Submitted By:
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NCCN Guidelines Panel: Antiemesis

On behalf of TESARO, I respectfully request the NCCN Antiemesis Guidelines Panel to review the enclosed information in support of the use of the NK-1 receptor antagonist (RA) VARUBITM (rolapitant) for the prevention of chemotherapy-induced nausea and vomiting (CINV) in adult patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC).

Specific Changes Requested to the guidelines:

- Based on category 1 high-level evidence from the three large, global, randomized, prospective, double-blind studies in patients receiving cisplatin-based HEC (two phase 3 and one phase 2) and one large, global, multi-center, randomized, prospective, double-blind study in patients receiving anthracycline/cyclophosphamide (AC)-based HEC (included in the MEC trial), which all met their primary endpoints and showed protection from CINV as demonstrated by statistically superior CR rates in the delayed (>24 hours; phase 3) or overall phases (0-120 hours; phase 2), we recommend inclusion of rolapitant in combination with a 5-HT3 RA and dexamethasone in adults on day 1 of each chemotherapy cycle for the prevention of CINV in patients receiving HEC.

- Based on a large population of patients in the phase 3 trial receiving non-AC MEC, where nearly 1/3 of the patients received carboplatin, and the remaining patients received MEC such as cyclophosphamide, irinotecan, paclitaxel, oxaliplatin, doxorubicin, and others, and rolapitant provided protection from CINV as demonstrated by statistically superior CR rates in the acute (<24 hours), delayed, and overall phases, (with carboplatin included in the analysis) we recommend inclusion of rolapitant in combination with a 5-HT3 RA and dexamethasone in adults on day 1 of each chemotherapy cycle for the prevention of CINV in patients receiving MEC.

- Based on a large population of patients in the phase 3 MEC trial receiving carboplatin, where rolapitant demonstrated significant protection from CINV in the delayed and overall phases in a post-hoc analysis, we recommend inclusion of rolapitant in combination with a 5-HT3 RA and dexamethasone in adults on day 1 of each cycle for the prevention of CINV in patients receiving carboplatin-based chemotherapy regimens.

- Since rolapitant is neither an inhibitor nor an inducer of CYP3A4, unlike aprepitant/fosaprepitant and netupitant, we recommend including a footnote in both AE-2 and AE-3, which explains that no dose adjustment is needed for CYP3A4 substrates when administering rolapitant, and that dexamethasone (a CYP3A4 substrate drug) should be given at the guideline-prescribed dose of 20 mg. We also recommend adding language to MS-9 (Drug Interactions) explaining that rolapitant is neither an inducer nor an inhibitor CYP3A4, and therefore dexamethasone should be provided at the full-recommended dose of 20 mg, rather than the dose-reduced 12 mg as required with other NK-1 RAs.

FDA Clearance: The FDA has approved VARUBITM (rolapitant) in combination with other antiemetic agents in adults for the prevention of delayed chemotherapy-induced nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. The recommended oral dose is 180 mg taken approximately 1-2 hours prior to initiation of chemotherapy (day 1). Data from the studies referenced below as enclosures 3 and 4 are included in the US Prescribing Information for VARUBIT.

Rationale: Two identically designed, large, global, multi-center, randomized, prospective, double-blind phase 3 trials (HEC-1 and HEC-2) were conducted in patients scheduled to receive cisplatin-based chemotherapy (HEC-1 n=526; HEC-2 n=544). Patients were randomized to receive a single dose of either 180 mg oral rolapitant or placebo on day 1 prior to administration of chemotherapy, and all patients received current guideline-recommended doses of granisetron and dexamethasone. The results from these studies were fully published in Lancet Oncology on August 10, 2015. The main findings were:

- Both trials met their primary endpoint. Treatment with rolapitant resulted in a CR of 73% versus 58% in the delayed phase of HEC-1 (p=0.0006) and 70% versus 62% in the delayed phase of HEC-2 (p=0.0426).
• Time-to-first Emesis or Use of Rescue Medication was prolonged with rolapitant compared to control (HEC-1 p=0.0028; HEC-2 p=0.0175). The effect of rolapitant treatment began in the first day of chemotherapy (acute phase) as demonstrated by early separation of the Kaplan-Meier curves.

• A pooled analysis of HEC-1 and HEC-2 (n= 535 versus 535 control) showed statistical superiority of rolapitant CR rates across all phases of CINV: 71% versus 60% (p=0.0001) delayed phase; 84% versus 77% (p=0.0045) acute phase; 69% versus 59% (p=0.0005) overall phase. Additional endpoints of No emesis, No Nausea, No Significant Nausea, and Complete Protection were also significantly improved in the rolapitant arm across all phases (acute, delayed, and overall) of CINV.

• These results were consistent with a global, multi-center, randomized, prospective, double-blind phase 2 cisplatin HEC trial (n=454) that was fully published in Supportive Care in Cancer on May 5, 2015, which demonstrated statistical superiority of rolapitant in CR rates across all phases of CINV: 63.6% versus 48.9% (p=0.045) delayed phase; 87.6% versus 66.7% (p=0.001) acute phase; 62.5% versus 46.7% (p=0.032) overall phase.

A large, global, multi-center, randomized, prospective, double-blind phase 3 trial was conducted in patients receiving AC combination chemotherapy or MEC who were randomized 1:1 to receive either 180 mg rolapitant or placebo; all patients received guideline-recommended doses of granisetron and dexamethasone. AC was included with the MEC regimens in this trial because the study was designed prior to 2011, when AC was still considered MEC by the NCCN, ASCO, and MASCC guidelines. The results were fully published in Lancet Oncology on August 10, 2015. The main findings were:

• The trial met its primary endpoint. In the total population (n=666 rolapitant; n=666 control), treatment with rolapitant resulted in a superior CR rate of 71% versus 62% in the delayed phase (p=0.0002).

• Time-to-first emesis or use of rescue medication was prolonged with rolapitant compared to control (p<0.0001). The effect of rolapitant treatment began in the first day of chemotherapy (acute phase) as demonstrated by early separation of the Kaplan-Meier curves.

• No Emesis and Complete Protection rates were statistically superior in the delayed and overall phases for rolapitant.

• A pre-specified analysis of CR for patients receiving AC (n=703) versus non-AC MEC (n=629) and post-hoc analyses of additional endpoints provided support for the efficacy of rolapitant in both treatment populations. The CR results were published in Lancet Oncology on August 10, while the more detailed analysis of the MEC data, including the carboplatin sub-analysis, were presented at ASCO and MASCC 2015.

• Pre-specified analysis of delayed phase CR in the AC population was 67% versus 60% (p=0.0465); CR in the non-AC MEC population was 76% versus 64% (p=0.0008).

• An additional pre-specified analysis of CR in the non-AC MEC setting showed acute phase CR of 91% versus 84% (p=0.0163), and overall phase CR of 75% versus 61% (p=0.0003).

• The non AC MEC population included a large population of patients receiving carboplatin (n = 192 rolapitant; n=209 control). Complete response rates were higher with rolapitant in all phases and statistically significant in the delayed and overall phases: 82% vs. 66% (p<0.001) delayed phase; 80.2% vs 64.6% (p<0.001) overall phase (ASCO 2015).

• The non AC MEC population also included a large population of patients receiving MEC regimens other than carboplatin, including cyclophosphamide ≤1500 mg/m², irinotecan, premetrexed, oxaliplatin, and doxorubicin (n=130 rolapitant; n=98 control) presented at ASCO 2015. Rolapitant demonstrated a statistically significant reduction in CINV across the at risk period, (CR 66.9% vs 54.1%, p=0.049 in the overall phase). Data for the non AC MEC presented at ASCO 2015 included carboplatin with all other MEC agents.

CYP3A4 is responsible for the metabolism of 50-60% of pharmaceutical agents. CYP3A4 inhibitors can increase the plasma concentration of concomitantly administered substrate drugs, whereas CYP3A4 inducers can decrease the concentration of concomitantly administered substrate drugs. Studies of the effect of rolapitant in normal, healthy volunteers have found that rolapitant is neither an inhibitor nor inducer of CYP3A4, unlike the other approved NK-1 RAs, aprepitant/fosaprepitant (CYP3A4 inhibitor and inducer) and netupitant (CYP3A4 Inhibitor). Rolapitant should be avoided in patients that require chronic use of strong CYP3A4 inducers (e.g. rifampin), as rolapitant plasma concentrations may be significantly reduced when co-administered with these agents. Rolapitant is also contraindicated in patients receiving thioridazine, based on the inhibitory effect of rolapitant on CYP2D6 substrates which have a narrow therapeutic index.
The following enclosures are being submitted in support of the proposed changes:


We sincerely appreciate the opportunity to provide this information for consideration by the NCCN Antiemesis Panel. If any questions arise or if you require any additional information, please don’t hesitate to contact me by phone at 781-810-4770, or email me at hobirne@tesarobio.com.

Sincerely,

Helena O’Beirne, PhD, MA