On behalf of TESARO, I respectfully request the NCCN Antiemesis Guidelines Panel to review the enclosed information in support of the inclusion of the intravenous (IV) formulation of the NK-1 receptor antagonist (RA) VARUBI® (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:

Building on evidence that was used for oral rolapitant to gain category 1 status in HEC and MEC (results from four large, global, randomized, prospective, double-blind studies with oral rolapitant), a pivotal phase 1 bioequivalence study evaluating IV versus oral rolapitant in healthy volunteers showed that the two formulations are bioequivalent. Rolapitant IV was well tolerated and showed a limited drug-drug interaction profile in additional studies. Based on this additional evidence, we propose the inclusion of rolapitant IV as category 1 for HEC and MEC in alignment with oral rolapitant's current NCCN recommendation.

FDA Clearance:
The FDA has approved oral VARUBI® (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. A Prescription Drug User Fee Act (PDUFA) for rolapitant injectable emulsion for IV use ("rolapitant IV") has an action date of October 25, 2017 and is currently under regulatory review.

Rationale:

- Two previously published large, global, randomized, prospective, double-blind phase 3 studies in patients receiving cisplatin-based HEC and one large, global, multi-center, randomized, prospective, double-blind phase 3 study in patients receiving anthracycline/cyclophosphamide (AC)-based and carboplatin-based HEC (included in the MEC trial) all met their primary endpoints. These studies all showed that rolapitant promoted protection from CINV, as demonstrated by statistically superior complete response rates in the delayed (>24 hours) phase for oral rolapitant in combination with a 5-HT3 RA and dexamethasone when compared with 5-HT3 RA and dexamethasone alone. (Rapoport et al., 2015 and Schwartzberg et al., 2015)

- A large population of patients in the phase 3 MEC trial (“50%) received non-AC MEC. This population included (1) patients who received carboplatin (“60%), and (2) patients who received cyclophosphamide, irinotecan, pemetrexed, oxaliplatin, doxorubicin, and other MEC agents.
  - In a post hoc analysis of the large population of patients who received carboplatin, oral rolapitant in combination with a 5-HT3 RA and dexamethasone demonstrated significant protection from CINV in the delayed and overall phases when compared with a 5-HT3 RA and dexamethasone alone (Hesketh et al., 2016).
  - In a prospective analysis of the large population of patients who received non-AC MEC agents, oral rolapitant in combination with a 5-HT3 RA and dexamethasone provided protection from CINV when compared with a 5-HT3 RA and dexamethasone alone, as demonstrated by statistically superior CR rates in the acute, delayed, and overall phases (Hesketh et al., 2015 and Schwartzberg et al., 2015).

- A randomised, open-label, parallel-group, phase 1 study was conducted in healthy volunteers who were administered rolapitant as a 180 mg oral dose or a 166.5 mg IV infusion. This study showed that a 166.5 mg IV infusion of rolapitant met the bioequivalence criteria based on AUC to a 180 mg oral dose and was well tolerated. A peer reviewed article reporting these data was recently published in the Journal of Clinical Pharmacology (Wang et al., 2017a).

- Two open label phase 1 studies evaluated the safety and drug-drug interactions of a single dose of rolapitant IV (166.5 mg) with oral digoxin (0.5 mg) or sulfasalazine (500 mg), probe substrates for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), respectively. Administration of intravenous rolapitant with the substrates did not result in clinically
significant effects on digoxin and sulfasalazine pharmacokinetics. Adverse events were mild to moderate in severity in the absence or presence of rolapitant. No abnormal clinical laboratory results and no findings on ECG occurred. In conclusion, rolapitant IV was safe and well tolerated and displayed minimal effects on P-gp or BCRP, thereby limiting its potential for drug-drug interactions. A peer reviewed article reporting these data was recently published in the *Journal of Clinical Pharmacology* (Wang et al., 2017b).

- A ready-to-use (RTU) injectable emulsion formulation of rolapitant for IV use was recently assessed for compatibility and stability when admixed with dexamethasone (10 mg or 20 mg) or palonosetron (0.25 mg) under various handling conditions. Admixtures of rolapitant injectable emulsion with dexamethasone in glass vials were physically and chemically compatible and stable for 6 hours at room temperature and for 7 days under refrigeration. Admixtures of rolapitant injectable emulsion with palonosetron in glass vials were physically and chemically compatible and stable for 48 hours at room temperature and for 7 days under refrigeration. These results were recently published in two peer reviewed articles in the *International Journal of Pharmaceutical Compounding* (Wu et al., 2017a and b).

The following enclosures are being submitted in support of the proposed changes:


9. VARUBI (rolapitant) tablets for oral use. Highlights of prescribing information.

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) 257-2536, or email me at mhuber@tesarobio.com.

Sincerely,

Martin Huber, MD