

# Differential pharmacology and clinical utility of rolapitant in chemotherapy-induced nausea and vomiting

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**Abstract:** Chemotherapy-induced nausea and vomiting (CINV) is a debilitating side effect of many cytotoxic chemotherapy regimens. CINV typically manifests during two well-defined time periods (acute and delayed phases). The acute phase is the first 24 hours after chemotherapy and is largely managed with 5-hydroxytryptamine 3 receptor antagonists. The delayed phase, a 5-day at-risk period during which patients are not often in direct contact with their health care provider, remains a significant unmet medical need. Neurokinin-1 (NK-1) receptor antagonists have demonstrated protection against acute and delayed CINV in patients treated with highly emetogenic chemotherapy and moderately emetogenic chemotherapy when used in combination with a 5-hydroxytryptamine 3 receptor antagonist and dexamethasone. Furthermore, recent data indicate that this protection is maintained over multiple treatment cycles. Rolapitant, a selective and long-acting NK-1 receptor antagonist, is approved as oral formulation for the prevention of delayed CINV in adults. This review discusses the differential pharmacology and clinical utility of rolapitant in preventing CINV compared with other NK-1 receptor antagonists.

**Keywords:** antiemetics, highly emetogenic chemotherapy, moderately emetogenic chemotherapy, delayed chemotherapy-induced nausea and vomiting, emesis, neurokinin-1 receptor antagonists

## Introduction Management of chemotherapy-induced nausea and vomiting (CINV)

Nausea and vomiting are the most feared side effects of cytotoxic chemotherapy<sup>1,2</sup> and are most frequently reported following the administration of cisplatin, carboplatin, cyclophosphamide, and doxorubicin.<sup>3</sup> CINV can have a negative impact on health-related quality of life (QoL),<sup>4,5</sup> compromise treatment outcomes,<sup>3,6,7</sup> and increase health care resource utilization.<sup>8</sup>

CINV typically manifests during two time periods, the acute phase and the delayed phase, over a 5-day period. The acute phase occurs within the first 24 hours after chemotherapy and is largely mediated by 5-hydroxytryptamine 3 (5-HT<sub>3</sub>) receptors in the intestine.<sup>6</sup> In this phase, free radicals generated after administration of chemotherapy induce the release of serotonin from enterochromaffin cells located in the intestinal mucosa.<sup>6</sup> Serotonin then interacts with 5-HT<sub>3</sub> receptors located on vagal afferent nerves in the intestinal wall, which project to the area postrema and the nucleus tractus solitarius (NTS), stimulating the vomiting reflex. Acute CINV is therefore particularly sensitive to 5-HT<sub>3</sub> receptor antagonists;<sup>9</sup> however, these agents have little impact on delayed CINV,<sup>9</sup> suggesting that the pathophysiologic

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mechanisms during the delayed emetic phase may differ from those in the acute phase. The delayed phase of CINV starts on day 2 after chemotherapy and can last up to day 5. Delayed CINV is predominantly driven by a central pathway involving the neurotransmitter/neuromodulator substance P, which is a member of the mammalian tachykinin family of peptides.<sup>10</sup> Substance P is released from neurons in response to chemotherapy and binds to neurokinin-1 (NK-1) receptors in the area postrema and NTS, thereby mediating the induction of vomiting.<sup>11</sup> NK-1 receptors are also located on vagal afferent terminals in the gastrointestinal tract, suggesting that substance P, when released from enterochromaffin cells in response to chemotherapy, may also play a role in the acute phase of CINV.<sup>12</sup> The critical role of substance P in delayed CINV is demonstrated by the effectiveness of NK-1 receptor antagonists in preventing CINV during this phase.<sup>6</sup>

While acute CINV is reasonably well managed with serotonin (5-HT<sub>3</sub>) receptor antagonists in the majority of patients,<sup>13</sup> delayed CINV continues to present a treatment challenge.<sup>14,15</sup> Corticosteroids have been used for many years predominantly as prophylaxis against delayed CINV, although their exact mechanism of action is unknown. The antiemetic efficacy of 5-HT<sub>3</sub> or dopamine receptor antagonists increases when they are used in combination with corticosteroids;<sup>16</sup> therefore, these agents are typically administered concurrently. Benefits with olanzapine, an atypical antipsychotic drug that blocks dopaminergic, serotonergic, adrenergic, and histamine receptors, have been reported for delayed nausea control, particularly when it has been evaluated in combination with 5-HT<sub>3</sub> receptor antagonist and corticosteroids.<sup>17–19</sup> The growing understanding of the role of substance P in emesis led to the development of NK-1 receptor antagonists for the treatment of delayed CINV. The first oral NK-1 receptor antagonist, aprepitant, was approved in 2003, followed by fosaprepitant (a prodrug of aprepitant that is administered intravenously) in 2008 and netupitant (administered as a fixed oral combination with the 5-HT<sub>3</sub> receptor antagonist palonosetron) in 2014. In September 2015, oral rolapitant was approved by the US Food and Drug Administration (FDA) for use in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC). In March 2016, a marketing authorization application for oral rolapitant was submitted to the European Medicines Agency. Several evidence-based guidelines for the prevention of CINV have been developed by international professional societies,<sup>3,20,21</sup> which are rela-

**Table 1** Summary of evidence-based guidelines for CINV prophylaxis with intravenous chemotherapy

Emetic risk category	Guideline recommendation
High (including anthracycline–cyclophosphamide combinations)	NK-1 receptor antagonist + 5-HT <sub>3</sub> receptor antagonist + dexamethasone <sup>3,20,21</sup> or Olanzapine + 5-HT <sub>3</sub> receptor antagonist + dexamethasone <sup>3</sup>
Moderate	5-HT <sub>3</sub> receptor antagonist + dexamethasone (±NK-1 receptor antagonist) <sup>3,58</sup> or Olanzapine + 5-HT <sub>3</sub> receptor antagonist + dexamethasone <sup>3</sup> or 5-HT <sub>3</sub> receptor antagonist + dexamethasone <sup>20</sup>
Low	Dexamethasone <sup>3,20,58</sup> or Dopamine receptor antagonist or 5-HT <sub>3</sub> receptor antagonist <sup>3,20</sup>
Minimal	No prophylactic antiemetic <sup>3,20,58</sup>

**Notes:** \*An NK-1 receptor antagonist should be added for patients with additional risk factors or who are failing 5-HT<sub>3</sub> receptor antagonist + dexamethasone.<sup>3</sup> The NK-1 receptor antagonist recommended in the American Society of Clinical Oncology guidelines is aprepitant.<sup>58</sup>

**Abbreviations:** 5-HT<sub>3</sub>, 5-hydroxytryptamine 3; CINV, chemotherapy-induced nausea and vomiting; NK-1, neurokinin-1.

tively consistent in their key recommendations (Table 1). In general, the guidelines recommend prescribing an NK-1 receptor antagonist along with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone for the prevention of CINV in patients receiving HEC and a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in patients receiving moderately emetogenic chemotherapy (MEC).<sup>3,20,21</sup> The National Comprehensive Cancer Network and the American Society of Clinical Oncology also recommend the use of an NK-1 receptor antagonist in patients treated with MEC, particularly those with additional risk factors for CINV.<sup>3,21</sup> This review provides a summary of the differential pharmacology and clinical utility of rolapitant, a long-acting NK-1 receptor antagonist, in the prevention of CINV.

## Overview of rolapitant pharmacology and comparison to other NK-1 antagonists

Rolapitant is a highly selective NK-1 receptor antagonist with high-affinity binding to the human NK-1 receptor (K<sub>i</sub> 0.66 nmol/L) over the NK-2 and -3 subtypes.<sup>22</sup> The nanomolar affinity of rolapitant for NK-1 receptors is similar to that of other NK-1 receptor antagonists (Table 2). In a Phase I positron emission tomography (PET) study in 14 healthy individuals given a single oral dose of rolapitant, the drug

**Table 2** Pharmacologic and pharmacokinetic profile of marketed NK-1 antagonists

NK-1 receptor antagonist	Affinity pKi	Recommended dosing	% RO (h)	Plasma [c] at >90% RO	Elimination half-life (h)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	References
Rolapitant	9.1	Oral, single dose: 180 mg on day 1; 2 h prior to chemotherapy	Striatum: 73% (120 h) Cortex: 90% (120 h)	>348 ng/mL	~180	968	4	22,23,26,27
Aprepitant	10.1	Multiple doses: 125 mg orally on day 1 and 80 mg orally on days 2 and 3	Striatum <sup>a</sup> : ≥99% (4 h), ≥99% (24 h), ≥97% (48 h), and ~54% (120 h)	~21–100 ng/mL	~9–13	1600 on day 1 1400 on day 3	4	24,29
Fosaprepitant <sup>b</sup>	8.9	Single dose: 150 mg IV over 20–30 min, ~30 min prior to chemotherapy	Striatum: 100% (0.5 h), 100% (24 h), ≥97% (48 h), and ~60% (120 h)	~21–100 ng/mL	~9–13	4200	0.5	24,28
Netupitant	9.0	Single dose: 300 mg. It is administered with 0.5 mg palonosetron, orally on day 1, ~1 h prior to chemotherapy	Striatum: 98% (6 h), 91% (24 h), 89% (48 h), 80% (72 h), and 77% (96 h)	~225 ng/mL	~96	434	5	25,30

**Notes:** <sup>a</sup>A single oral dose of 165 mg aprepitant was administered.<sup>24</sup> <sup>b</sup>Fosaprepitant is converted to aprepitant within 30 min. Plasma [c], half-life, and C<sub>max</sub> values refer to aprepitant following administration of fosaprepitant.

**Abbreviations:** C<sub>max</sub>, maximum concentration; h, hours; IV, intravenous; min, minutes; NK-1, neurokinin-1; pKi, -log Ki; RO, receptor occupancy; T<sub>max</sub>, time to reach C<sub>max</sub>.

was shown to cross the blood–brain barrier and exhibited >90% NK-1 receptor binding in the cortex and 73% receptor binding in the striatum when measured 5 days after administration.<sup>23</sup> NK-1 receptor occupancy in the cortex was directly related to rolapitant dose and plasma concentration. A single administration of 200 mg of rolapitant hydrochloride, which is equivalent to 180 mg of rolapitant freebase, resulted in concentrations >348 ng/mL at 120 hours, which corresponds to >90% NK-1 receptor occupancy (Table 2). Similar PET studies have evaluated brain NK-1 receptor occupancy for marketed NK-1 receptor antagonists in healthy subjects (Table 2).<sup>24,25</sup> In one study,<sup>24</sup> receptor occupancy in the striatum was ~54% for aprepitant (165 mg; single oral administration) and ~60% for fosaprepitant (150 mg; single IV administration) on day 5. In the same study, plasma concentrations for aprepitant and fosaprepitant were 142 and 92 ng/mL on day 3, and they were <10 ng/mL for both drugs on day 4. In a separate study,<sup>25</sup> receptor occupancy in the striatum for netupitant (300 mg; single oral administration) was 89% on day 2 and 77% on day 4, corresponding to an average of 93 and 41 ng/mL plasma concentration, respectively.

Pharmacokinetic analyses performed on healthy fasting individuals who received a single dose of rolapitant (180 mg) showed that the maximum plasma concentration was 968 ng/mL, with a time to maximum concentration of ~4 hours.<sup>26</sup> Administration of a high-fat meal did not have

any significant effect on the pharmacokinetic profile of rolapitant.<sup>26</sup> At the recommended doses, oral administration of aprepitant, fosaprepitant, and netupitant resulted in peak plasma concentrations of 1600–1400 ng/mL (at 4 hours), 4200 ng/mL (at 0.5 hour), and 434 ng/mL (at 5 hours), respectively.

The half-life of rolapitant (169–183 hours)<sup>26,27</sup> is longer than that of the NK-1 receptor antagonists aprepitant, fosaprepitant (9–13 hours),<sup>28,29</sup> and netupitant (80 ± 20 hours)<sup>30</sup> (Table 2), and it supports a single-dose regimen that per the US label is administered 1–2 hours prior to chemotherapy for the prevention of CINV across the entire 5-day at-risk period. Furthermore, rolapitant is primarily metabolized by the cytochrome P450 (CYP) enzyme CYP3A4 to form M19 (SCH720 881), its major circulating metabolite.<sup>31</sup> Median time to maximum concentration for M19 is 120 hours, and mean half-life of M19 is 158 hours.<sup>26</sup> Multiple covariates including age, gender, race, chemotherapy regimen, creatinine clearance, concomitant medications, and neutrophil count had no effect on the pharmacokinetics of rolapitant.<sup>32</sup>

## Clinical utility of rolapitant and comparison to other NK-1 receptor antagonists

The efficacy of NK-1 receptor antagonists for the prevention of delayed CINV when used in combination with a 5-HT<sub>3</sub> receptor antagonist and a corticosteroid has been established

in a number of randomized controlled trials. A summary of complete response (CR) rates (defined as no emesis and no use of rescue medication) across agents is shown in Table 3.

The first group of trials to evaluate the addition of aprepitant to ondansetron plus dexamethasone reported increased protection against delayed CINV in patients receiving both HEC<sup>33,34</sup> and MEC.<sup>35</sup> For example, in a Phase III, randomized, double-blind HEC study in patients scheduled to receive treatment with high-dose cisplatin, CR rates during the delayed phase were 68% in the aprepitant group and 47% (Table 3) in the active control

group ( $P<0.001$ ), which was administered as intravenous ondansetron 32 mg and oral dexamethasone 20 mg on day 1 and oral dexamethasone 8 mg twice daily on days 2–4.<sup>34</sup> Although aprepitant was associated with an improvement in the proportion of patients who did not experience delayed vomiting, between-treatment differences in rates of no significant nausea (73% vs 65%) were not statistically significant (data not shown). In a similar HEC study in patients receiving high-dose cisplatin, CR rates during the delayed phase were 75% in the aprepitant group and 56% (Table 3) in the active control group ( $P<0.001$ ).<sup>33</sup> As in the

**Table 3** Summary of complete response (%) in cycle I of chemotherapy after administration of marketed NK-1 receptor antagonists

Treatments drug vs control	Chemotherapy	Phase	Complete response drug vs control	P-value	Reference
Aprepitant vs ondansetron + dexamethasone	HEC; high-dose cisplatin	Acute phase (0–24 h)	89 vs 78	$\leq 0.001$	33
		Delayed phase (24–120 h)	75 vs 56	$\leq 0.001$	
		Overall phase (0–120 h)	73 vs 52	$\leq 0.001$	
Aprepitant vs ondansetron + dexamethasone	HEC; high-dose cisplatin	Acute phase (0–24 h)	83 vs 68	$\leq 0.001$	34
		Delayed phase (24–120 h)	68 vs 47	$\leq 0.001$	
		Overall phase (0–120 h)	63 vs 43	$\leq 0.001$	
Aprepitant vs ondansetron + dexamethasone	MEC; with AC	Acute phase (0–24 h)	84 vs 72	$\leq 0.05$	35
		Delayed phase (24–120 h)	65 vs 53	$\leq 0.05$	
		Overall phase (0–120 h)	63 vs 47	$\leq 0.05$	
Aprepitant vs ondansetron + dexamethasone	MEC; non-AC	Acute phase (0–24 h)	93 vs 88	NS	35
		Delayed phase (24–120 h)	76 vs 69	NS	
		Overall phase (0–120 h)	74 vs 65	NS	
Fosaprepitant vs aprepitant + ondansetron + dexamethasone	HEC; first course cisplatin-based chemotherapy ( $\geq 70$ mg/m <sup>2</sup> )	Acute phase (0–24 h)	72 vs 72	NS	37
		Delayed phase (24–120 h)	89 vs 88	NS	
		Overall phase (0–120 h)	74 vs 74	NS	
Fosaprepitant vs ondansetron + dexamethasone	MEC; non-AC	Acute phase (0–24 h)	93 vs 91	NS	38
		Delayed phase (24–120 h)	79 vs 68	$\leq 0.001$	
		Overall phase (0–120 h)	77 vs 67	$\leq 0.001$	
NEPA vs palonosetron + dexamethasone	HEC; cisplatin-based chemotherapy	Acute phase (0–24 h)	98 vs 90	$\leq 0.01$	39
		Delayed phase (24–120 h)	90 vs 80	$\leq 0.05$	
		Overall phase (0–120 h)	90 vs 76	$\leq 0.01$	
NEPA vs palonosetron + dexamethasone	HEC; with AC	Acute phase (0–24 h)	88 vs 85	$\leq 0.05$	40
		Delayed phase (24–120 h)	77 vs 69	$\leq 0.01$	
		Overall phase (0–120 h)	74 vs 67	$\leq 0.01$	
Rolapitant vs ondansetron + dexamethasone	HEC (Phase II); cisplatin-based chemotherapy ( $\geq 70$ mg/m <sup>2</sup> )	Acute phase (0–24 h)	88 vs 67	$\leq 0.001$	41
		Delayed phase (24–120 h)	64 vs 49	$\leq 0.05$	
		Overall phase (0–120 h)	63 vs 47	$\leq 0.05$	
Rolapitant vs granisetron + dexamethasone	HEC 1; first course (cisplatin-based chemotherapy; $\geq 60$ mg/m <sup>2</sup> )	Acute phase (0–24 h)	84 vs 74	$\leq 0.01$	42
		Delayed phase (24–120 h)	73 vs 58	$\leq 0.001$	
		Overall phase (0–120 h)	70 vs 56	$\leq 0.01$	
Rolapitant vs granisetron + dexamethasone	HEC 2; first course of cisplatin-based chemotherapy ( $\geq 60$ mg/m <sup>2</sup> )	Acute phase (0–24 h)	83 vs 79	NS	42
		Delayed phase (24–120 h)	70 vs 62	$\leq 0.05$	
		Overall phase (0–120 h)	68 vs 60	NS	
Rolapitant vs granisetron + dexamethasone	MEC; with AC	Acute phase (0–24 h)	77 vs 77	NS	43
		Delayed phase (24–120 h)	67 vs 60	$\leq 0.001$	
		Overall phase (0–120 h)	63 vs 55	$\leq 0.001$	
Rolapitant vs granisetron + dexamethasone	MEC; non-AC carboplatin-based	Acute phase (0–24 h)	92 vs 88	NS	44
		Delayed phase (24–120 h)	82 vs 66	$< 0.001$	
		Overall phase (0–120 h)	80 vs 65	$< 0.001$	

**Abbreviations:** AC, anthracycline–cyclophosphamide-based chemotherapy; h, hours; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; NEPA, netupitant plus palonosetron; NK-1, neurokinin-1; NS, not significant.

previous study, aprepitant had a significant benefit with respect to rates of emesis but not nausea. Significant differences between aprepitant and active control on delayed CINV were also reported for CR rates in a population including patients receiving MEC and patients receiving anthracycline–cyclophosphamide-based chemotherapy (AC) (65% for aprepitant vs 53% for active control), with AC classified at the time as MEC, but not in patients receiving MEC.<sup>35</sup> In an open-label, randomized Phase III trial, significant differences in CR rates between the aprepitant group and the active control group were reported on overall and delayed CINV in patients with colorectal cancer receiving oxaliplatin-based chemotherapy.<sup>36</sup>

Single-dose fosaprepitant was approved for use in delayed CINV based on the results of a Phase III non-inferiority trial versus aprepitant (administered once daily for 3 days) in patients receiving HEC and treated with ondansetron and dexamethasone.<sup>37</sup> No significant difference in CR rates for the acute, delayed, and overall phases was reported between the fosaprepitant and aprepitant arms in patients receiving cisplatin-based chemotherapy.<sup>37</sup> A recent Phase III study evaluated the addition of fosaprepitant to ondansetron and dexamethasone in patients receiving non-AC MEC.<sup>38</sup> In this randomized, double-blind, placebo-controlled study, fosaprepitant significantly improved rates of delayed CR (79% vs 68%;  $P \leq 0.001$ ; Table 3). The impact of fosaprepitant on nausea in the delayed phase of this study was not described.

In 2014, netupitant was approved for the prevention of CINV. Netupitant is administered as a fixed oral combination with palonosetron (NEPA), and this formulation has been evaluated in randomized controlled trials in patients receiving cisplatin-based HEC<sup>39</sup> and HEC with AC (considered MEC at the time of the study).<sup>40</sup> In the Phase II cisplatin-based HEC study,<sup>39</sup> a CR during the delayed phase was reported in 90% of the NEPA plus dexamethasone group compared with 80% (Table 3) of the control group receiving palonosetron plus dexamethasone ( $P \leq 0.05$ ), with significant benefits reported in terms of both vomiting and nausea.<sup>39</sup> In the Phase III HEC with AC study,<sup>40</sup> the percentage of patients with a CR during the delayed phase was significantly higher with NEPA plus dexamethasone than with palonosetron plus dexamethasone (77% vs 69%;  $P \leq 0.01$ ; Table 3).<sup>40</sup> Likewise, NEPA plus dexamethasone was associated with significantly higher rates of no emesis (82% vs 75%;  $P = 0.004$ ) and no significant nausea (77% vs 71%;  $P = 0.014$ ).

The efficacy of rolapitant in preventing CINV when added to granisetron, a 5-HT<sub>3</sub> receptor antagonist, plus

dexamethasone has been evaluated in one Phase II study in patients receiving HEC,<sup>41</sup> in two Phase III clinical trials in patients receiving HEC<sup>42</sup> (HEC 1 and HEC 2 studies), and one Phase III clinical trial in patients receiving MEC or AC (which was initially considered to be MEC and is now classified by all major guideline groups as HEC).<sup>43</sup> In all four studies, rolapitant significantly improved CR in the delayed phase compared with the active control (Table 3). For example, in the Phase III HEC 1 study (Table 3), CR in the delayed phase was 73% for rolapitant recipients versus 58% for active control recipients (odds ratio [OR]: 1.9; 95% confidence interval [CI]: 1.3–2.7;  $P = 0.0006$ ).<sup>42</sup> The addition of rolapitant to active therapy also produced a significantly higher rate of no emesis and no clinically significant nausea in the delayed phase. Similar results were obtained in the Phase III HEC 2 study (Table 3).<sup>42</sup> In the Phase III MEC study in patients treated with AC, the addition of rolapitant improved CR rates in the delayed phase compared with active control (67% vs 60%; OR: 1.4; 95% CI: 1.0–1.9;  $P = 0.0465$ ; Table 3),<sup>43</sup> with significant benefits noted in the prevention of vomiting but not of nausea. The benefit of rolapitant on CR in the delayed phase was maintained in patients who were not treated with AC and received carboplatin-based chemotherapy (82% for rolapitant vs 66% for active control;  $P < 0.001$ ).<sup>44</sup> An additional analysis in the subgroup of patients treated with carboplatin-based chemotherapy found that the absolute benefit observed with rolapitant (the absolute difference between the proportion of rolapitant and active control respondents) was 15.3 percentage points for CR in the delayed phase.<sup>44</sup>

These four clinical trials demonstrated that a single 180 mg oral dose of rolapitant administered ~1–2 hours prior to HEC or MEC in combination with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone provided superior CINV protection across the delayed phase compared with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone alone.<sup>42,43</sup> Based on these results, the National Comprehensive Cancer Network added oral rolapitant to their clinical practice guidelines for preventing CINV as a treatment option for patients receiving HEC and MEC, and it is recommended for the subset of patients with additional risk factors or treatment failure with a steroid plus 5-HT<sub>3</sub> antagonist alone.<sup>35</sup> In addition to recommending rolapitant as part of the prophylactic regimen for patients receiving HEC, a 2016 update to the antiemetic guidelines from the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology recommended rolapitant in patients receiving carboplatin-based MEC.<sup>37</sup>



## Safety and tolerability of rolapitant and comparison to other NK-1 receptor antagonists

NK-1 receptor antagonists are generally well tolerated. The most commonly reported treatment-emergent adverse events (TEAEs) with NK-1 receptor antagonists in clinical trials included headache, constipation, fatigue, and hiccups, which appeared with a similar frequency as seen in active control groups (Table 4).<sup>6</sup> The adverse event (AE) profile of NK-1 receptor antagonists as a class, mirrors that associated with other classes of antiemetic agents,<sup>45</sup> with the most commonly reported TEAEs being fatigue, constipation, neutropenia, alopecia, diarrhea, and headache.<sup>46</sup>

Rolapitant has a similar safety and tolerability profile to other NK-1 receptor antagonists, with headache, constipation, fatigue, and hiccups among the most commonly reported TEAEs<sup>41–43</sup> (Table 4). In Phase II and III trials, rolapitant had a similar frequency of AEs to those seen in the active control groups. Grade 1–2 AEs were reported in

<10% of patients. No patient had a serious TEAE, nor did any patient die from a TEAE. When assessed across multiple cycles of chemotherapy,<sup>47</sup> rolapitant was well tolerated, with an incidence of TEAEs similar to that seen in cycle 1. The incidence of TEAEs did not increase with increasing cycles of chemotherapy, and cumulative toxicity was not evident. In an integrated safety analysis of the three Phase III and one Phase II randomized trials, the incidence of TEAEs was similar between the rolapitant and control arms in the subgroup of patients who used concomitant CYP2D6, breast cancer resistance protein (BCRP), or CYP3A4 substrate drugs.<sup>46</sup> This suggests that the risk of drug interactions is low when rolapitant is coadministered with such drugs, although caution should be exercised when using rolapitant concomitantly with CYP2D6, BCRP, and P-glycoprotein substrates with a narrow therapeutic index. Unlike other marketed NK-1 receptor antagonists,<sup>28–30</sup> rolapitant does not inhibit or induce CYP3A4 and has not shown effects on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam.<sup>31</sup> Thus, dose

**Table 4** Safety and tolerability of marketed NK-1 receptor antagonists

NK-1 receptor antagonist	Chemotherapy	Incidence of drug-related AEs	Difference relative to control	Potential drug–drug interactions	References
Rolapitant	HEC	Dyspepsia (<1%) Headache (<1%) Constipation (<1%) Hiccups (<1%)	No	CYP2D6 <sup>a</sup> BCRP <sup>b</sup>	26,42,43
	MEC	Constipation (3%) Fatigue (3%) Dizziness (1%) Headache (2%)	No		
Aprepitant/fosaprepitant	HEC	Anorexia (3%) Fatigue (3%) Constipation (2%) Diarrhea (2%)	No	CYP3A4 <sup>c</sup> substrates CYP3A4 <sup>d</sup> inhibitors CYP3A4 <sup>e</sup> inducers Warfarin <sup>f</sup>	28,29,33–35
	MEC	Constipation (<1%) Fatigue (<1%) Headache (<1%) Diarrhea (<1%)	No	Hormonal contraceptives <sup>g</sup>	
Netupitant	HEC	Hiccups (5%) Leukocytosis (2%) ALT increased (2%) Bundle branch block (2%)	No	CYP3A4 <sup>c</sup> substrates CYP3A4 <sup>d</sup> inhibitors CYP3A4 <sup>e</sup> inducers	30,39,59
	MEC	Headache (3%) Constipation (2%)	No		

**Notes:** <sup>a</sup>CYP2D6 substrates with a narrow therapeutic index (e.g., dextromethorphan, thioridazine, pimozide) may increase plasma concentration of concomitant drug with potential for AEs. <sup>b</sup>BCRP substrates with a narrow therapeutic index (e.g., methotrexate, topotecan, irinotecan, rosuvastatin) may increase plasma concentration of concomitant drug. <sup>c</sup>CYP3A4 substrates (e.g., pimozide, benzodiazepines, dexamethasone, methylprednisolone, some chemotherapeutics) may increase plasma concentration of concomitant drug. <sup>d</sup>Strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir, diltiazem) may increase plasma concentrations of aprepitant or netupitant with increased risk of AEs. <sup>e</sup>Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) may decrease plasma concentrations of aprepitant or netupitant and reduce efficacy. <sup>f</sup>International normalized ratio of prothrombin time may decrease. <sup>g</sup>Efficacy may be decreased for up to 28 days following last dose.

**Abbreviations:** AEs, adverse events; ALT, alanine aminotransferase; BCRP, breast cancer resistance protein; CYP, cytochrome P450; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; NK-1, neurokinin-1.

adjustments are not required when rolapitant is concomitantly administered with other drugs metabolized by CYP3A4 such as dexamethasone.<sup>26</sup> However, strong CYP3A4 inducers such as rifampin may significantly reduce plasma concentrations of rolapitant; therefore, concurrent use should be avoided (Table 4).<sup>26</sup> Rolapitant is also a moderate inhibitor of the CYP2D6 enzyme, BCRP, and P-glycoprotein, meaning that concomitant use of substrates of these proteins with a narrow therapeutic index should be avoided or the patient should be monitored for adverse reactions (Table 4).<sup>26</sup> Overall, the low risk of drug–drug interactions with rolapitant compared with other NK-1 receptor antagonists makes this drug particularly safe to use and potentially beneficial in older people who typically take multiple medications.

## Impact of rolapitant on QoL

CINV negatively affects patient QoL. Poorly controlled nausea and vomiting is one of the most dreaded side effects of chemotherapy, ranking worse than depression, fatigue, and diarrhea, with poorly controlled CINV ranking second only to death.<sup>2</sup> The impacts of CINV are manifested not only in a patient's QoL but also in medical costs, use of health care resources, and compliance with further chemotherapy.<sup>4,8,12,48–50</sup>

Surveys indicate that oncologists and oncology nurses can accurately predict the incidence of acute CINV after HEC; however, there is a perception gap between health professionals and patients with respect to the incidence of delayed CINV after HEC that is often underestimated. In one study, the predicted incidence of delayed nausea was 39% (95% CI: 30%–48%), whereas the observed incidence was 60% (95% CI: 48%–72%), and the predicted incidence of delayed vomiting was 22% (95% CI: 12%–31%), whereas the observed incidence was 50% (95% CI: 37%–63%).<sup>14</sup> Delayed CINV has also been underestimated in patients receiving MEC.<sup>14,51</sup> Misperceptions regarding the incidence of delayed CINV may have implications for treatment. For example, in a UK study, patients who experienced acute vomiting in cycle 1 were significantly more likely to have a change in antiemetic therapy in subsequent cycles; by contrast, delayed vomiting or nausea at any stage did not lead to changes in subsequent antiemetic regimens.<sup>52</sup>

Delayed CINV has a significant detrimental effect on a patient's daily life,<sup>4,5,53</sup> even in the absence of acute CINV. In a representative sample of 298 treatment-naive patients receiving HEC or MEC and given CINV prophylaxis under then-current patterns of clinical practice, the impact of CINV on daily life was assessed using the Functional Living Index-Emesis (FLIE) questionnaire on day 6 of cycle 1.<sup>4</sup> Only 32%

of patients who experienced delayed vomiting without acute vomiting reported that CINV had no or minimal impact on daily life, similar to the proportion of patients who experienced only acute vomiting (30%). In the same study, 80% of patients who experienced acute nausea without delayed nausea reported that emesis did not affect their daily life; by contrast, only 56% of those who experienced delayed nausea without acute nausea reported no or minimal impact. The FLIE is an 18-item questionnaire<sup>54,55</sup> comprising two domains (nausea and vomiting); in each domain, the patient answers one question on the magnitude of the symptom (nausea or vomiting) followed by eight questions to assess the impact of the symptom on the patient's ability to enjoy meals/liquids, prepare meals/do household tasks, perform daily functions, and engage in usual recreation/leisure activities, as well as his/her willingness to spend time with family and friends and the extent to which symptoms have caused personal hardship.<sup>54,55</sup> Patient responses are recorded using a seven-point visual analog scale, with higher scores corresponding to a higher QoL and an average item score >6 (or FLIE total score >108) defined as no impact of CINV on daily life. In a prospective, placebo-controlled, randomized, double-blind Phase III trial conducted in patients with multiple myeloma undergoing autologous transplantation after high-dose melphalan conditioning, aprepitant significantly improved QoL compared with active control. Mean total FLIE score ( $\pm$  standard deviation [SD]) was 114 ( $\pm$ 18) for the aprepitant group and 106 ( $\pm$ 26) for the active control group ( $P<0.001$ ). A pooled analysis of Phase III trials (HEC 1, HEC 2, and MEC) demonstrated that rolapitant significantly improved QoL in patients receiving both HEC and MEC compared with active control.<sup>56,57</sup> In the HEC studies, the mean ( $\pm$ SD) FLIE total score was 114 ( $\pm$ 17) for the rolapitant group and 109 ( $\pm$ 24) for the active control group ( $P<0.001$ ); in the MEC study, it was 113 ( $\pm$ 20) for the rolapitant group and 109 ( $\pm$ 23) for the active control group ( $P>0.001$ ). Overall, these Phase III clinical trials demonstrated that a single oral administration of rolapitant significantly improved patient QoL.

## Conclusion and place in therapy

Therapy for delayed CINV, the 5-day at-risk period during which patients are not often in direct contact with caregivers, remains a significant unmet medical need for multiple reasons. For example, appropriate prophylactic antiemetics may be inadequately prescribed because of an underestimation of delayed CINV control or patients may be nonadherent to prescribing instructions when pills need to be taken at home. The discovery and development of NK-1 receptor

antagonists bring additional treatment options for patients at risk for CINV. The recent approval of rolapitant for the prevention of delayed CINV in combination with other antiemetic agents may provide adult patients with significant benefits beyond those of previously approved NK-1 receptor antagonists. Specifically, the combination of the longer half-life and sustained efficacy of rolapitant, compared with these other agents, and its single oral administration prior to chemotherapy may lead to better control while on treatment. This is particularly important given that failure to protect against CINV during the first cycle of chemotherapy is the most significant independent risk factor for delayed CINV during subsequent cycles. Additionally, the mild-to-moderate adverse effects of rolapitant, which were not significantly different than those of the active controls, and the lack of interactions with drugs metabolized by CYP3A4 such as dexamethasone may also be beneficial, particularly in older patients who tend to take more medications.

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Ruggero Galici, PhD (Ashfield Healthcare, Haddam, CT, USA), drafted and revised the manuscript based on content outline provided by the author. Shannon Davis (Ashfield Healthcare) copyedited and styled the manuscript per journal requirements.

## Author contribution

Dr Rapoport was responsible for the conception and analysis of this review, for revising the scientific and medical content and drafts, and for approving the final version for publication; he is accountable for the accuracy and integrity of the work.

## Disclosure

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