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ABSTRACT

Introduction: The addition of neurokinin-1 receptor antagonists (NK1RAs) to standard prophylaxis of 5-hydroxytryptamine-3 RA (5-HT3RA) plus dexamethasone more effectively prevents chemotherapy-induced nausea and vomiting (CINV) associated with highly and moderately emetogenic chemotherapy.

Areas covered: This review presents the evidence base for the use of oral and intravenous (IV) NK1RAs, focusing on the pharmacologic and clinical properties as a class, and highlighting differences between agents. A PubMed literature search was conducted from 2000 to 2018.

Expert opinion: Adherence to international antiemetic guidelines remains a clinical challenge. Strategies to simplify antiemetic regimens and facilitate their administration may improve compliance and treatment outcomes. The use of fixed-combination antiemetics offers clinical utility, in combining an NK1RA with a 5-HT3RA in a single oral dose. The use of long-lasting NK1RAs and administering CINV prophylaxis closer to the time of chemotherapy may also assist with guideline and treatment compliance, diminishing the need for home-based administration, and potentially reducing resource utilization. The availability of IV and oral formulations of NK1RAs and NK1RA–5-HT3RA fixed combinations offers further utility, particularly for those patients unsuited for oral administration. However, safety considerations with respect to injection site toxicity and hypersensitivity reactions of the new NK1RA IV formulations deserve close attention.

1. Introduction

Chemotherapeutic agents are classed in clinical practice guidelines of the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) as highly emetogenic (HEC), moderately emetogenic (MEC), and low emetogenic chemotherapy [10–12]. This categorization is made on the basis of the drug’s ability to provoke nausea and vomiting in the first 24 h after administration in the absence of appropriate antiemetic prophylaxis. Antiemetic classification is continuously revised to include new agents or data from existing agents and/or combinations. For example, anthracycline-cyclophosphamide combinations (AC) are now classified as HEC (previously MEC), and certain carboplatin-based regimens have recently been reclassified as HEC (previously MEC) [12] or are considered HEC in terms of their prophylactic recommendations [10,11].

Up to the 1990s, dopamine receptor antagonists (RAs), such as metoclopramide and prochlorperazine, and corticosteroids were the standard prophylactic treatment for CINV [13,14]. Subsequent clinical data demonstrated that the combination of a 5-HT3RA and dexamethasone was effective in preventing acute and delayed emesis in 70% of patients receiving HEC [15,16], and showed a better safety profile for 5-HT3RAs [17]. The further addition of an NK1RA reduced emesis in approximately 84% of

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Department of Hematology, Oncology and Palliative Care, Klinikum Neuperlach, Munich, Germany; Department of Hematology, Oncology and Palliative Care, Klinikum Harlaching, Munich, Germany; Department of Oncology, Odense University Hospital, Odense, Denmark; Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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It is suggested that clinicians should follow international antiemetic guidelines in order to minimize the negative impact of chemotherapy-induced nausea and vomiting (CINV) in patients with cancer.  

- Triple treatment regimens of neurokinin-1 receptor antagonist (NK1RA), 5-hydroxytryptamine-3 receptor antagonist (5-HT3RA), and dexamethasone provide superior control of CINV associated with highly emetogenic chemotherapy (HEC, including anthracycline plus cyclophosphamide) and carboplatin-based regimens compared with 5-HT3RA-dexamethasone alone, and are therefore recommended by international guidelines.  

- Strategies to simplify antiemetic regimens and facilitate their ease of administration are essential to improve clinician adherence to guidelines and patient treatment compliance. The fixed-combination agent NEPA, composed of the NK1RA netupitant and the 5-HT3RA palonosetron, targets in a single dose the two key signaling pathways involved in emesis via overlapping and synergistic mechanisms.  

- NK1RAs with prolonged half-life, such as netupitant and rolapitant, help reduce the number of doses needed.  

- Achieving complete control of nausea remains a major obstacle in antiemetic treatment, and while the improvement in the control of delayed nausea of both aprepitant- and rolapitant-based regimens is not clear, NEPA plus dexamethasone has shown superiority over 5-HT3RA-dexamethasone.  

- Finally, the availability of intravenous (IV) formulations of antiemetics is of special value to patients who cannot swallow oral medications. IV NEPA has shown similar tolerability compared with the oral formulation. However, hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur following fosaprepitant, IV aprepitant (injectable emulsion), or IV rolapitant (injectable emulsion) administration, and infusion site toxicities have been observed with fosaprepitant and IV rolapitant (injectable emulsion).

Information regarding bioequivalence between oral and intravenous (IV) doses of NEPA was provided by Helsinn.

3. The emetic pathway

Activation of the emetic pathway following treatment with certain chemotherapeutic agents involves the release of neurotransmitters, such as dopamine (D2), muscarine, choline, histamine (H1), serotonin (5-HT), and substance P [24]. The release of serotonin activates 5-HT3 receptors on vagal afferent neurons, the chemoreceptor trigger zone (CTZ), and the nucleus of the tractus solitarius (NTS), which stimulates the vomiting center (VC) in the medulla oblongata in the brain [25]. Substance P binds to NK1 receptors in the area postrema and NTS, which then transfer the signal to the CTZ and VC (Figure 1) [26]. Although substance P acts primarily in the central nervous system (CNS), the peripheral activation of NK1 receptors in the gut may also contribute to CINV [8,27,28].

4. Antiemetic guidelines

Major antiemetic guidelines recommend the NK1RA–5-HT3RA–dexamethasone combination as the most effective regimen for controlling acute and delayed CINV associated with HEC, or with AC-based regimens (Table 1) [10–12]. Alternatively, a quadruple regimen involving the addition of olanzapine to NK1RA–5-HT3RA–dexamethasone is recommended [11,12]. Recent guideline revisions now recommend prophylaxis with the NK1RA–5-HT3RA–dexamethasone triplet for patients receiving carboplatin-based regimens (any dose of carboplatin [10], or at a carboplatin area under the concentration-time curve [AUC] of ≥4 mg/mL/minute [11,12]). For patients receiving MEC, prophylaxis with a 5-HT3RA plus dexamethasone on day 1 is advised [10–12], and on days 2 and 3 if necessary [12]. For selected patients with high-risk factors for CINV or for whom previous 5-HT3RA and dexamethasone treatment has failed, NCCN guidelines advise the use of the NK1RA–5-HT3RA–dexamethasone triplet [12]. For the prevention of nausea [12], use of NEPA may provide potential benefits over the acute, delayed, and overall periods; among 5-HT3RAs, use of palonosetron and subcutaneous granisetron extended-release injection are preferred for the prevention of delayed nausea following MEC; addition of olanzapine to the NK1RA–5-HT3RA–dexamethasone regimen may improve the control of delayed nausea for patients receiving HEC.

The implementation of antiemetic prophylaxis that is consistent with guidelines has been shown to improve CINV control [29]; however, adherence to guidelines is suboptimal in many countries [29–31], due to various factors, including underestimation of CINV incidence by physicians and nurses [32–34], lack of physician awareness, budgetary issues [35,36], and poor patient adherence [31].

5. NK1RA family

NK receptors belong to the tachykinin family of G-protein coupled receptors. With three family members (NK1,2,3 receptors), endogenous substance P has been shown to bind with highest affinity to the NK1 receptor, localized in the CNS [37]. The NK1RA antiemetic family acts by blocking the binding of patients receiving HEC [16,18]. A number of studies and recent meta-analyses have demonstrated that the triplet regimen provides superiority over 5-HT3RA–dexamethasone in CINV control associated with HEC, MEC, and carboplatin-based regimens [19–23] without added toxicities from the oral NK1RAs [21,22]. This review provides an overview of currently available NK1RAs for the prevention of CINV and discusses the similarities and differences between these agents.

2. Methods

A search of PubMed was conducted for published clinical data from 1 January 2000 to 31 December 2018, using the following terms: CINV, NK1RA, aprepitant, aprepitant injectable emulsion, HTX-019, fosaprepitant, netupitant, NEPA, rolapitant, rolapitant injectable emulsion, CINV guidelines. Relevant reports published during this time were chosen for analysis; earlier manuscripts were included if they were cited in the chosen reports and, after evaluation, were deemed to contain information pertinent to the review topic. The search was limited to studies performed in adult healthy subjects and adult cancer patients. For data reporting the pharmacologic aspects of NK1RAs, a search of the summary of product characteristics, prescribing information, studies presented at international congresses during 2014–2018, and PubMed was conducted using the following terms and criteria in the title or abstract: aprepitant or fosaprepitant or rolapitant or netupitant or fosnetupitant or NEPA, and pharmacology, and CINV.
substance P at NK1 receptors in the brain stem emetic center [38]. This mechanism of action is dependent on adequate CNS penetration and central NK1 receptor occupancy (NK1RO) [38].

NK1RAs approved for the prevention of CINV include [10–12]:

1. Aprepitant, available for oral administration [39], as an injectable emulsion [40], and as the IV water-soluble prodrug of aprepitant, fosaprepitant, which is converted to active aprepitant within 30 min of administration [41];
2. Rolapitant, available as an oral agent and an injectable emulsion [42]. Despite its approval, rolapitant injectable emulsion is currently not included in the major antiemetic guidelines [10–12]. The distribution of rolapitant for injection has recently been suspended in reaction to a US Food and Drug Administration (FDA) safety warning due to postmarketing reports of serious hypersensitivity reactions including anaphylaxis and anaphylactic shock [43];
3. Netupitant, available as an oral fixed-combination agent with the 5-HT3RA palonosetron (oral NEPA) and as an IV fixed combination of a water-soluble prodrug of netupitant, fosnetupitant, and palonosetron (IV NEPA) [44]. Following IV NEPA administration, fosnetupitant is rapidly converted to netupitant, with maximum concentrations of netupitant and palonosetron in plasma reached at the end of the 30-min infusion [45]. IV NEPA is approved as a lyophilized powder for reconstitution; a ready-to-use solution is under development. Additionally, a different formulation of fosnetupitant alone is currently being evaluated in a phase 3 trial in Japan.

As a fixed-combination antiemetic (administered as a single dose on day 1 only), NEPA targets the two key signaling pathways involved in emesis, not only via direct inhibition of their respective receptors by netupitant and palonosetron, but also via palonosetron-mediated inhibition of signaling cross-talk between 5-HT3 and NK1 receptors. In addition, both palonosetron and netupitant can inhibit substance P, with evidence that the combination produces synergistic effects [46,47]. At a mechanistic level, this synergy may arise as a result of the two drugs triggering NK1 receptor internalization in an additive fashion [48].

6. Pharmacologic properties of NK1RAs
6.1. NK1RO

Approved NK1RAs are all highly selective for the human NK1 receptor, with inhibitory constants of 0.12 nM, 0.66 nM, and 1.0 nM for aprepitant [49], rolapitant [50], and netupitant [51], respectively. Binding affinity for NK2 and NK3 receptors is significantly lower for all NK1RAs. NK1 receptors can be
### Table 1. Guideline recommendations for antiemetic use in the moderately and highly emetogenic chemotherapy settings.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>MEC (acute phase)</th>
<th>MEC (delayed phase)</th>
<th>Non-AC HEC (acute phase)</th>
<th>Non-AC HEC (delayed phase)</th>
<th>AC HEC (acute phase)</th>
<th>AC HEC (delayed phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCO [11]</strong></td>
<td>5-HT, RA + DEX</td>
<td>DEX*</td>
<td>NEPA + OLZ + DEX</td>
<td>OLZ + DEX</td>
<td>NEPA + OLZ + DEX</td>
<td>OLZ</td>
</tr>
<tr>
<td><strong>If carboplatin AUC ≥4 mg/mL/min:</strong></td>
<td>If carboplatin AUC ≥4 mg/mL/min:</td>
<td>None or APR‡ or DEX ± OLZ + DEX or DEX</td>
<td>If oral NK, RA (APR/FOS/ROL + 5-HT, RA + DEX)</td>
<td>If oral NK, RA (APR/FOS/ROL + 5-HT, RA + DEX)</td>
<td>If oral NK, RA (APR/FOS/ROL + 5-HT, RA + DEX)</td>
<td>If oral NK, RA (APR/FOS/ROL + 5-HT, RA + DEX)</td>
</tr>
<tr>
<td>NEPA + DEX</td>
<td>or NK, RA (APR/FOS/ROL + 5-HT, RA + DEX)</td>
<td>or APR‡ or DEX + OLZ + DEX or DEX</td>
<td>or APR‡ or DEX + OLZ + DEX or DEX</td>
<td>or APR‡ or DEX + OLZ + DEX or DEX</td>
<td>or APR‡ or DEX + OLZ + DEX or DEX</td>
<td>or APR‡ or DEX + OLZ + DEX or DEX</td>
</tr>
<tr>
<td><strong>MASCC/ESMO [10]</strong></td>
<td>5-HT, RA + DEX</td>
<td>DEX*</td>
<td>NEPA + DEX</td>
<td>DEX</td>
<td>NEPA + DEX</td>
<td>None¹</td>
</tr>
<tr>
<td><strong>If carboplatin (any dose):</strong></td>
<td>If carboplatin (any dose):</td>
<td>None or APR‡</td>
<td>None or APR‡</td>
<td>None or APR‡</td>
<td>None or APR‡</td>
<td>None¹</td>
</tr>
<tr>
<td>NEPA + DEX</td>
<td>or NK, RA (APR/FOS/ROL + 5-HT, RA + DEX)</td>
<td>or APR‡</td>
<td>or APR‡</td>
<td>or APR‡</td>
<td>or APR‡</td>
<td>or APR‡</td>
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<tr>
<td><strong>NCCN [12]</strong></td>
<td>5-HT, RA + DEX</td>
<td>DEX* or 5-HT, RA²</td>
<td>NEPA + DEX</td>
<td>NEPA + DEX</td>
<td>NEPA + DEX</td>
<td>OLZ²</td>
</tr>
<tr>
<td><strong>If oral NK, RA:</strong></td>
<td>If oral NK, RA:</td>
<td>(NEPA + DEX) or NK, RA (APR/ROL) + 5-HT, RA + DEX*</td>
<td>(APR‡ + DEX) ± OLZ²</td>
<td>(APR‡ + DEX) ± OLZ²</td>
<td>(APR‡ + DEX) ± OLZ²</td>
<td>(APR‡ + DEX) ± OLZ²</td>
</tr>
<tr>
<td>NEPA + DEX</td>
<td>or NK, RA (APR/ROL) + 5-HT, RA + DEX*</td>
<td>or DEX*</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
</tr>
<tr>
<td>or OLZ + PALO + DEX⁶</td>
<td>or DEX⁶</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
</tr>
<tr>
<td><strong>If oral NK, RA:</strong></td>
<td>If oral NK, RA:</td>
<td>(NEPA + DEX) or NK, RA (APR/ROL) + 5-HT, RA + DEX*</td>
<td>(APR‡ + DEX) ± OLZ²</td>
<td>(APR‡ + DEX) ± OLZ²</td>
<td>(APR‡ + DEX) ± OLZ²</td>
<td>(APR‡ + DEX) ± OLZ²</td>
</tr>
<tr>
<td>NEPA + DEX</td>
<td>or NK, RA (APR/ROL) + 5-HT, RA + DEX*</td>
<td>or DEX*</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
</tr>
<tr>
<td>or IV NK, RA³</td>
<td>or DEX³</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
</tr>
<tr>
<td><strong>(IV NEPA + DEX or NK, RA [APR/ROL] + 5-HT, RA + DEX³)</strong></td>
<td>(IV NEPA + DEX or NK, RA [APR/ROL] + 5-HT, RA + DEX³)</td>
<td>± DEX³</td>
<td>± DEX³</td>
<td>± DEX³</td>
<td>± DEX³</td>
<td>± DEX³</td>
</tr>
<tr>
<td>or OLZ + PALO + DEX⁶</td>
<td>or DEX⁶</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
<td>or DEX</td>
</tr>
</tbody>
</table>

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*Palonosetron 0.25 mg IV or granisetron 10 mg subcutaneous administered only once are the preferred options.

†With or without lorazepam, and with or without either an H2 blocker or a proton pump inhibitor.

‡If carboplatin AUC ≥4 mg/mL/min.

§In patients with additional risk factors or for whom a previous treatment with steroid plus 5-HT, RA had failed, an NK, RA can be added.

**Aprepitant injectable emulsion 130 mg on day 1. Not interchangeable with IV fosaprepitant.

‖If cyclophosphamide, doxorubicin, oxaliplatin, and other drugs known to induce delayed nausea and/or vomiting.

¶If aprepitant 125 mg is used on day 1, then use once-daily aprepitant 80 mg on days 2–3.

#If oral dolasetron 100 mg was administered on day 1, administer oral dolasetron 100 mg on days 2–3. If granisetron 2 mg oral, or 0.01 mg/kg IV was administered on day 1, administer granisetron 1–2 mg daily oral or 0.01 mg/kg daily on days 2 and 3. If ondansetron 16–24 mg oral or 8–16 mg IV was administered on day 1, administer ondansetron 8 mg oral twice daily or 16 mg oral daily, or 8–16 mg IV daily on days 2 and 3.

§If olanzapine is given on day 1, it should also be administered on days 2–3 (MEC) or days 2–4 (HEC).

‖Dexamethasone 8 mg oral/IV daily on days 2–3 (MEC) or days 2–4 (HEC); if fosaprepitant was used on day 1 administer dexamethasone 8 mg oral/IV on day 2 and 8 mg oral/IV twice daily on days 3–4.

¶If aprepitant 125 mg is used on day 1, then use dexamethasone 8 mg x 1 + aprepitant 80 mg x 1 (days 2–3) or dexamethasone 8 mg x 1 + metoclopramide 20 mg x 4.

#If an NK, RA is not available, use of palonosetron is preferred.

¶If NEPA, fosaprepitant, or rolapitant was given on day 1.

‖Dexamethasone 4 mg x 2 (days 2–3).

§S-HT, RA: 5-hydroxytryptamine-3 receptor antagonist; AC: anthracycline plus cyclophosphamide; APR: aprepitant; APR: aprepitant injectable emulsion; ASCO: American Society of Clinical Oncology; AUC: area under the concentration-time curve; DEX: dexamethasone; ESMO: European Society for Medical Oncology; FOS: fosaprepitant; HEC: highly emetogenic chemotherapy; IV: intravenous; IV NEPA: fixed combination of fosnetupitant 235 mg/palonosetron 0.25 mg; MASCC: Multinational Association of Supportive Care in Cancer; MCP: metoclopramide; MEC: moderately emetogenic chemotherapy; NCCN: National Comprehensive Cancer Network; NEPA: fixed combination of netupitant 300 mg/palonosetron 0.50 mg; NK, RA: neurokinin-1 receptor antagonist; OLZ: olanzapine; PALO: palonosetron; ROL: rolapitant.
found in different regions of the CNS, primarily in the locus coeruleus and ventral striatum and to a lesser extent in the cerebral cortex, hippocampus, and amygdala [37].

NK₁,RO by aprepitant was analyzed in two randomized, placebo-controlled studies. In the first, 12 healthy subjects received oral aprepitant at doses of 10, 30, 100, or 300 mg once daily for 14 days, with two individuals receiving placebo. Four additional healthy subjects were enrolled in a second study, in which three subjects received aprepitant 30 mg and one received placebo control. Plasma aprepitant concentration and NK₁,RO in the striatum were evaluated by positron emission tomography (PET) predose and 24 h after the last dose [52]. NK₁,RO in the striatum was shown to correlate with the dose and plasma concentration of aprepitant. The aprepitant plasma concentration of approximately 100 ng/mL was estimated to achieve >90% striatal NK₁,RO [52]. After oral administration of the standard aprepitant regimen consisting of a single 125-mg dose on day 1 then 80 mg once daily on days 2–3, a maximum plasma concentration (Cₘₐₓ) of approximately 1.6 µg/mL and 1.4 µg/mL was reached on days 1 and 3, respectively [39]. Thus, therapeutic doses of aprepitant are expected to result in >90% NK₁,RO in the striatum, which was used subsequently as the threshold for antiemetic efficacy.

Rolapitant NK₁,RO was investigated in a single-dose, phase 1 PET study of healthy subjects [53]. Fourteen volunteers were enrolled in six rolapitant dose cohorts ranging from 4.5 to 180 mg, and an aprepitant 125-mg cohort (two subjects per cohort). Escalating doses of rolapitant correlated with increased NK₁,RO in different cortical regions of the brain, but not in a dose-proportional manner. Rolapitant dose and plasma concentration were correlated with NK₁,RO in the cortex. Using pharmacokinetic/pharmacodynamic modeling, after rolapitant 180-mg dosing, plasma concentrations of >348 ng/mL were predicted to result in >90% NK₁,RO in the cortex for up to 120 h. In the striatum, the predicted NK₁,RO was 73% at 120 h after single-dose administration of rolapitant 180 mg [42].

Netupitant NK₁,RO was analyzed in a single-dose, randomized PET study of six healthy subjects who received a single oral dose of 100, 300, or 450 mg netupitant [54]. More than 90% NK₁,RO in the striatum was achieved with the 300-mg and 450-mg oral doses, with prolonged RO. A netupitant Cₘₐₓ of 225 ng/mL was predicted to achieve 90% NK₁,RO in the striatum. After a single dose of netupitant 300 mg, Cₘₐₓ was ~550 ng/mL, confirming that therapeutic doses of netupitant meet the threshold for antiemetic efficacy.

Although the relationship between NK₁,RO in the striatum and NK₁,RA clinical efficacy has not been directly established, striatal NK₁,RO >90% is considered a predictor of treatment efficacy in CINV, since NK₁ receptor density is highest in the striatum [37]. In addition, PET studies have shown that radiolabeled NK₁ receptor ligand analogues produced the strongest signals in the striatum [52,54,55], and therapeutic doses of aprepitant and netupitant were shown to achieve striatal NK₁,RO >90% [52,54]. However, for rolapitant, administration of therapeutic doses has been correlated with highest occupancy of cortical NK₁ receptors [56]. A better understanding of the role of NK₁ receptors in different brain regions may help predict antiemetic responses and explain interindividual differences in response.

### 6.2. Absorption

Following oral administration of the standard aprepitant regimen in healthy volunteers, i.e., 125-mg dose on day 1 and 80 mg once daily on days 2–3, the AUC from time 0 to 24 h (AUC₀–₂₄) was 19.6 µg·h/mL on day 1 and 21.2 µg·h/mL on day 3. The Cₘₐₓ of 1.6 µg/mL and 1.4 µg/mL were reached after approximately 4 h on days 1 and 3, respectively [39]. A 20-min infusion of a single 150-mg dose of fosaprepitant in healthy volunteers resulted in an AUC from time 0 to infinity (AUC₀–∞) of aprepitant of 37.4 µg·h/mL and a Cₘₐₓ of 4.2 µg/mL [41]. Conversion of fosaprepitant to aprepitant was rapid, with nondetectable fosaprepitant in plasma within 30 min after the end of infusion. Following administration of a single 130-mg dose of IV aprepitant as a 2-min injection or 30-min infusion in healthy volunteers, the AUC from time 0 to 72 h (AUC₀–₇₂) of aprepitant was 45.6 µg·h/mL and 43.9 µg·h/mL, and the Cₘₐₓ was 13.9 µg/mL and 6.1 µg/mL, respectively [40]. For both fosaprepitant and IV aprepitant, the Cₘₐₓ of aprepitant was reached at 30 min from the start of infusion [57].

After single oral administration of rolapitant 180-mg dose in healthy volunteers, a Cₘₐₓ of 968 ng/mL was reached in 4 h [42]. Following a 30-min infusion of a single IV 166.5-mg dose of rolapitant in healthy volunteers, the Cₘₐₓ of 1986 ng/mL was reached at the end of the infusion [42].

Following single oral administration of NEPA, the AUC₀–∞ of netupitant was 14.4 and 17.4 µg·h/mL, and the Cₘₐₓ was 434 and 496 ng/mL in healthy volunteers and cancer patients, respectively; the Cₘₐₓ was reached in 4 to 5 h [44]. For palonosetron, the AUC₀–∞ was 56.7 and 58.3 ng·h/mL, and the Cₘₐₓ was 1.53 and 0.95 ng/mL in healthy volunteers and cancer patients, respectively; the Cₘₐₓ was reached within 5 h from administration. After a 30-min infusion of a single IV NEPA dose in cancer patients or 235 mg fosnetupitant in healthy volunteers, the AUC₀–∞ of netupitant was 12.0 and 8.9 µg·h/mL, and the Cₘₐₓ was 841 and 590 ng/mL, respectively [44]. The AUC₀–∞ of palonosetron following IV NEPA was 28 ng·h/mL, and the Cₘₐₓ was 0.8 ng/mL. Peak plasma concentrations of both netupitant and palonosetron were reached at the end of the 30-min infusion, showing rapid conversion of the prodrug to netupitant.

### 6.3. Elimination half-life

Among NK₁,RA, aprepitant has the shortest apparent terminal half-life, ranging from 9 to 13 h [39]. The elimination half-life of the newer NK₁,RA is considerably longer: in NEPA, both netupitant (~96 h) and palonosetron (>40 h) have a prolonged elimination half-life [47], and rolapitant has a half-life of 180 h [42]. These differences determine the dosing schedule of NK₁,RA-based regimens for overall CINV prevention. Per chemotherapy cycle, aprepitant is administered on 3 consecutive days starting on the day of chemotherapy, whereas for NEPA and rolapitant, a single dose administered before the start of chemotherapy is sufficient. For multiple-day high-dose chemotherapy regimens (e.g., conditioning regimens before stem cell transplantation [SCT]), aprepitant-based regimens are administered on each day of a high-dose SCT preparative
regimen, plus on 1 or 3 additional days [58]. In contrast, pharmacokinetic modeling predicted that four doses of netupitant 300 mg administered over 7–8 days would be safe and well tolerated [59]. A phase 2 study to evaluate the safety and efficacy of weekly administration of NEPA plus dexamethasone in patients receiving radiotherapy and weekly cisplatin for at least 5 weeks is ongoing (NCT03668639). However, the long half-life of rolapitant limits its frequency of use, since two consecutive doses should be separated by at least a 2-week interval [42]. Hence, usage of rolapitant may not be appropriate in this setting.

7. Drug–drug interactions

The simultaneous use of multiple medications is common in cancer patients, increasing the potential for drug–drug interactions with clinically relevant effects. A summary of drug–drug interactions of NK1RAs is presented in Table 2 [39–42,44,60].

7.1. Aprepitant

Aprepitant is a substrate as well as a weak/moderate inhibitor and inducer of the cytochrome P450 (CYP) 3A4 enzyme [61,62]. Dexamethasone is also metabolized by CYP3A4 and its dosage must be reduced when administered concomitantly with aprepitant [39,40]. In pharmacokinetic studies, no clinically significant interactions were observed for aprepitant and several CYP3A4-metabolized chemotherapy agents or 5-HT3 RAs [39,63]. Nevertheless, several case studies have reported a suspected interaction between aprepitant and ifosfamide, leading to an increased risk of encephalopathy [64,65]. The effect on CYP3A4 inhibition might be weaker with fosaprepitant due to the lack of intestinal exposure and reduced inhibition of the first-pass effect. However, the oral dexamethasone dose should also be reduced on days 1 and 2 when coadministered with fosaprepitant [66]. As a mild inducer of CYP2C9, a decrease in warfarin plasma concentration and in prothrombin time have been described when aprepi tant and warfarin are coadministered [67]. Despite being a substrate of the P-glycoprotein (P-gp) transporter, aprepitant does not affect the pharmacokinetics of other P-gp substrates, including digoxin [68] and melphalan [69].

7.2. Rolapitant

Rolapitant is also metabolized by CYP3A4; however, it does not induce or inhibit CYP3A4, and dose adjustments are not required when administered concomitantly with dexamethasone. Rolapitant is a moderate inhibitor of the CYP2D6 transporter [42], and its use with thioridazine is contraindicated, since the combination may result in QT prolongation and Torsades de Pointes. The use of rolapitant with other CYP2D6 substrates with a narrow therapeutic index should be avoided, since it may result in QT interval prolongation. Although CYP2D6 participates in the metabolism of all 5-HT3 RAs except granisetron [70], no clinically relevant effects have been described upon concomitant administration of rolapitant with ondansetron. Additionally, rolapitant is an inhibitor of breast cancer resistance protein (BCRP) and P-gp. Therefore, rolapitant should not be used concomitantly with BCRP, or P-gp substrates with a narrow therapeutic index.

7.3. NEPA

Similar to aprepitant, netupitant is a substrate and moderate inhibitor of CYP3A4, and interactions with CYP3A4 substrates have been reported [71]. Increased exposure of dexamethasone when coadministered with netupitant has been observed; therefore, the dose of dexamethasone was reduced in pivotal NEPA clinical trials [72–75]. Systemic exposure to docetaxel, etoposide, and cyclophosphamide, which are also metabolized primarily by CYP3A4, has been shown to be higher (35%, 28%, and 20%, respectively) after coadministration with NEPA than with palonosetron alone. However, a pooled analysis of four pivotal studies of NEPA found no evidence of an increased frequency of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs) of interest in patients receiving either etoposide or docetaxel [76]. A manuscript presenting the safety findings of NEPA when coadministered with chemotherapeutic agents metabolized by CYP3A4 is currently in development. Potential drug–drug interactions when netupitant is coadministered with other chemotherapy agents metabolized predominantly by CYP3A4 have not been fully investigated [44]. No clinically relevant interactions between NEPA and oral contraceptives have been described [77].

Furthermore, netupitant is neither an inducer nor inhibitor of CYP2C9 and CYP2D6, and it is unlikely to interact with drugs that are substrates of the P-gp transporter [44].

In summary, each NK1RA has a distinct drug–drug interaction profile. Understanding the nature of these interactions and the strategies for the correct management of patients is important to minimize potential clinical consequences.

8. Administration schedule

The complexity of NK1RA-based regimens’ administration schedules differs on the basis of their individual pharmacologic properties. A graphic representation of the administration schedule of NK1RA-based regimens for the prevention of CINV associated with HEC and MEC is shown in Figure 2 [78].

Aprepitant is administered orally as a 125-mg dose on day 1, and at 80 mg on days 2 and 3, 1 h prior to chemotherapy (or in the morning if no chemotherapy is given on days 2 and 3) together with a 5-HT3RA and dexamethasone [39]. For IV administration, aprepitant is delivered as a single-dose, 20- to 30-min infusion of a 150-mL solution containing fosaprepitant 150 mg on day 1, together with 5-HT3RA and dexamethasone [41]. IV aprepitant emulsion is infused over 30 min or injected over a 2-min period, completing the IV administration approximately 30 min before chemotherapy. IV aprepitant emulsion is administered together with a 5-HT3RA and dexamethasone [40] in a single 130-mg dose on day 1 to patients receiving HEC, and in a single 100-mg dose on day 1, followed by oral aprepitant 80 mg on days 2 and 3, in the MEC setting.

Rolapitant is administered as a single dose on day 1 within 2 h before the administration of chemotherapy plus a 5-HT3 RA and dexamethasone also on day 1. Multiple doses of the 5-HT3 RA and/or dexamethasone may also be required on days
<table>
<thead>
<tr>
<th>NK,RA</th>
<th>Change in chemotherapy exposure</th>
<th>Change in NK,RA exposure</th>
<th>Change in drug exposure</th>
<th>No change in drug exposure</th>
<th>NK,RA in striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/IV APR, FOS [39–41,60]</td>
<td>CYP3A4</td>
<td>Enzyme</td>
<td>Increased exposure</td>
<td>Increased exposure</td>
<td>Strong CYP3A inducers: rifampin, carbamazepine, phenytoin</td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td>Strong CYP3A inhibitors: diltiazem, ketoconazole, itraconazole, nefazodone, troglitazone, clarithromycin, ritonavir, neflinavir</td>
<td>Pimozide&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>CYP3A4</td>
<td>May increase exposure of CYP3A4 substrates&lt;sup&gt;c&lt;/sup&gt; (eg, Docetaxel&lt;sup&gt;d&lt;/sup&gt;, paclitaxel, etoposide&lt;sup&gt;e&lt;/sup&gt;, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine)</td>
<td>Moderate/Strong CYP3A inhibitors: diltiazem, ketoconazole, itraconazole, nefazodone, troglitazone, clarithromycin, ritonavir, neflinavir</td>
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<tr>
<td></td>
<td>CYP3A4</td>
<td>Oral/IV NEPA&lt;sup&gt;a&lt;/sup&gt; [44]</td>
<td>CYP3A4</td>
<td>Strong CYP3A inducers: rifampin</td>
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<tr>
<td></td>
<td>CYP3A4</td>
<td>May increase exposure of CYP3A4 substrates&lt;sup&gt;c&lt;/sup&gt; (eg, Docetaxel&lt;sup&gt;d&lt;/sup&gt;, paclitaxel, etoposide&lt;sup&gt;e&lt;/sup&gt;, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine)</td>
<td>Strong CYP3A inhibitors: diltiazem, ketoconazole, itraconazole, nefazodone, troglitazone, clarithromycin, ritonavir, neflinavir</td>
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<td></td>
<td>CYP3A4</td>
<td>Oral/IV ROL [42]</td>
<td>CYP2C9</td>
<td>Strong CYP3A inducers: rifampin</td>
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<td></td>
<td>CYP3A4</td>
<td>May increase exposure of CYP3A4 substrates&lt;sup&gt;c&lt;/sup&gt; (eg, Docetaxel&lt;sup&gt;d&lt;/sup&gt;, paclitaxel, etoposide&lt;sup&gt;e&lt;/sup&gt;, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine)</td>
<td>Strong CYP3A inhibitors: diltiazem, ketoconazole, itraconazole, nefazodone, troglitazone, clarithromycin, ritonavir, neflinavir</td>
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<tr>
<td></td>
<td>CYP3A4</td>
<td>BCRP</td>
<td>BCRP substrates: rosuvastatin&lt;sup&gt;h,p&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>P-gp</td>
<td>P-gp substrates (eg, diltiazem&lt;sup&gt;h&lt;/sup&gt;)</td>
<td></td>
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<td></td>
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</tbody>
</table>

<sup>a</sup>Serotonin syndrome can occur with 5-HT3, RAs alone or used concomitantly with serotonergic drugs. NEPA should be discontinued if symptoms appear.

<sup>b</sup>No dose adjustments needed.

<sup>c</sup>No change in the safety profile of NEPA has been observed when coadministered with chemotherapeutic agents that are CYP3A4 substrates, such as etoposide and docetaxel.

<sup>d</sup>Concomitant use of the NK,RA should be avoided.

<sup>e</sup>Concomitant administration with NK,RA may increase the risk of adverse reactions.

<sup>f</sup>No single dose of oral or IV NEPA is administered, no dose adjustment is needed.

<sup>g</sup>Digoxin concentrations should be monitored and dosage adjusted as necessary.

<sup>h</sup>NK,RA is contraindicated.

<sup>i</sup>No change in the safety profile of NEPA has been observed when coadministered with chemotherapeutic agents that are CYP3A4 substrates, such as etoposide and docetaxel.

<sup>j</sup>Concomitant administration with NK,RA may increase the risk of adverse reactions.

<sup>k</sup>Monitoring of drug-related adverse reactions needed.

<sup>l</sup>No dose adjustments needed.

<sup>m</sup>No change in the safety profile of NEPA has been observed when coadministered with chemotherapeutic agents that are CYP3A4 substrates, such as etoposide and docetaxel.

<sup>n</sup>Concomitant use of the NK,RA should be avoided.

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<sup>t</sup>Monitoring of drug-related adverse reactions needed.

<sup>u</sup>No dose adjustments needed.

<sup>v</sup>No change in the safety profile of NEPA has been observed when coadministered with chemotherapeutic agents that are CYP3A4 substrates, such as etoposide and docetaxel.

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<sup>yy</sup>NK,RA is contraindicated.

<sup>zz</sup>Concomitant administration with NK,RA may increase the risk of adverse reactions.
Concomitant use of drugs that are CYP3A4 substrates should be avoided for a week. If not possible, a reduction in the dose of CYP3A4 substrates should be considered. Netupitant is metabolized marginally by CYP2C9. Netupitant and its metabolites are neither inducers nor inhibitors of CYP2C9, and palonosetron is not a CYP2C9 inducer. Thus, no substantial increase in the systemic exposure of warfarin is expected. However, the warfarin INR should be monitored and warfarin dose should be adjusted as needed.

Use of the lowest effective dose of rosuvastatin is recommended.

Decreased hormonal exposure occurs during the administration and for 28 days after the last dose. Use of alternative contraception methods is needed.

Monitoring of prothrombin time and INR recommended, and warfarin dose should be adjusted as needed.

No dose adjustment of dexamethasone is needed.

Determined by positron emission tomography at 24 h after the last oral dose of daily 10 mg and 100 mg aprepitant for 14 consecutive days in healthy volunteers. The mean trough plasma concentration following the oral aprepitant 3-day regimen was >500 mg/mL, which was predicted to result in >95% NK-RA in the brain.

Determined by positron emission tomography after single oral dose of 300 mg netupitant in healthy volunteers.

Determined by positron emission tomography after single oral dose of 180 mg rolapitant in healthy volunteers.

Netupitant \( t_{1/2} \) after administration of a single capsule of oral NEPA in cancer patients.

Netupitant \( t_{1/2} \) after single infusion of IV NEPA in cancer patients.

After administration of a single dose of oral rolapitant (4.5 to 180 mg) in cancer patients.

After infusion of a single dose of IV rolapitant (18 to 180 mg) in cancer patients.

**9.1.1. Aprepitant**

Fosaprepitant, approved by the FDA and EMA in 2008, is rapidly converted to aprepitant, with high-voltage-controlled activity, and is 30% bioavailable and comparable to aprepitant, with which it shows bioequivalence [41,86,87]. In patients receiving chemotherapy and dexamethasone in the overall phase [88], fosaprepitant was as effective as the 3-day aprepitant regimen, both in combination with chemotherapy and dexamethasone and in delayed patients with no vomiting and CR in all phases (acute, delayed, overall) after chemotherapy, compared with standard ondansetron-5-hydroxytryptamine-3 receptor antagonist (5-HT3RA) and dexamethasone in the prevention of CINV associated with cisplatin treatment [79]. In a randomized trial of 515 patients with cisplatin-based regimens, the addition of aprepitant to standard 5-HT3RA delayedonset 3-day aprepitant regimen in combination with ondansetron-5-HT3RA demonstrated consistent superiority in prevention of emesis and rescue medication use compared with either usual care or standard 5-HT3RA plus dexamethasone [80]. In a later study of 849 patients with various tumor types receiving AC and non-AC (25% prophyphylaxis, AC; 48% MEC; 52% prophylaxis, AC) chemotherapy, the benefit was sustained over four cycles of chemotherapy and overall. CR in the aprepitant arm was higher in patients receiving chemotherapy and dexamethasone (46% MEC; 52% prophylaxis, AC) chemotherapy, compared with standard ondansetron-5-HT3RA treatment [81].

**9.1.2. Fosaprepitant**

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**9. NK-RA: clinical experience**

**9.1.1. Aprepitant**

Aprepitant, the first-in-class NK-RA, received FDA and European Medicines Agency (EMA) approval in 2003 for the prevention of CINV associated with HEC and MEC regimens [39]. Early clinical data illustrated the combination of aprepitant, granisetron (5-HT3RA), and dexamethasone in the prevention of CINV associated with cisplatin treatment [79]. A randomized trial of 515 patients with cisplatin treatment [79]. The benefit was sustained over four cycles of chemotherapy and overall. CR in the aprepitant arm was higher in patients receiving chemotherapy and dexamethasone (46% MEC; 52% prophylaxis, AC) chemotherapy, compared with standard ondansetron-5-HT3RA treatment [81].
9.1.3. IV aprepitant

Whereas fosaprepitant, an IV water-soluble phosphoryl prodrug of aprepitant, is associated with systemic and infusion site reactions attributed in part to the synthetic surfactant, polysorbate 80 [91], IV aprepitant is formulated as a surfactant-free injectable emulsion. Potentially allergic excipients for patients with hypersensitivity to egg and soybean proteins remain a part of this formulation. The clinical experience of IV aprepitant is limited to multiple studies of healthy volunteers in which IV aprepitant was shown to be bioequivalent to fosaprepitant [57,90,92]. In one phase 1 study of 97 healthy volunteers, single-dose aprepitant 130 mg or fosaprepitant 150 mg administered IV over 30 min were shown to be bioequivalent [57]. Another phase 1 study enrolled 24 healthy volunteers into three cohorts that received IV aprepitant 130 mg over 15, 5, or 2 min [92]. In part B of the same study, another 50 subjects received either a 2-min injection or 30-min infusion, with bioequivalence demonstrated for the aprepitant injection and infusion.

9.1.4. Oral rolapitant

Rolapitant was approved by the FDA in 2015 [93] and by the EMA in 2017 [94] in combination with a 5-HT3RA and dexamethasone for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy. In a global, randomized, double-blind phase 3 trial, 1369 chemotherapy-naive patients received either one oral dose of rolapitant or placebo 1–2 h before administration of MEC or AC regimens [95]. All patients also received granisetron and dexamethasone. Prophylaxis with a rolapitant-based regimen was superior to control in the CR rate in the delayed and overall phases. CR rates in the acute phase were similar in phases (p < 0.005) [88]. A phase 3 study in patients receiving MEC showed that a single IV dose of fosaprepitant significantly improved the CR rate in the delayed and overall periods compared with placebo-ondansetron-dexamethasone [89]. As will be discussed under safety, IV fosaprepitant formulated with polysorbate 80 has been associated with hypersensitivity reactions, including anaphylaxis, and infusion-site reactions and infusion-site AEs [90]. As a consequence, the FDA has included a warning on the label [41].
both arms. The incidence of AEs was similar in the rolapitant and control groups.

Two randomized, double-blind phase 3 trials investigated the efficacy of oral rolapitant compared with placebo in patients receiving cisplatin-based HEC (HEC-1, n = 526; HEC-2, n = 544) [96]. All patients also received granisetron and dexamethasone. Data analysis for the individual and pooled studies was performed. The CR rate in the delayed phase was significantly superior in the rolapitant group compared with the control group. CR rates were only significantly higher in the rolapitant arm in the acute and overall phases in HEC-1 and pooled studies. No significant differences were observed in the HEC-2 study in terms of acute and overall CR rates between the rolapitant and control arms. The incidence of AEs was similar across treatment groups.

9.1.5. IV rolapitant
No efficacy data of IV rolapitant in cancer patients have been reported.

9.1.6. Netupitant: oral NEPA
Oral NEPA was approved by the FDA in 2014 [97] and by the EMA in 2015 [98] for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy. Three pivotal clinical trials have evaluated the efficacy and safety of oral NEPA in chemotherapy-naive patients with solid tumors who received a variety of HEC and MEC [72–74].

A dose-ranging phase 2 study designed to identify the best dose-combination of NEPA in patients receiving cisplatin-based HEC [73] compared three different oral doses of netupitant (100, 200, and 300 mg) plus palonosetron 0.50 mg versus oral palonosetron 0.50 mg, all administered with dexamethasone on day 1. Patients in all arms also received dexamethasone on days 2–4. A standard 3-day aprepitant regimen with ondansetron-dexamethasone was included for exploratory purposes. All oral NEPA doses showed superior overall CR rates compared with palonosetron. NEPA 300 mg was significantly more effective than palonosetron and numerically better than aprepitant plus ondansetron for all secondary efficacy endpoints of no emesis, no significant nausea (NSN), and complete protection rates (CR plus NSN) during the acute, delayed, and overall phases. The combination of oral netupitant plus palonosetron was well tolerated with a similar safety profile to palonosetron and to apre- pitant plus ondansetron.

A randomized phase 3 trial investigated the efficacy of single-dose oral NEPA and dexamethasone versus single-dose oral palonosetron and dexamethasone in preventing CINV in patients receiving AC-based chemotherapy [72]. The primary endpoint was CR during the delayed phase of cycle 1. Results showed that the percentage of patients with CR during the acute, delayed, and overall phases was significantly higher in the NEPA group compared with palonosetron. In addition, NEPA was superior to palonosetron during the delayed and overall phases for all secondary efficacy endpoints of no emesis, NSN, and complete protection.

A multinational, randomized (3:1) phase 3 study evaluated the safety of a single oral dose of NEPA plus dexamethasone compared with aprepaten-palonosetron-dexamethasone over multiple cycles of HEC or non-AC MEC in 412 chemotherapy-naive patients [74]. Patients completed 161 total chemotherapy cycles (76% of patients received MEC and 24% HEC), with 75% completing at least four cycles. The incidence and type of AEs were comparable in both groups and there was no indication of increasing toxicity over multiple cycles. Although the study was not powered to detect differences in efficacy, the overall CR and NSN rates were numerically higher in the oral NEPA arm, across four chemotherapy cycles [99] (Table 3) [74,99,100].

Recently, the only head-to-head comparison of two NK1RA-based oral regimens was performed in Asia. A randomized, noninferiority phase 3 study enrolled 828 patients treated with HEC who received oral NEPA plus dexamethasone or a 3-day oral aprepaten-granisetron-dexamethasone regimen [100] (Table 3) [74,99,100]. Noninferiority of a single dose of oral NEPA plus dexamethasone in terms of overall CR rates was demonstrated (NEPA: 73.8% versus aprepaten-granisetron: 72.4%, 95% CI [−4.5%, 7.5%]; noninferiority defined as a lower 95% CI greater than the noninferiority margin set at −10%). Rates of no emesis and NSN in the delayed and overall phases were numerically higher for NEPA. Rates of no rescue medication in the delayed and overall phases (p < 0.05 each) were significantly higher for patients receiving NEPA. The incidence of CINV (p = 0.0063), emesis (p = 0.009), and significant nausea (p = 0.024) on day 5 was significantly lower in the NEPA group [101]. NEPA treatment also increased patients’ quality of life, as a higher percentage of patients reported no impact on daily living due to nausea in the delayed phase compared with aprepaten-granisetron (71.1% versus 65.1%) [100] (Table 3) [74,99,100].

9.1.7. Fosnetupitant: IV NEPA
Approved by the FDA in 2018 in combination with dexamethasone for the prevention of CINV associated with HEC [44]. IV NEPA is composed of free-base fosnetupitant 235 mg (corresponding to a 260-mg dose of fosnetupitant chloride hydrochloride) and palonosetron 0.25 mg. Fosnetupitant 235 mg is bioequivalent in terms of overall exposure to netupitant 300 mg in oral NEPA (Helsinn, data on file). Palonosetron 0.25 mg is the approved dose for IV bolus administration [102]. In a phase 3 study in cancer patients receiving HEC, IV palonosetron 0.25 mg administered as a 30-min infusion was noninferior to the approved 30-s IV bolus [103]. The recommended dexamethasone dose is reduced as for oral NEPA [44,75].

A phase 3 safety study recently compared IV NEPA with oral NEPA, both in combination with dexamethasone, in patients receiving HEC. Although not powered to detect differences in efficacy, IV and oral NEPA showed high CINV control, with CR rates of 77% and 84%, respectively, and no-emesis rates of 84% and 89%, respectively, during the overall phase [75]. A post-hoc analysis compared the efficacy of IV NEPA in this phase 3 study (N = 203) with that of pooled data from the oral NEPA pivotal studies in a total of 823 patients receiving non-AC HEC and showed comparable efficacy in terms of overall CR rates between the two NEPA formulations [104]. Currently, a study evaluating IV NEPA in patients receiving AC-based regimens is ongoing.
Table 3. Summary of efficacy and safety results from the studies comparing oral NK,RAs: NEPA versus aprepitant plus granisetron [100] or NEPA versus aprepitant plus palonosetron [74,99].

<table>
<thead>
<tr>
<th>Efficacy outcomes, %</th>
<th>NEPA + DEX</th>
<th>APR + GRAN + DEX</th>
<th>NEPA + DEX</th>
<th>APR + PALO + DEX</th>
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<tbody>
<tr>
<td><strong>Complete response</strong></td>
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<td>Acute</td>
<td>84.5</td>
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<td>92.9/94.6/96.1/96.6</td>
<td>94.2/91.7/95.6/96.3</td>
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<tr>
<td>Delayed</td>
<td>79.4</td>
<td>74.3</td>
<td>83.2/88.8/91.5/91.0</td>
<td>77.7/82.3/87.8/87.7</td>
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<tr>
<td>Overall</td>
<td>73.8</td>
<td>72.4</td>
<td>80.6/86.1/90.7/90.1</td>
<td>75.7/81.3/86.7/87.7</td>
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<tr>
<td><strong>No emesis</strong></td>
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<td></td>
</tr>
<tr>
<td>Acute</td>
<td>85.2</td>
<td>87.5</td>
<td>90.6/95.4/96.1/97.0</td>
<td>93.2/92.7/93.3/95.1</td>
</tr>
<tr>
<td>Delayed</td>
<td>79.4</td>
<td>76.2</td>
<td>85.1/87.5/90.0/91.8</td>
<td>81.6/86.5/84.4/86.4</td>
</tr>
<tr>
<td>Overall</td>
<td>75.0</td>
<td>74.0</td>
<td>84.1/86.8/89.6/91.8</td>
<td>80.6/86.5/83.3/86.4</td>
</tr>
<tr>
<td><strong>No significant nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>89.8</td>
<td>87.3</td>
<td>90.6/95.4/96.1/97.0</td>
<td>93.2/92.7/93.3/95.1</td>
</tr>
<tr>
<td>Delayed</td>
<td>78.2</td>
<td>72.8</td>
<td>85.1/87.5/90.0/91.8</td>
<td>81.6/86.5/84.4/86.4</td>
</tr>
<tr>
<td>Overall</td>
<td>75.7</td>
<td>70.4</td>
<td>84.1/86.8/89.6/91.8</td>
<td>80.6/86.5/83.3/86.4</td>
</tr>
<tr>
<td><strong>No rescue medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>98.8</td>
<td>98.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delayed</td>
<td>97.6\textsuperscript{a}</td>
<td>94.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>96.6\textsuperscript{a}</td>
<td>93.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>No impact on daily life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nausea domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>81.8</td>
<td>80.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delayed</td>
<td>71.1\textsuperscript{h}</td>
<td>65.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Vomiting domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>87.9</td>
<td>86.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delayed</td>
<td>81.3</td>
<td>77.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Combined domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>86.2</td>
<td>83.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delayed</td>
<td>76.0</td>
<td>70.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Safety outcomes, type of AE, %</strong></td>
<td>n = 413</td>
<td>n = 416</td>
<td>n = 308\textsuperscript{i}</td>
<td>n = 104\textsuperscript{j}</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>58.1</td>
<td>57.5</td>
<td>64.6</td>
<td>61.5</td>
</tr>
<tr>
<td>Serious AE</td>
<td>4.8</td>
<td>4.6</td>
<td>5.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Any TRAE\textsuperscript{g}</td>
<td>18.4</td>
<td>14.4</td>
<td>5.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Serious TRAE\textsuperscript{g}</td>
<td>0.5</td>
<td>0.5</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Most common TRAE\textsuperscript{g} (≥2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8.0</td>
<td>6.3</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>Hiccups</td>
<td>2.7</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TRAE\textsuperscript{c} leading to discontinuation</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Total deaths</td>
<td>0</td>
<td>1.0\textsuperscript{b}</td>
<td>2.3</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Complete response defined as no emesis and no use of rescue medication.

\textsuperscript{b}No significant nausea defined as a score of <25 mm on a 100-mm visual analog scale, where 0 mm is ‘no nausea’ and 100 mm ‘nausea as bad as it could be.’

\textsuperscript{c}Impact on daily life was assessed using the Functional Living Index-Emesis questionnaire.

\textsuperscript{d}Considered by the investigator to be possibly, probably, or definitely related to study drug.

\textsuperscript{e}By Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 preferred term.

\textsuperscript{f}Noninferiority efficacy study [101].

\textsuperscript{g}p <0.05 versus APR + GRAN + DEX, based on the Cochran-Mantel-Haenszel test with gender as a stratifying variable.

\textsuperscript{h}Statistically significant difference versus APR + GRAN + DEX using a two-sided Cochran-Mantel-Haenszel test stratified by gender.

\textsuperscript{i}Events were considered unrelated to study drug.

\textsuperscript{j}Safety study [75].

\textsuperscript{k}Cycle 1 safety data.

AC: anthracycline plus cyclophosphamide; APR: aprepitant; AE: adverse event; DEX: dexamethasone; GRAN: granisetron; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; NEPA: fixed combination of netupitant 300 mg/palonosetron 0.50 mg; NK,RAs: neurokinin-1 receptor antagonist; PALO: palonosetron; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.

9.2. NK,RAs safety considerations

9.2.1. Safety of oral formulations

Clinical studies have shown that oral NK,RAs are generally well tolerated with few additional AEs, mostly mild, when compared to 5-HT\textsubscript{3}RA plus dexamethasone (Table 3 [74,99,100] and Table 4 [8,72,73,81,83,95,96]). The most frequent AEs associated with oral NK,RAs are fatigue, hiccups, headache, and constipation [8,72–75,81,86,87,95,96,105,106]. No significant effects on the QT interval were observed at supratherapeutic doses of NK,RAs [39,41,42,44,107]. Although patients were randomized 3:1 to the NEPA versus aprepitant-palonosetron arms in the phase 3 Gralla et al. 2014 study [74], the direct comparison between netupitant and aprepitant showed a similar safety profile between the two NK,RAs (Table 3) [74,99,100]. The safety results from the only phase 3 head-to-head study between two NK,RAs, NEPA versus aprepitant-granisetron, are also presented in Table 3 [74,99,100].

9.2.2. Safety of IV formulations

The safety profile of IV NK,RAs is summarized in Table 5 [42,75,86,89,90]. Fosaprepitant is generally well tolerated [86,88,89], and presents a safety profile similar to that of aprepitant [86]. However, in phase 3 randomized studies, the incidence of infusion site AEs was higher with fosaprepitant–5-HT\textsubscript{3}RA–dexamethasone compared with 5-HT\textsubscript{3}RA–dexamethasone (HEC: 24% versus 12%; moderate grade: 3.4% versus 1.8% [88];...
Table 4. Summary of oral NK1RA safety data during the first treatment cycle.

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Oral aprepitant</th>
<th>Oral NEPA</th>
<th>Oral rolapitant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy setting</td>
<td>Cisplatin-based HEC</td>
<td>Cisplatin-based HEC</td>
<td>AC-based HEC</td>
</tr>
<tr>
<td></td>
<td>APR + OND + DEX (n = 438)</td>
<td>NEPA + DEX (n = 725)</td>
<td>PALO + DEX (n = 725)</td>
</tr>
<tr>
<td>Type of AE, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>63.1</td>
<td>61.4</td>
<td>72.7</td>
</tr>
<tr>
<td>Serious AE</td>
<td>16.1</td>
<td>17.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>14.6</td>
<td>11.0</td>
<td>19.5</td>
</tr>
</tbody>
</table>

Most common TEAE/ TRAE

- Constipation
  - 8.0\(^a\) 12.1\(^d\) 12.4\(^d\) 12.3\(^d\) 12.3\(^g\) 18.0\(^g\) - - 2.1\(^i\) 2.1\(^i\) <1\(^k\) 1\(^k\) <1\(^k\) 0\(^k\) 3\(^k\) 3\(^k\)
  - Headache
    - 9.9\(^d\) 11.6\(^d\) - - - - 3.3\(^i\) 3.0\(^i\) 0\(^k\) <1\(^k\) 1\(^k\) <1\(^k\) 2\(^k\) 2\(^k\)
  - Hiccups
    - 13.8\(^d\) 6.8\(^d\) - - - 5.1\(^i\) 3.7\(^i\) - - 0\(^k\) 0\(^k\) <1\(^h\) 1\(^k\) - -
  - Diarrhea
    - 0.7\(^d\) 2.2\(^i\) - - - - - - - - -
  - Stable branch block
    - 2.2\(^d\) 0\(^d\) - - - - - - - - -
  - Diarrhea
    - 1.6\(^d\) 1.2\(^d\) - - - - - - - - -
  - Nausea
    - 1.0\(^d\) 8.9\(^d\) 12.6\(^d\) - - - - - - - - -
  - Anorexia
    - 15.2\(^d\) 14.4\(^d\) - - - - - - - - -
  - Vomiting
    - 17.2\(^d\) 9.5\(^d\) 18.4\(^d\) 14.0\(^d\) - - - - - - - - -

Includes patients who experienced nausea after day 5.

\(^a\)Includes patients who experienced vomiting after day 5.

\(^k\)Includes patients who experienced nausea after day 5. Only the results of the NEPA\(_{300} +\) DEX arm are shown (commercially approved dose).
### Table 5: Summary of intravenous NK1RA safety data during the first treatment cycle.

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Fosaprepitant</th>
<th>IV NEPA</th>
<th>IV rolapitant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients in IV formulation</td>
<td>Edetate disodium, polysorbate 80, lactose anhydrous, sodium hydroxide, and/or hydrochloric acid</td>
<td>Edetate disodium, mannitol, sodium hydroxide, and/or hydrochloric acid</td>
<td>Dibasic sodium phosphate, anhydrous, medium chain triglycerides, polyoxyl 15 hydroxy stearate, sodium chloride, soybean oil, water for injection and may contain hydrochloric acid and/or sodium hydroxide</td>
</tr>
<tr>
<td>chemotherapy setting</td>
<td>Cisplatin-based HEC [86]</td>
<td>MEC (non-AC) [89]</td>
<td>None⁸</td>
</tr>
<tr>
<td>Type of AE and % of patients</td>
<td>FOS + OND + DEX (n = 1,143)</td>
<td>APR + OND + DEX (n = 1,169)</td>
<td>IV APR (n = 196)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>NR</td>
<td>NR</td>
<td>61.9</td>
</tr>
<tr>
<td>Serious AE</td>
<td>NR</td>
<td>NR</td>
<td>7.7</td>
</tr>
<tr>
<td>Serious TRAE⁸</td>
<td>NR</td>
<td>NR</td>
<td>8.3</td>
</tr>
<tr>
<td>Any infusion site TEAE</td>
<td>2.2</td>
<td>0.4</td>
<td>NR</td>
</tr>
<tr>
<td>Most common TEAE (≥5%)</td>
<td>Constipation</td>
<td>10.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiccups</td>
<td>5.6</td>
<td>6.3</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>-</td>
<td>-</td>
<td>8.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.6</td>
<td>11.6</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>5.9</td>
<td>6.9</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.6</td>
<td>5.6</td>
<td>-</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6.6</td>
<td>9.1</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.8</td>
<td>8.7</td>
<td>12.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alopecia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Somnolence</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased AST</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infusion site TEAEs</td>
<td>Infusion site pain</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Erythema</td>
<td>0.5</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Induration</td>
<td>0.2</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>site pain</td>
<td>0.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Vessel puncture</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>0</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>0</td>
<td>0.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

(Continued)
Table 5. (Continued).

<table>
<thead>
<tr>
<th>Excipients in IV formulation</th>
<th>Study drug</th>
<th>Fosaprepitant</th>
<th>IV aprepitant</th>
<th>IV NEPA</th>
<th>IV rolepitant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg lecithin, ethanol, sodium oleate, soybean oil</td>
<td>MEC (non-AC)</td>
<td>None (^a)</td>
<td>None (^b)</td>
<td>None/Healthy subjects (^d)</td>
<td>None/Healthy subjects (^d)</td>
</tr>
<tr>
<td>Dibasic sodium phosphate, anhydrous, medium chain triglycerides, polyoxyl 15 hydroxyethyl ester, soy oil, water for injection and may contain hydrochloric acid and/or sodium hydroxide</td>
<td>Cisplatin-based HEC (^{[86]})</td>
<td>Healthy subjects (^9)</td>
<td>HEC regimen (^{[75]})</td>
<td>Postmarketing experience (^{[42]})</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of AE and % of patients</th>
<th>Swelling</th>
<th>Injection site extravasation</th>
<th>Infusion site extravasation</th>
<th>Injection site reaction</th>
<th>Phlebitis superficial</th>
<th>Thrombophlebitis superficial</th>
<th>TEAE/TRAER leading to</th>
<th>Total deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyos + OND + DEX (^{[1,143]})</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>APR + OND + DEX (^{[1,169]})</td>
<td>1.6</td>
<td>0.4</td>
<td>0.4</td>
<td>1</td>
<td>2</td>
<td>0.5 (^e)</td>
<td>3.0 (^f)</td>
<td>0.0 (^f)</td>
</tr>
</tbody>
</table>

\(^a\)For NEPA studies, by Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 preferred term.
\(^b\)Includes patients who experienced nausea after day 5.
\(^c\)Includes patients who experienced vomiting after day 5.
\(^d\)Percentage of patients who experienced TRAEs leading to treatment discontinuation were reported.
\(^e\)Includes patients who experienced severe systemic reactions reported occurring within minutes of infusion, including hypersensitivity reactions including anaphylaxis, anaphylactoid reactions, and anaphylactic shock, abdominal pain, erythema, feeling hot, and generalized flushing and dizziness.
\(^f\)Includes infusion site reactions reported in healthy volunteers included warmth, dizziness, abdominal pain, and paresthesia.
In a phase 1 pharmacokinetic study of cancer patients at therapeutic doses in healthy volunteers, infusion site AEs were reported in the IV rolapitant group (13% versus 6%), with 2.8% of patients in the IV rolapitant group reporting AEs. Similar in both groups, and all events were mild or moderate intensity. Bioequivalence between IV rolapitant 166.5 mg (n = 71) and infusion, may occur. This formulation, hypersensitivity reactions, including anaphylaxis and anaphylactic shock, have been associated with fospirapitant, and strict monitoring of patients during and after infusion is advised.

The increased incidence of infusion site AEs could be attributed to the presence of polysorbate 80, a synthetic non-ionic surfactant present in the IV formulation. Moreover, several factors that increase the risk of infusion site AEs have been identified, including infusion in peripheral veins, coadministration of vesicant anthracycline-based regimens, number of doses of fospirapitant, and fospirapitant concentration. Serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, have been associated with fospirapitant, and strict monitoring of patients during and after infusion is advised.

The IV aprepitant emulsion formulation does not contain polysorbate 80 in its composition and has not been associated with toxicity in the infusion site. In multiple studies of healthy volunteers, IV aprepitant was shown to be better tolerated than fospirapitant, with fewer overall and treatment-related AEs. In a pooled analysis of two randomized, two-way crossover studies enrolling 200 healthy volunteers, AEs were reported in 17% of patients receiving IV aprepitant compared with 29% of those receiving fospirapitant, with the difference between the two formulations predominantly explained by higher rates of infusion site AEs (2% versus 10%, respectively), headache (3% versus 7%), and dyspnea, nausea, and abdominal pain (1% versus 3%, each) for fospirapitant. Another phase 1 study of 100 healthy volunteers reported that IV aprepitant administered as either a 2-min injection or a 30-min infusion was well tolerated, with a similar proportion of subjects experiencing AEs (14% versus 18%, respectively). The most common AEs in >2% of subjects were headache (4% versus 4%), fatigue (2% versus 6%), diaphoresis (4% versus 0), and dizziness (0 versus 4%) in the 2-min injection and 30-min infusion groups, respectively, and all events were mild. Despite the improved toxicity profile of this formulation, hypersensitivity reactions, including anaphylaxis associated with the administration of IV aprepitant emulsion, may occur.

In a phase 1 study of healthy volunteers that showed bioequivalence between IV rolapitant 166.5 mg (n = 71) and oral rolapitant 180 mg (n = 67), the incidence of AEs was similar in both groups, and all events were mild or moderate in intensity. However, slightly more rolapitant-related AEs were reported in the IV rolapitant group (13% versus 6%), with 2.8% of patients in the IV rolapitant group reporting infusion site AEs, compared with 0 in the oral rolapitant group. At therapeutic doses in healthy volunteers, infusion site AEs were reported in 2.6% of subjects, including sensation of warmth, abdominal pain, dizziness, and paresthesia. IV rolapitant safety was evaluated in two phase 1 studies of healthy volunteers receiving supratherapeutic single and multiple ascending doses of IV rolapitant. The most common IV rolapitant-related AEs were infusion site reactions in 16% of patients, including headache and dizziness. In 2018, the FDA issued a warning letter due to the association of rolapitant IV emulsion formulation with serious hypersensitivity reactions including anaphylaxis and anaphylactic shock. The letter advised physicians to determine if patients are hypersensitive to any component of the formulation, including soybean oil, and to legumes or other related allergens that may increase the risk for anaphylaxis before its administration. As a result, the distribution of IV rolapitant has been suspended.

IV NEPA showed a safety profile comparable with that of oral NEPA. Hypersensitivity reactions including anaphylaxis associated with palonosetron, one of the components of NEPA, have been reported. In a phase 3 safety study that included 404 cancer patients, IV NEPA was well tolerated, with a similar safety profile to oral NEPA in initial and subsequent cycles of HEC therapy. Notably, no infusion site AEs or anaphylactic reactions related to IV administration were reported. In a phase 1 pharmacokinetic study of cancer patients receiving HEC, no injection site reactions related to IV NEPA were observed. This finding translates to a very low risk for unexpected allergic reactions, which is explained by the lack of need for surfactants, emulsifiers, solubility enhancers, or allergens such as soybean and egg derivatives in the IV formulation. Fosnetupitant with a different excipient composition has been evaluated in a phase 2 trial in Japan, where a low rate of injection site reactions were reported, and it is currently being evaluated in a phase 3 study in Japanese cancer patients. To further facilitate the convenience of IV NEPA administration, a pre-mixed IV NEPA solution formulation, also lacking surfactants, emulsifiers, solubility enhancers, or allergens, is currently being developed.

10. Conclusion
Antiemetic therapy has advanced over the past 15 years with the advent of the NK₁RAs. The aim of this review was to examine clinical and pharmacologic data of currently available NK₁RAs. The shortcomings of this review include limited real-world experience, especially with the recently approved IV formulations of all NK₁RAs. In addition, many trials are ongoing or unpublished, specifically those of the newer IV formulations. Nevertheless, this review collects key data on each of the NK₁RAs and provides an overview of this antiemetic class.

It is crucial that physicians follow antiemetic guidelines in order to minimize the negative impact of CINV in cancer patients, especially those receiving HEC. All NK₁RAs are selective antagonists of human substance P/NK₁ receptors. Clinical trials have consistently demonstrated the benefits of adding an NK₁RA to standard therapy of a 5-HT₃RA plus dexamethasone for CINV prevention associated with cisplatin-based or AC HEC, as well as with carboplatin and other MEC regimens, including after multiple cycles of chemotherapy. However, the benefit of a rolapitant–5
HT3RA–dexamethasone regimen over 5-HT3RA–dexamethasone for the prevention of acute CINV in patients receiving HEC and MEC is not clear [95,96]. To date, the only head-to-head study of two NK,RABased oral regimens in patients receiving HEC supports the noninferiority, in terms of overall CR rates, of single-dose NEPA compared with aprepitant-granisetron, and with rates of no rescue medication in the delayed and overall phases significantly favoring NEPA [100] (Table 3) [74,99,100]. Evaluated as secondary endpoints, NEPA also showed numerically higher rates of no emesis, NSN, and no rescue medication in the delayed and overall phases, significantly lower rates of CINV and emesis on day 5, and most importantly, significantly higher rates of NSN on days 3, 4, and 5 after chemotherapy [100,101,118]. In the absence of conclusive efficacy studies evaluating no nausea as the primary endpoint, a benefit in nausea control from adding an NK,RAB to the antiemetic regimen was only shown in terms of significantly higher NSN rates, evaluated as a secondary endpoint, with oral NEPA over oral palonosetron in patients receiving cisplatin and AC-based chemotherapy [72,73]. No significant improvement in nausea control has been shown for aprepitant nor rolapitant beyond that achieved with 5-HT3RAs plus dexamethasone [80–82,85,95,96]. A phase 3 study will be conducted to verify the efficacy and safety of fosnetupitant 235 mg combined with palonosetron 0.75 mg and dexamethasone, over the standard therapy.

In summary, the prophylactic use of NK,RAB-based antiemetic treatments in patients with cancer who are undergoing chemotherapy has reduced CINV considerably over the last decade. Incorporating tools to predict the risk of CINV before each chemotherapy cycle in an individualized manner will allow the design of patient-specific antiemetic treatments. Availability both of oral and IV formulations of NK,RAs should cover additional gaps to allow the correct administration of antiemetic treatments to all patients. Strategies that facilitate compliance with guideline recommendations from both the physician’s and patient’s perspective may be required to further improve CINV control.

11. Expert Opinion

Despite adherence to antiemetic guidelines having been shown to improve CINV control, physicians do not always follow the most recent antiemetic guidelines [29]. Recently, a prediction tool to determine the risk of CINV before each chemotherapy cycle was developed, which showed that the use of nonprescribed antiemetics at home was among the most relevant patient-related risk factors of CINV [30]. A survey among European oncologists reported that approximately one-third of patients make mistakes or miss doses during home administration of antiemetics [31]. Strategies that simplify antiemetic regimens and facilitate administration of antiemetics may improve compliance with international guidelines and treatment outcomes.

Several strategies may have utility. First, a reduction in the number of doses of antiemetics, especially in the outpatient setting, may be helpful. NEPA, a fixed-combination agent, includes both the NK,RAB and 5-HT3RA in a single dose, while aprepitant and rolapitant are coadministered with a 5-HT3RA. Second, administration of antiemetics closer to the time of chemotherapy initiation may improve the quality of life of cancer patients, reduce resource utilization, and facilitate compliance with antiemetic regimens on the day of chemotherapy. The administration timing of oral NK,RAs is 1 h before the start of chemotherapy for aprepitant and NEPA, and 1 to 2 h for rolapitant [39,42,44]. For NEPA, in a recent study based on a pharmacokinetic/pharmacodynamic model, PET and clinical data suggest that NEPA could be administered closer to the time of chemotherapy initiation [119,120]. The administration timing of oral 5-HT3RAs before chemotherapy, although not a consideration for NEPA, is 30 min for granisetron, from 30 to 60 min for ondansetron, and 60 min for palonosetron [72,83,95]. Oral dexamethasone is administered 30 min before chemotherapy [72,83,95]. Finally, oral NK,RAs are administered simply and conveniently, especially during home administration in the delayed period after chemotherapy. The availability of NEPA as a convenient single dose for oral administration per chemotherapy cycle, and with the assurance of correct administration of both active antiemetic agents under medical supervision, is valuable, especially in patients for whom compliance is an issue.

The availability of different formulations of antiemetics may have benefits, especially for many cancer patients with swallowing difficulties, for whom an IV formulation might be required to ensure compliance. In addition to the approved oral formulations of aprepitant, NEPA, and rolapitant, and the IV formulation of aprepitant (fosaprepitant), new IV formulations for aprepitant (emulsion), NEPA, and rolapitant (emulsion) have recently been approved by the FDA [40,42,44]. The IV formulations of all three NK,RAs show equivalent efficacy compared with their respective oral formulations. Safety profiles similar to the oral formulations have been described for IV NEPA and IV aprepitant emulsion, although no clinical data from cancer patients are available for aprepitant emulsion; as for oral aprepitant, hypersensitivity reactions associated with IV aprepitant emulsion may occur. In contrast, increased injection site toxicity and hypersensitivity reactions have been reported with fosaprepitant and IV rolapitant.

While new antiemetic compounds and alternative formulations have become available in recent years, further developments will focus on the optimized use of these new resources to design simple and convenient regimens that ensure guideline adherence and patient compliance. As patient-specific risk factors are better defined, individualized regimens for control of emesis and nausea, with the best-possible quality of life for patients will become the rule in antiemetic prophylaxis.

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