</div> <div data-bbox="1348 1166 1810 1352">(b) (4)</div> |
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|  | <p>In Trial 2, a significantly greater proportion of subjects responded to the combination of Varubi plus IV granisetron than to IV granisetron alone <u>in the delayed phase of CINV only</u>. In the delayed phase, 70.1% of Varubi plus IV granisetron-treated subjects experienced a CR as compared to 61.9% of subjects receiving IV granisetron alone (p=0.043). In Trial 2, (b) (4)</p> <p>(b) (4)</p> <p>note, that due to a large placebo response among males in this trial, the efficacy was driven predominantly by females, who constituted 32% of the trial population. The delta between Varubi and control for the delayed phase was 23.3% for females versus 1.1% for males.</p> <p>In Trial 3, a significantly greater proportion of subjects responded to the combination of Varubi plus oral granisetron than to oral granisetron alone <u>in the delayed phase of CINV only</u>. In the delayed phase, 71.3% of Varubi plus oral granisetron-treated subjects experienced a CR as compared to 61.6% of subjects receiving oral granisetron alone (p&lt;0.001). (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> | <p>(b) (4) I concur with their conclusion.</p> <p>The efficacy of Varubi in repeat cycles of chemotherapy was determined by patient recall and there was no pre-specified analysis plan to continue assessments of CR in the delayed phase of CINV using daily diaries. This was a scientifically less rigorous assessment than was used in the Akynzeo clinical development program, although it is acknowledged that the aprepitant program employed a similar approach. Because of this less rigorous approach, there are significant limitations in the interpretation of the data. This is concerning because our knowledge of the efficacy of the drug during repeat cycles of chemotherapy is largely unknown, despite the fact that there is a tendency for CINV symptoms to become progressively more severe with subsequent cycles of chemotherapy administration.</p> |
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|  | <p>(b) (4)</p> <p>The Phase 2 trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose ranging trial to evaluate the efficacy and safety of various single doses of Varubi administered with a single dose of IV ondansetron 32 mg to subjects receiving HEC (<math>\geq 70</math> mg/m<sup>2</sup> of cisplatin-based chemotherapy). Approximately 450 subjects were randomized to receive placebo or 9, 22.5, 90, or 180 mg of Varubi. The primary efficacy endpoint was CR in the overall phase of CINV following initiation of Cycle 1 of chemotherapy. Key secondary endpoints were the CR rate for the acute and delayed phases. The testing scheme was sequential, requiring success on the overall phase and the delayed phase, to allow testing of the acute phase.</p> <p>Ninety subjects were randomized to the 180 mg dose. Among those subjects assigned to the 180 mg dose cohort, 47% were women, 58% were Caucasian, and the mean age was 52.3 years.</p> <p>The overall CR rate for the 180 mg dose was 62.5% for Varubi-treated subjects compared with 46.7% for placebo-treated subjects (p=0.032). (b) (4)</p> <p>(b) (4)</p> <p>However, FDA statistical reviewers found data integrity issues in the submitted datasets which prompted them to conduct</p> | <p>Varubi can be taken with or without food.</p> <p>Rolapitant is not an inhibitor or inducer of CYP3A4; therefore, no dosage adjustment for dexamethasone, a CYP3A4 substrate, is needed when co-administered with Varubi.</p> |
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encountered additional issues with the Phase 2 trial data, including the conduct of an unblinded interim analysis, for which there was no formal independent data monitoring committee.

In all 3 trials, subjects were given the option of continuing into a multiple-cycle extension for up to 5 additional cycles of chemotherapy receiving the same treatment as assigned in Cycle 1. The anti-emetic activity of Varubi was evaluated at Day 6 to 8 following initiation of each subsequent cycle of chemotherapy and was based on recall by subjects using the following 2 questions: 1) Have you had any episode of vomiting or retching since your chemotherapy started in this cycle?; 2) Have you had any nausea since your chemotherapy started in this cycle that interfered with normal daily life? A total of 1868 subjects (945 on Varubi; 923 on placebo) completed Cycle 2 and 600 subjects (303 on Varubi; 297 on placebo) completed Cycle 6. The median number of cycles completed was 4. According to the Statistical Analysis Plan, "subject response of no emesis or nausea by cycle for the MITT populations was assessed to evaluate whether repeat dosing demonstrated sustained benefit of the use of rolapitant over multiple cycles." Unlike the Akynzeo multi-

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|             | <p>cycle extension trial, where there was a pre-specified analysis plan to continue assessments of CR in the delayed phase of CINV using daily diaries (not recall), no such rigor was applied to the Varubi program. There were numerically more Varubi-treated subjects than placebo-treated subjects who had no emesis/retching or nausea that interfered with normal daily life in <u>most</u> of the repeat cycles.</p> <p>Varubi can be taken with or without food.</p> <p>Rolapitant is not an inhibitor or inducer of CYP3A4; therefore, unlike with other approved substance P/NK<sub>1</sub> receptor antagonist products, no dosage adjustment for dexamethasone, a CYP3A4 substrate, is needed when co-administered with Varubi.</p>                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <u>Risk</u> | <p>The safety of Varubi was assessed in 1,567 cancer patients, including 781 subjects exposed to Varubi for at least 4 cycles of chemotherapy and 367 subjects exposed for at least 6 cycles. All subjects received a single oral dose of Varubi 1 to 2 hours prior to the start of chemotherapy, including 1,294 subjects who received the 180 mg dose and 273 subjects who received doses less than 180 mg. In all trials, dexamethasone and a 5-HT<sub>3</sub> receptor antagonist were co-administered.</p> <p>In subjects receiving cisplatin-based chemotherapy, the most common adverse reactions reported with Varubi treatment in Cycle 1 were: neutropenia (in 9%), hiccups (in 5%), and abdominal pain (in 3%). In subjects receiving MEC, including AC based chemotherapy, the most common adverse reactions reported in association with Varubi treatment in</p> | <p>There were no serious safety concerns identified in the Varubi clinical development program; however, there is the potential for serious drug-drug interactions.</p> <p>Rolapitant is a moderate inhibitor of CYP2D6. Varubi should be contraindicated in patients receiving thioridazine, a CYP2D6 substrate, because of the potential for QT prolongation and Torsades de Pointe. There is also a serious risk of QT prolongation when Varubi is co-administered with the CYP2D6</p> |

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|  | <p>Cycle 1 were: decreased appetite (in 9%), neutropenia (in 7%), dizziness (in 6%), dyspepsia, urinary tract infection, stomatitis (in 4% each), and anemia (in 3%). The safety profile in subsequent chemotherapy cycles was similar to that observed in Cycle 1.</p> <p>Because of a non-clinical signal for convulsions observed in multiple species (mice, rats, and monkeys) receiving acute and/or subchronic administration of rolapitant, the Agency requested safety analyses to assess for potential neurotoxicity. In the Varubi clinical trials, there was no difference in the incidence of treatment-emergent adverse events (TEAEs) in the system organ class Nervous System between Varubi-treated subjects and control subjects. The most common Nervous System Preferred Terms reported in both treatment groups were headache and dizziness. Neurologic exams were conducted in all subjects during each treatment cycle. These examinations included assessments of cerebellar function, cranial nerves, gait and station, reflexes, and sensation. No pattern of clinically significant neurological events associated with Varubi use was detected. Eight subjects (4 receiving Varubi 180 mg, 2 receiving Varubi &lt;180 mg, and 2 receiving placebo) experienced a convulsion during the clinical trials. None appeared to be drug related.</p> <p>In the Varubi clinical development program five cases met laboratory criteria for Hy's Law. Four cases occurred in patients in the control arm; one case occurred in a patient in a Phase 2 trial taking Varubi 9 mg. In this patient, laboratory criteria for Hy's Law were first met at Cycle 1/Visit 2. The</p> | <p>substrate, pimozide, and concomitant use should be avoided. Patients receiving other CYP2D6 substrate drugs with narrow therapeutic indices should be monitored for adverse reactions of those drugs when used concomitantly with Varubi, if such use cannot be avoided.</p> <p>Rolapitant is an inhibitor of BCRP. Concomitant administration of rolapitant with BCRP substrates with a narrow therapeutic index can increase plasma concentrations of the concomitant drug and the potential for adverse reactions. These patients should be monitored for adverse reactions related to the concomitant drug if use of Varubi cannot be avoided, and when possible, patients should be prescribed the lowest effective dose of the concomitant drug.</p> <p>The use of Varubi in patients who require chronic administration of strong CYP3A4 inducers should be avoided because concomitant use can decrease the efficacy of Varubi.</p> <p>Rolapitant is an inhibitor of P-gp.</p> |
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|  | <p>elevations had resolved by the next Visit. The patient went on to receive Varubi for three additional cycles and laboratory elevations did not recur. Given that laboratory criteria for Hy's Law did not recur upon drug rechallenge, this case appears highly unlikely to represent a true Hy's Law case. Elevations in ALT, AST and/or bilirubin were noted in <math>\leq 1\%</math> of Varubi-treated subjects and in a comparable percentage of placebo-treated subjects across the phase 3 clinical trials.</p> <p>Posterior reversible encephalopathy syndrome (PRES) was observed in one Varubi-treated subject and no placebo-treated subjects. This subject received treatment with 5-FU, irinotecan, and bevacizumab. Bevacizumab is known to be associated with PRES. The significance of this finding in a single patient in the Varubi clinical development program is unclear.</p> <p>Rolapitant is a moderate CYP2D6 inhibitor. The inhibitory effects on CYP2D6 last at least 7 days and may last longer after a single dose administration of Varubi. The most commonly administered CYP2D6 substrates in the Varubi clinical trials were ondansetron, metoclopramide, and ranitidine. The incidence of TEAEs was higher in subjects with concomitant use of CYP2D6 substrates than in those without; however, the incidence of TEAEs among CYP2D6 substrate users was similar between Varubi and control subjects, with the exception of slightly higher rates of neutropenia and diarrhea in the Varubi arm.</p> <p>Rolapitant is a moderate inhibitor of the BCRP transporter.</p> | <p>Concomitant administration of rolapitant with P-gp substrates with a narrow therapeutic index can increase plasma concentrations of the concomitant drug and the potential for adverse reactions. Patients should be monitored for adverse reactions related to the concomitant drug if use of Varubi cannot be avoided, and when appropriate, drug levels should be monitored.</p> <p>A non-clinical signal for convulsions observed in acute and sub-chronic toxicity studies was not seen in the chronic toxicity studies. There were no concerning neurological TEAEs observed in the clinical development program.</p> <p>Non-clinical signals of adverse effects on the thyroid and liver were determined to not have human relevance.</p> |
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|  | <p>The most commonly administered BCRP substrates in the Varubi clinical trials were doxorubicin, fluorouracil, and docetaxel. The incidence of TEAEs was higher in subjects who reported concomitant use of BCRP substrates than in those without concomitant use; however, the incidence of TEAEs among subjects taking BCRP substrates was similar between Varubi and control subjects.</p> <p>Rolapitant is a substrate for CYP 3A4. Once daily oral dosing of 600 mg rifampin, a strong inducer of CYP 3A4, reduced the <math>C_{max}</math> and AUC of rolapitant by 30% and 85%, respectively, compared to rolapitant alone, and decreased the mean half-life from 176 hours without rifampin to 41 hours with concurrent rifampin.</p> <p>Rolapitant is an inhibitor of the P-gp transporter. When rolapitant was coadministered with digoxin, a P-gp substrate, the <math>C_{max}</math> and AUC of digoxin were increased 70% and 30%, respectively.</p> <p>In repeat-dose oral toxicology studies in rodents with rolapitant hydrochloride, adverse effects identified in the liver and thyroid of rats were not felt to be of relevance to humans.</p> <p>Convulsions that were observed with acute and/or subchronic administration of rolapitant hydrochloride in multiple species (mice, rats, and monkeys), were not observed in the chronic oral toxicity studies in rats and monkeys at doses that were 4.9- and 2.9-times, respectively,</p> |  |
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|                                      | <p>the recommended human dose on a body surface area basis.</p> <p>In an oral fertility and early embryonic development study conducted in female rats, rolapitant hydrochloride caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. Slight decreases in the number of corpora lutea and implantation sites were also noted.</p>                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p><u><b>Risk Management</b></u></p> | <p>Rolapitant is a moderate inhibitor of CYP2D6, and the duration of inhibition is at least 7 days.</p> <p>Rolapitant is an inhibitor of BCRP. Concomitant administration of rolapitant with BCRP substrates with a narrow therapeutic index can increase plasma concentrations of the concomitant drug and the potential for adverse reactions.</p> <p>Rolapitant is an inhibitor of the P-gp transporter. Concomitant administration of digoxin and Varubi results in increased plasma concentrations of digoxin, and may result in potential adverse reactions.</p> <p>Rifampin, a strong inducer of CYP 3A4, reduced the <math>C_{max}</math> and AUC of rolapitant and decreased the mean half-life of rolapitant.</p> | <p>Product labeling will carry a Contraindication for patients receiving thioridazine, a CYP2D6 substrate, due to the risk of QT prolongation and Torsades de Pointe from increased plasma concentrations of thioridazine. Product labeling will also carry a Warning that Varubi be avoided in patients who are receiving pimozide, a CYP2D6 substrate, due to the potential for increased plasma concentrations of pimozide and risk of QT prolongation.</p> <p>The Warnings and Precautions section of product labeling will note that the inhibitory effect of Varubi on CYP2D6 lasts at least 7 days and may last longer. The applicant will be required to study the duration of CYP2D6 inhibition in an <i>in vivo</i> drug interaction study.</p> |

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|  |  | <p>The Drug Interactions section of product labeling will note that concomitant use of Varubi with BCRP substrates with a narrow therapeutic index results in increased plasma concentration of the BCRP substrate which may result in potential adverse reactions. Product labeling will recommend monitoring patients for adverse reactions related to the concomitant drug if use of Varubi cannot be avoided. Product labeling will also caution that (b) (4) the lowest effective dose of rosuvastatin should be used.</p> <p>The Drug Interactions section of product labeling will note that concomitant use of Varubi with P-gp substrates with a narrow therapeutic index results in increased plasma concentration of the P-gp substrate, including digoxin, which may result in potential adverse reactions. Product labeling will recommend monitoring for increased digoxin levels in patients receiving concomitant treatment with Varubi, and monitoring for adverse reactions related to other P-gp</p> |
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|  |  | <p>substrate drugs if concomitant use of Varubi cannot be avoided.</p> <p>The Drug Interactions section of product labeling will recommend that patients who require chronic administration of strong CYP3A4 inducers should avoid use of Varubi because concomitant use can decrease the efficacy of Varubi.</p> <p>There are no serious safety concerns that warrant the need for a REMS.</p> <p>To fulfill the PREA requirement, the following studies will be required:</p> <ul style="list-style-type: none"> <li>• GLP toxicology study in juvenile rats</li> <li>• A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of rolapitant in pediatric patients ages 0-17 years old</li> <li>• A study to evaluate the efficacy and safety of a single oral dose of rolapitant in pediatric patients ages 0-17 years old</li> </ul> <p>To further characterize the inhibitory potential of rolapitant on renal and hepatic transporters, and to</p> |
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|  |  | <p>characterize the duration of CYP2D6 inhibitory potential, the applicant has agreed to perform the following studies as post-marketing commitments:</p> <ul style="list-style-type: none"> <li>• <i>In vivo</i> drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant</li> <li>• <i>In vitro</i> studies to evaluate the inhibitory potential of rolapitant on renal transporters, i.e., organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3)</li> <li>• <i>In vitro</i> study to evaluate the inhibitory potential of rolapitant on OATP1B1, and OATP1B3. The <i>in vitro</i> study results will determine the need for subsequent clinical assessments of drug interactions (b) (4)</li> </ul> |
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## **Other Background**

### **Regulatory History**

In October 2005, a pre-IND meeting was held. A key agreement reached included that the proposed primary endpoint of CR during 0-120 hours (b) (4)

(b) (4)

In April 2010, an End-of-Phase 2 study was held. The Agency concurred with the dose to be carried forward into Phase 3 trials, (b) (4) (b) (4)

(b) (4)

In July 2011, a Type C meeting was held. The Agency agreed that if supported by a successful Phase 2/3 HEC program, a single MEC trial would be acceptable if a sufficient number of patients were enrolled and at least 50% of the patients were receiving AC based therapy.

A pre-NDA meeting was held in July 2014. The Agency advised the applicant that the indication statement may not contain the terms HEC and MEC as the Agency was moving away from these designations and currently embracing a broader CINV indication.

The NDA was submitted on September 4, 2014.

### **Dosing**

Varubi is administered orally as two 90 mg tablets 1 to 2 hours prior to chemotherapy. Varubi should be administered prior to the initiation of each chemotherapy cycle. A two-week interval between chemotherapy cycles was the shortest interval studied in the clinical trials. Given the long half-life of rolapitant and the lack of safety information from the clinical trials for intervals less than two weeks, labeling will recommend that Varubi be used at intervals of no less than 2 weeks.

### **Product Quality**

There are no product quality issues that preclude approval.

ONDP granted the applicant's claim for the Categorical Exclusion for the Environmental Assessment. Additionally, clinical and non-clinical data and the literature were reviewed for any signals of estrogenic, androgenic, or thyroid activity, and no signals were found.

The applicant demonstrated bioequivalence between 50 mg rolapitant hydrochloride capsules (used in Phase 1/2) and 100 mg rolapitant hydrochloride tablets (used in Phase 3).

ONDP concluded that the proposed dissolution test and acceptance criterion are satisfactory.

The Office of Process and Facilities' final reports of manufacturing facility inspections were completed on May 1, 2015, and were found acceptable.

### **Non-clinical Pharmacology/Toxicology**

There are no pharmacology/toxicology issues that preclude approval.

The half-life of rolapitant is markedly longer in humans (169-183 hours) than in Cynomolgus monkeys and rats (6-8 hours). Therefore, comparison of steady-state  $AUC_{0-24h}$  values in the animals to the  $AUC_{0-\infty}$  value produced by a single dose in humans does not reflect the cumulative total exposure in animals relative to exposure in humans over the same timeframe. Therefore, the Pharmacology/Toxicology review team has provided exposure multiples estimated on a body surface area (BSA) basis. This is how the data will be conveyed in labeling as well.

In an oral fertility and early embryonic development study in male rats, rolapitant hydrochloride did not affect fertility or general reproductive performance.

In embryofetal development studies in rats and rabbits, there were no significant treatment-related effects on reproductive parameters or fetal external, visceral, or skeletal malformations.

Rolapitant hydrochloride was not genotoxic. The major metabolite, M19, was also negative for genotoxic effects.

In 2-year oral carcinogenicity studies in mice and rats, there were no statistically significant, treatment-related neoplastic findings in mice or in rats.

*In vitro* studies showed that rolapitant hydrochloride inhibited hERG channel with an  $IC_{50}$  at exposures at least 278-fold over the free drug  $C_{max}$  at the clinical dose. Rolapitant hydrochloride produced no treatment-related changes in heart rate, blood pressure, ECG intervals, or ECG morphology in telemetered monkeys. The  $IC_{50}$  for inhibition of hERG channel current by M19 was higher than that of rolapitant hydrochloride. In safety pharmacology studies, rolapitant hydrochloride did not produce any effects on respiratory, CNS, renal, or gastrointestinal parameters.

### **Clinical Pharmacology**

There are no clinical pharmacology issues that preclude approval.

Following oral administration of a single dose of Varubi, peak plasma concentrations were achieved in about 4 hours. Following multiple oral doses of Varubi, accumulation of rolapitant was approximately 5-fold.

Across the range of doses tested (4.5 mg to 180 mg), rolapitant  $C_{\max}$  and AUC were dose-proportional following administration of single oral doses in healthy subjects. The mean half-life of rolapitant in healthy subjects is approximately seven days. Rolapitant is eliminated primarily through the hepatic/biliary route.

Rolapitant is metabolized primarily by CYP 3A4 to form a major active metabolite, M19, which is the major circulating metabolite. The median time to peak concentration of M19 is approximately 120 hours (range: 24 to 168), and the mean half-life of M19 is approximately 158 hours.

***QT prolongation potential.*** Rolapitant, at doses up to four times higher than the recommended dose, had no significant QTc prolonging effects.

***Effect of age.*** Overall, in clinical trials of Varubi in cancer patients, 25% were over 65 years of age. There were no overall differences in safety or efficacy observed in these patients compared with younger patients. Population PK analyses indicated that age had no significant impact on the pharmacokinetics of rolapitant.

***Renal impairment.*** Based on population pharmacokinetic (PK) analyses, creatinine clearance at baseline did not show a significant effect on rolapitant PK in cancer patients with mild or moderate renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal impairment and the PK of rolapitant was not studied in patients with end-stage renal disease requiring dialysis. However, based on the primary elimination pathway and PK profile of rolapitant, the possibility of accumulation is of less concern in patients with severe renal impairment or end-stage renal disease. Unlike the Akynzeo label which recommends against use of the product in patients with severe renal impairment or end-stage renal disease, the Varubi label will carry no such recommendation. Section 12 of labeling will provide the population PK data on Varubi in patients with renal impairment.

***Hepatic impairment.*** No dosage adjustment for Varubi is necessary for patients with mild to moderate hepatic impairment. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment. However, because the drug has a long half-life in healthy subjects and potentially longer in patients with severe hepatic impairment, accumulation after repeated dosing in patients with severe hepatic impairment could result in rolapitant levels that may result in toxicity. Product labeling will recommend that use of Varubi should be avoided in patients with severe hepatic impairment, and if use cannot be avoided, patients should be monitored for adverse reactions related to Varubi.

## Clinical/Statistical - Efficacy

### *Pivotal trials.*

The table below provides a summary of the primary and key efficacy results of the three pivotal Phase 3 trials, two conducted in subjects receiving HEC and one in subjects receiving MEC.

**Table 1: Primary and key secondary efficacy results**

| Endpoint                                           | Trial 1 (HEC) |          |         | Trial 2 (HEC) |          |         | Trial 3 (MEC) |          |         |
|----------------------------------------------------|---------------|----------|---------|---------------|----------|---------|---------------|----------|---------|
|                                                    | Varubi        | Control  | p-value | Varubi        | Control  | p-value | Varubi        | Control  | p-value |
|                                                    | N=264         | N=262    |         | N=271         | N=273    |         | N=666         | N=666    |         |
|                                                    | Rate (%)      | Rate (%) |         | Rate (%)      | Rate (%) |         | Rate (%)      | Rate (%) |         |
| Complete Response – Delayed<br><br>(Primary)       | 72.7          | 58.4     | <0.001  | 70.1          | 61.9     | 0.043   | 71.3          | 61.6     | <0.001  |
| Complete Response – Acute<br><br>(Key Secondary)   | (b) (4)       |          |         |               |          |         |               |          |         |
| Complete Response – Overall<br><br>(Key Secondary) |               |          |         |               |          |         |               |          |         |

The Office of Scientific Investigations (OSI) conducted inspections of nine clinical investigator sites and the applicant site. OSI concluded that “the studies appear to have been conducted adequately, and the data generated by these studies appears acceptable in support of the respective indication.”

The Office of Study Integrity and Surveillance (OSIS) conducted inspections of the analytical portion for two bioequivalence studies. OSIS concluded that the clinical and analytical portions of the bioequivalence studies are acceptable for review.

## **Advisory Committee**

In the U.S., there are currently two NK<sub>1</sub> receptor antagonists approved for the prevention of CINV. This application was not referred to an advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of disease, and outside expertise was not necessary.

## **Pregnancy Considerations**

Consistent with the Pregnancy and Lactation Labeling Rule guidelines, The **Use in Specific Populations** section, **Pregnancy** subsection, of the product label will state that there are no available data on Varubi use in pregnant women to inform any drug-associated risks.

In animal reproduction studies, no teratogenic effects or effects on embryo-fetal development were observed following oral administration of rolapitant hydrochloride in pregnant rats and rabbits during the period of organogenesis at doses up to 1.2 times and 2.9 times, respectively, the maximum recommended human dose (MRHD) based on body surface area (BSA). Pre- and post-natal developmental effects of rolapitant hydrochloride were assessed in rats administered oral doses up to 1.2 times the MRHD based on BSA. Offspring effects observed at this dose included decreased postnatal survival, and decreased body weights and body weight gain; however, this may be related to the maternal toxicity observed. At a dose approximately 0.5 times the MRHD based on BSA, a decrease in memory in female pups in a maze test and a decrease in pup body weight were observed.

It is not known whether Varubi is present in human milk. Rolapitant hydrochloride administered orally to lactating female rats was present in milk. Product labeling will caution that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Varubi and any potential adverse effects on the breastfed infant from Varubi or from the underlying maternal condition or the use of concomitant chemotherapy.

## **Pediatrics**

**Pediatric Use.** The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Varubi have not been established in pediatric patients.

**Required Pediatric Studies.** Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new acting ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA will defer the pediatric study requirement because Varubi is ready for approval for use in adults and the pediatric studies have not been completed. The deferred pediatric studies that will be required are:

1. A GLP toxicology study in juvenile rats.
2. A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of Varubi (rolapitant) in pediatric patients ages 0-17 years old.
3. A study to evaluate the efficacy and safety of a single oral dose of Varubi (rolapitant) in pediatric patients ages 0-17 years old.

### **Other Relevant Regulatory Issues**

#### **Tradename Review**

The applicant's proposed tradename "Varubi" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on March 31, 2015.

#### **Consults**

##### **Safety Endpoints and Labeling Development (SEALD)**

SEALD was consulted to review the applicant's [REDACTED] (b) (4)

##### **Controlled Substance Staff (CSS)**

CSS was consulted to evaluate abuse-related preclinical and clinical data submitted in the NDA. CSS concluded that "in primate self-administration and physical dependence studies, there were no signals of abuse or withdrawal." The clinical safety data related to abuse potential were too limited to draw conclusions regarding abuse potential. Physical dependence and withdrawal symptoms in humans were not evaluated. CSS recommended that Varubi not be scheduled under the Controlled Substances Act, [REDACTED] (b) (4)

##### **Division of Medical Policy Programs (DMPP)**

DMPP reviewed the patient package insert (PPI). In their collaborative review with the Office of Prescription Drug Promotion, they simplified wording and clarified concepts; ensured consistency of the PPI with the prescribing information; removed unnecessary or redundant information; ensured that the PPI was free of promotional language or suggested revisions to ensure that it is free of promotional language; ensured that the PPI met the criteria specified in

FDA's *Guidance for Useful Written Consumer Medication Information*; and ensured that the PPI was consistent with the approved comparator labeling where applicable.

### **Division of Medication Error, Prevention, and Analysis (DMEPA)**

DMEPA was consulted to review the proposed prescribing information and carton labels for possible sources of medication errors. DMEPA recommended changes to increase the readability and prominence of important information on the label to promote the safe use of the product.

### **Division of Pediatric and Maternal Health**

The Division of Pediatric and Maternal Health (DPMH) was consulted to provide input for appropriate labeling of the pregnancy and lactation subsections of the Varubi label. There have been no studies with Varubi in pregnant women. Two women became pregnant during the phase 2 trials; both of them had unremarkable pregnancies. A review of the published literature revealed no data with rolapitant hydrochloride use in pregnant or lactating women. DPMH recommended edits to the Varubi label to ensure compliance with the Pregnancy and Lactation Labeling Rule guidelines.

### **Risk Evaluation and Mitigation Strategies (REMS)**

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology provided a consultative review to determine if a risk evaluation and mitigation strategy (REMS) is needed for Varubi (rolapitant), a new molecular entity. DRISK concluded that “the benefit-risk profile for rolapitant is acceptable and the risks can be adequately communicated through professional labeling.”

### **Postmarketing Requirements and Commitments**

See PREA Post Marketing Requirements above.

#### *Post Marketing Commitments*

1. *In vivo* drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of Varubi (rolapitant).
2. *In vitro* studies to evaluate the inhibitory potential of Varubi (rolapitant) on renal transporters i.e., organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3).

3. *In vitro* study to evaluate the inhibitory potential of Varubi (rolapitant) on OATP1B1 and OATP1B3. The in vitro study results will determine the need for a subsequent clinical assessment of a drug interaction between Varubi (rolapitant) (b) (4)

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/s/  
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AMY G EGAN  
09/01/2015