



# Prevention of chemotherapy induced nausea and vomiting in adults: netupitant/palonosetron

Evidence summary

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[www.nice.org.uk/guidance/esnm69](http://www.nice.org.uk/guidance/esnm69)

## Key points from the evidence

The content of this evidence summary was up-to-date in March 2016. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Netupitant/palonosetron shows statistically significant benefits compared with palonosetron alone (both in combination with dexamethasone) in people receiving emetogenic chemotherapy, mainly in the prevention of delayed nausea and vomiting. There are limited data comparing netupitant/palonosetron with other neurokinin-1 receptor antagonists (such as, aprepitant) and 5-HT<sub>3</sub> receptor antagonists (such as ondansetron or granisetron) given in combination. Netupitant/palonosetron capsules are given as a single dose prior to each chemotherapy cycle.

**Regulatory status:** Netupitant/palonosetron capsules ([Akynzeo](#)) received a UK marketing authorisation in May 2015 and were launched in the UK in September 2015.

Effectiveness	Safety
<ul style="list-style-type: none"><li>• During the delayed phase of the first cycle of an anthracycline plus cyclophosphamide chemotherapy regimen, statistically significantly more participants taking netupitant/palonosetron 300 mg/500 microgram had a complete response (no emesis and no rescue medication) and no significant nausea compared with palonosetron 500 microgram (complete response: 76.9% compared with 69.5%; and no significant nausea: 76.9% compared with 71.3% respectively) [1 RCT; n=1455].</li><li>• During the overall phase of the first cycle of a cisplatin-based chemotherapy regimen, statistically significantly more participants taking netupitant/palonosetron 300 mg/500 microgram had a complete response (no emesis and no rescue medication) compared with palonosetron 500 microgram (89.6% compared with 76.5%) [1 RCT; dose ranging study n=694 in total; n=135 and n=136 for the netupitant/palonosetron 300 mg/500 microgram and palonosetron groups respectively].</li></ul>	<ul style="list-style-type: none"><li>• The European public assessment report (<a href="#">EPAR</a>) concluded that netupitant/palonosetron was well tolerated with many adverse reactions likely to be associated with either the underlying condition or associated cytotoxic treatments.</li><li>• Netupitant/palonosetron is contraindicated in pregnancy. Severe constipation and complications due to constipation may also occur (summary of product characteristics [<a href="#">SPC</a>]). In-line with the other 5-HT<sub>3</sub> receptor antagonists the SPC also includes warnings and precautions on the risk of serotonin syndrome and QT prolongation.</li><li>• The <a href="#">SPC</a> lists headache, constipation and fatigue as common adverse reactions (occurring in 1 in 100 or more to less than 1 in 10 people).</li></ul>

Patient factors	Resource implications
<ul style="list-style-type: none"><li>Netupitant/palonosetron capsules are given as a single dose prior to each chemotherapy cycle. This may simplify the treatment regimen and be preferable for some people.</li></ul>	<ul style="list-style-type: none"><li>Netupitant/palonosetron costs £69.00 for each chemotherapy cycle.</li><li>Costs for other 5-HT<sub>3</sub> receptor antagonist and neurokinin-1 receptor antagonist treatment regimens range from approximately £48 to £103 for each chemotherapy cycle.</li></ul>

## Introduction and current guidance

Chemotherapy regimens vary in the extent to which they cause nausea and vomiting, usually classed as having a minimal, low, moderate or high degree of emetogenicity. People can also vary in their susceptibility to drug-induced nausea and vomiting; those affected more often include women, people under 50 years of age, people with anxiety and those who have motion sickness. Guidelines including the Multinational Association for Supportive Care in Cancer ([MASCC](#)) and the European Society of Medical Oncology ([ESMO](#)) [antiemetic guidelines](#) recommend regimens including both a 5-HT<sub>3</sub> receptor antagonist and a neurokinin-1 receptor antagonist for the prevention of nausea and vomiting in people receiving highly emetogenic or anthracycline plus cyclophosphamide based chemotherapy regimens.

Full text of [introduction and current guidance](#).

## Product overview

Akynzeo capsules contain 300 mg netupitant (a neurokinin-1 receptor antagonist) and 500 micrograms palonosetron (a 5-HT<sub>3</sub> receptor antagonist). Netupitant/palonosetron ([Akynzeo](#)) is licensed in adults for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy or moderately emetogenic cancer chemotherapy. The dose recommended in the SPC is one netupitant/palonosetron 300 mg/500 microgram capsule to be taken approximately 1 hour before the start of each chemotherapy cycle.

Full text of [product overview](#).

## Evidence review

This evidence summary discusses the best available evidence on the safety and efficacy of netupitant/palonosetron. This is a phase 3 [RCT](#) comparing netupitant/palonosetron with palonosetron in 1455 adults (the majority were women with breast cancer) having anthracycline plus cyclophosphamide based chemotherapy ([Aapro et al. 2014](#)) and a phase 3 RCT that assessed the safety of netupitant/palonosetron in 308 people having moderately or highly emetogenic chemotherapy ([Gralla et al. 2014](#)). The study programme also included a phase 2 dose-ranging study comparing 3 different doses of netupitant/palonosetron with palonosetron in people having highly emetogenic cisplatin-based chemotherapy ([Hesketh et al. 2014](#)).

- In Aapro et al. (2014), participants were randomised to receive either netupitant/palonosetron 300 mg/500 microgram or palonosetron 500 microgram (both given in combination with dexamethasone) given on the day of the first cycle of chemotherapy. The primary outcome was complete response (defined as no emesis and no rescue medication) during the delayed phase of cycle 1 (25 to 120 hours after chemotherapy). Statistically significantly more participants in the netupitant/palonosetron group achieved this outcome compared with the palonosetron group (76.9% [557/724] compared with 69.5% [504/725]; odds ratio [OR] 1.48, 95% [confidence interval](#) [CI] 1.16 to 1.87,  $p=0.001$ ). Statistically significantly more participants in the netupitant/palonosetron group also had a complete response during the acute phase of cycle 1 (0 to 24 hours after chemotherapy) compared with the palonosetron group, although the difference was small (88.4% [640/724] compared with 85.0% [616/725]; OR 1.37, 95% CI 1.00 to 1.84,  $p=0.047$ ). More participants in the netupitant/palonosetron group had no significant nausea (defined as a score of less than 25 mm on a visual analogue scale from 0 mm [no nausea] to 100 mm ['nausea as bad as it could be']) during the delayed phase of cycle 1 compared with the palonosetron group (76.9% compared with 71.3%,  $p=0.014$ ). However for the acute phase there was no statistically significant difference between the 2 groups for this outcome (87.3% compared with 87.9%,  $p=0.74$ ).
- In Hesketh et al. (2014), statistically significantly more people achieved the primary outcome of complete response during the overall phase (0 to 120 hours after chemotherapy) of cycle 1 with netupitant/palonosetron 300 mg/500 microgram compared with palonosetron 500 microgram (89.6% [121/135] compared with 76.5%

[104/136]; p=0.004).

- In both Aapro et al. (2014) and Hesketh et al. (2014) netupitant/palonosetron was compared with palonosetron. There are no data from a published RCT with a predefined analysis comparing netupitant/palonosetron with other 5-HT<sub>3</sub> receptor antagonists and neurokinin-1 receptor antagonists given in combination.
- The [EPAR](#) for netupitant/palonosetron capsules states that a total of 1538 people received netupitant/palonosetron at the licensed dose during the clinical study programme, with 1169 people with cancer having at least 1 dose while participating in a phase 2 or 3 study and 317 people having 6 or more cycles of treatment. Overall, the EPAR concluded that netupitant/palonosetron was well tolerated with many adverse reactions likely to be associated with either the underlying condition or associated cytotoxic treatments. Similarly serious adverse events and deaths reflect the patient population and current treatment. In Aapro et al. (2014) and Gralla et al. (2014) the most common treatment-related adverse events were constipation, dyspepsia, eructation and headache.
- As stated in the EPAR cases of severe constipation and complications due to constipation were seen during the clinical trial programme and information on this has been included in the SPC. In-line with the other 5-HT<sub>3</sub> receptor antagonists the SPC also includes warnings and precautions on the risk of serotonin syndrome and QT prolongation. Netupitant/palonosetron is contraindicated in pregnancy (animal studies of netupitant have shown reproductive and teratogenic toxicity). Netupitant is a moderate inhibitor of CYP3A4, therefore the SPC includes information on potential interactions. See the [SPC](#) for further information on contraindications, warnings and precautions, potential interactions and adverse effects of netupitant/palonosetron.

Full text of [evidence review](#).

## Context

Netupitant/palonosetron capsules ([Akynzeo](#)) are the first combination preparation to contain both a 5-HT<sub>3</sub> receptor antagonist and a neurokinin-1 receptor antagonist. Palonosetron is already available in oral and injectable formulations. Two other 5-HT<sub>3</sub> receptor antagonists are also available in the UK: ondansetron (available in oral, injectable and rectal formulations) and granisetron (available in oral, injectable and transdermal formulations). Two neurokinin-1 receptor antagonists are available in the UK: aprepitant capsules and intravenous fosaprepitant (a pro-drug of aprepitant) [see [summaries of](#)

[product characteristics](#)].

Full text of [context](#).

## Estimated impact for the NHS

Guidelines such as the [MASCC/ESMO antiemetic guidelines](#) (2010) recommend regimens including both a 5-HT<sub>3</sub> receptor antagonist and a neurokinin-1 receptor antagonist for the prevention of nausea and vomiting in people receiving highly emetogenic or anthracycline plus cyclophosphamide based chemotherapy regimens. Netupitant/palonosetron capsules are given as a single dose prior to each chemotherapy cycle, which may simplify the treatment regimen and be preferable to some people.

Netupitant/palonosetron costs £69.00 for each chemotherapy cycle. Costs for other 5-HT<sub>3</sub> receptor antagonist and neurokinin-1 receptor antagonist treatment regimens range from approximately £48 to £103 for each chemotherapy cycle. Example costs provided here do not include the cost of dexamethasone.

Full text of [estimated impact for the NHS](#).

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Full evidence summary

### Introduction and current guidance

Nausea and vomiting are distressing side effects of chemotherapy. Chemotherapy regimens vary in the extent to which they cause nausea and vomiting (usually classed as having a minimal, low, moderate or high degree of emetogenicity). For example, the Multinational Association for Supportive Care in Cancer ([MASCC](#)) and the European

Society of Medical Oncology ([ESMO](#)) [antiemetic guidelines](#) classify the following (if given intravenously) as moderately emetogenic: cyclophosphamide (at doses of less than 1500 mg/m<sup>2</sup>), doxorubicin, epirubicin, carboplatin and as highly emetogenic: cisplatin and cyclophosphamide (at doses of 1500 mg/m<sup>2</sup> or more).

Nausea and vomiting symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment) or anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management. People can vary in their susceptibility to drug-induced nausea and vomiting; those affected more often include women, people under 50 years of age, people with anxiety and those who have motion sickness. Susceptibility also increases with repeated exposure to the cytotoxic drug (British National Formulary [[BNF](#)]).

Netupitant/palonosetron capsules ([Akynzeo](#)) are the first combination preparation to contain both a 5-HT<sub>3</sub> receptor antagonist (palonosetron) and a selective antagonist of human substance P/neurokinin-1 receptors (netupitant). Palonosetron is already available as a single-component preparation (available in oral and injectable formulations). Two other single-component 5-HT<sub>3</sub> receptor antagonists are also available in the UK: ondansetron (available in oral, injectable and rectal formulations) and granisetron (available in oral, injectable and transdermal formulations). Two single-component neurokinin-1 receptor antagonists are available in the UK: aprepitant capsules and intravenous fosaprepitant (a pro-drug of aprepitant) [see [summaries of product characteristics](#)].

Local chemotherapy anti-emetic treatment protocols can vary, but are often based on MASCC/ESMO antiemetic guidelines, the American Society of Clinical Oncology ([ASCO](#)) antiemetic guidelines and the National Comprehensive Cancer Network ([NCCN](#)) antiemetic guidelines. For an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide based regimen or highly emetogenic chemotherapy, the MASCC/ESMO antiemetic guidelines (2010) recommend a combination of a 5-HT<sub>3</sub> receptor antagonist and aprepitant on the day of chemotherapy (day 1) followed by aprepitant post chemotherapy on days 2 and 3 (with dexamethasone on either days 1 to 4 for highly emetogenic chemotherapy or day 1 only for anthracycline plus cyclophosphamide based chemotherapy). Intravenous fosaprepitant could be given as an alternative to aprepitant; however this would be given on day 1 only rather than days 1 to 3. For non-anthracycline plus cyclophosphamide moderately emetogenic chemotherapy these guidelines recommend palonosetron on the day of chemotherapy (with dexamethasone on days 1 to 3). [ASCO antiemetic guidelines](#)

recommend similar regimens. The [NCCN antiemesis guideline](#) (2015) recommendations include regimens which include both a 5-HT<sub>3</sub> receptor antagonist and a neurokinin 1 receptor antagonist. Both of these guidelines classify anthracycline plus cyclophosphamide based chemotherapy as highly emetogenic. Recent updates of the ASCO and NCCN guidelines both include netupitant/palonosetron as an option for highly emetogenic chemotherapy. The NCCN antiemetic guidelines also include netupitant/palonosetron as an option for moderately emetogenic chemotherapy.

## Product overview

### Drug action

Akynzeo capsules contain 300 mg netupitant and 500 micrograms palonosetron. Netupitant is a selective antagonist of human substance P/neurokinin 1 receptors and palonosetron is a 5-HT<sub>3</sub> receptor antagonist (summary of product characteristics [SPC]: [Akynzeo](#)).

### Licensed therapeutic indication

Netupitant/palonosetron ([Akynzeo](#)) is licensed in adults for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy or moderately emetogenic cancer chemotherapy.

### Course and cost

The dose of netupitant/palonosetron ([Akynzeo](#)) is one 300 mg/500 microgram capsule to be taken approximately 1 hour before the start of each chemotherapy cycle. The SPC recommends that the dose of oral dexamethasone should be reduced by approximately 50% when it is given in combination with netupitant/palonosetron. This is based on a dexamethasone regimen of 20 mg on day 1, followed by 8 mg twice daily from day 2 to 4. The studies discussed in this evidence summary used a dexamethasone regimen of 12 mg on day 1 plus 8 mg a day on days 2 to 4 for participants allocated to netupitant/palonosetron given highly emetogenic chemotherapy. The dose of dexamethasone for participants allocated to netupitant/palonosetron given anthracycline plus cyclophosphamide based or moderately emetogenic chemotherapy was 12 mg on day 1.

The cost of 1 netupitant/palonosetron 300 mg/500 microgram capsule is £69.00 ([MIMS](#):

January 2016).

## Evidence review

This evidence summary discusses the best available evidence on the safety and efficacy of netupitant/palonosetron. This is a phase 3 randomised controlled trial (RCT) comparing netupitant/palonosetron with palonosetron in people having anthracycline plus cyclophosphamide based chemotherapy (Aapro et al. 2014) and a phase 3 RCT which assessed the safety of netupitant/palonosetron in people having moderately or highly emetogenic chemotherapy (Gralla et al. 2014). A phase 2 dose-ranging study which compared 3 different doses of netupitant/palonosetron with palonosetron in people having highly emetogenic cisplatin-based chemotherapy is also briefly discussed (Hesketh et al. 2014). Information from these RCTs has been supplemented and clarified using the European public assessment report (EPAR) for netupitant/palonosetron capsules.

### Aapro et al. 2014

- Design: double-blind, double-dummy, randomised controlled trial (RCT). Conducted at 177 sites in 15 countries (Argentina, Belarus, Brazil, Bulgaria, Croatia, Germany, Hungary, India, Italy, Mexico, Poland, Romania, Russia, Ukraine and the United States). Allocation was concealed.
- Population: 1455 adults (median age 54 years; 98% women) who had not previously received chemotherapy and were due to receive their first course of an anthracycline plus cyclophosphamide chemotherapy regimen for a solid malignant tumour. The majority of the population (97.5%) had breast cancer. The chemotherapy regimen consisted of cyclophosphamide (500 mg/m<sup>2</sup> to 1500 mg/m<sup>2</sup>) and either doxorubicin or epirubicin (all given via the intravenous route). Participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. Participants who were scheduled to receive highly emetogenic chemotherapy from day 1 to 5 or additional moderately emetogenic chemotherapy from day 2 to 5 were not eligible for inclusion. Other exclusion criteria included participants due to receive radiotherapy to the abdomen or pelvis or participants scheduled to have a bone marrow or stem-cell transplant. Participants with any serious cardiovascular disease history were also excluded. Netupitant is a moderate inhibitor of CYP3A4 and participants taking certain medications were also excluded.
- Interventions and comparisons: participants were randomised to receive either

netupitant/palonosetron 300 mg/500 microgram plus 12 mg dexamethasone or palonosetron 500 microgram plus 20 mg dexamethasone on day 1 of chemotherapy; all given via the oral route of administration. Netupitant/palonosetron and palonosetron were given 60 minutes before chemotherapy and dexamethasone was given 30 minutes before chemotherapy. Use of rescue medication (excluding other 5-HT<sub>3</sub> or neurokinin-1 receptor antagonists) was allowed but was considered as treatment failure. After the first cycle of chemotherapy participants had the option of continuing in a multiple-cycle extension phase, receiving the same treatment as they were assigned in cycle 1 (results from the multiple-cycle extension phase were not presented in Apro et al. [2014]).

- **Outcomes:** the primary outcome was complete response (defined as no emesis and no rescue medication) during the delayed phase of cycle 1 (25 to 120 hours after chemotherapy). An emetic episode was defined as 1 or more continuous vomits or retches. Key secondary outcomes were complete response during the acute (0 to 24 hours after chemotherapy) and overall (0 to 120 hours after chemotherapy) phases of cycle 1. Additional secondary outcomes included complete protection (complete response and no significant nausea) and no significant nausea during the acute, delayed and overall phases of cycle 1. Severity of nausea was evaluated on a daily basis using a visual analogue scale (VAS) from 0 mm (no nausea) to 100 mm ('nausea as bad as it could be'). No significant nausea was defined as a VAS score of less than 25 mm. The functional living index emesis (FLIE) questionnaire was used to assess the impact of nausea and vomiting on participants' daily lives. The questionnaire consists of 9 nausea-specific and 9 vomiting-specific items. No impact on daily life was classed as a total FLIE score of greater than 108.

**Table 1 Summary of Apro et al. 2014**

	<b>Netupitant/ palonosetron</b>	<b>Palonosetron</b>	<b>Analysis</b>
Randomised	n=726	n=729	
<b>Efficacy<sup>a</sup></b>	n=724	n=725	
Primary outcome: complete response during delayed phase of cycle 1 <sup>b</sup>	76.9% (557/724)	69.5% (504/725)	OR 1.48 (95% CI 1.16 to 1.87, <u>p</u> =0.001) <sup>c</sup>
Selected secondary outcomes:			

Complete response during the acute phase of cycle 1 <sup>b</sup>	88.4% (640/724)	85.0% (616/725)	OR 1.37 (95% CI 1.00 to 1.87, p=0.047) <sup>c</sup>
Complete response during the overall phase of cycle 1 <sup>b</sup>	74.3% (538/724)	66.6% (483/725)	OR 1.47 (95% CI 1.17 to 1.85, p=0.001) <sup>c</sup>
No significant nausea during delayed phase of cycle 1 <sup>d</sup>	76.9%	71.3%	p=0.014
Complete protection during delayed phase of cycle 1 <sup>e</sup>	67.3%	60.3%	p=0.005
No significant nausea during acute phase of cycle 1 <sup>d</sup>	87.3%	87.9%	No statistically significant difference, p=0.747
Complete protection during acute phase of cycle 1 <sup>e</sup>	82.3%	81.1%	No statistically significant difference, p=0.528
<b>Safety<sup>f</sup></b>	n=725	n=725	
Patients reporting serious treatment-emergent adverse events	1.8% (13/725)	1.7% (12/725)	No statistical analysis presented
Treatment-related <sup>g</sup> adverse events leading to discontinuation	0	0.3% (2/725)	No statistical analysis presented
Treatment-related headache	3.3% (24/725)	3.0% (22/725)	No statistical analysis presented
Treatment-related constipation	2.1% (15/725)	2.1% (15/725)	No statistical analysis presented

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup> Efficacy population: all participants who were randomised and received protocol-required anthracycline plus cyclophosphamide based chemotherapy and study treatment.

<sup>b</sup> Complete response defined as no emesis and no rescue medication. The delayed phase was 25 to 120 hours after chemotherapy, the acute phase was 0 to 24 hours after chemotherapy and the overall phase was 0 to 120 hours after chemotherapy.

<sup>c</sup> ORs taken from the European public assessment report (EPAR) for netupitant/  
palonosetron.

<sup>d</sup> No significant nausea defined as a visual analogue scale score of less than 25 mm on a scale from 0 mm (no nausea) to 100 mm ('nausea as bad as it could be').

<sup>e</sup> Complete protection defined as complete response and no significant nausea.

<sup>f</sup> Safety population: all participants who received study treatment and had at least 1 safety assessment.

<sup>g</sup> Treatment related adverse events: those considered by the investigator to be possibly, probably or definitely related to the study drug.

## Gralla et al. 2014

- Design: double-blind, double-dummy RCT. Conducted at 59 sites in 10 countries (Bulgaria, Czech Republic, Germany, Hungary, India, Poland, Russia, Serbia, Ukraine and the United States). Allocation was concealed.
- Population: 413 adults (median age 58 years; 50% women) who had not previously received chemotherapy and were due to receive their first course of repeated consecutive courses of moderately or highly emetogenic chemotherapy. Approximately 24% of participants had highly emetogenic chemotherapy (the majority of whom had cisplatin) and approximately 76% had moderately emetogenic chemotherapy. Participants who were scheduled to receive moderately or highly emetogenic chemotherapy from day 2 to 5 were excluded from the study. The group had a variety of cancer types (including 37% with lung or respiratory cancer, 12% with ovarian cancer and 9% with colon cancer). Patients with breast cancer due to receive anthracycline plus cyclophosphamide chemotherapy were excluded from the study.
- Interventions and comparisons: participants were randomly allocated in a 3:1 ratio to receive netupitant/palonosetron 300 mg/500 microgram (taken on the day of chemotherapy [day 1]) or oral palonosetron 500 microgram and aprepitant 125 mg on

day 1 and aprepitant 80 mg on days 2 and 3. Open-label dexamethasone was also given as part of the antiemetic treatment with a dosage regimen dependent on whether the chemotherapy regimen was moderately or highly emetogenic (12 mg on day 1 for moderately and highly emetogenic chemotherapy plus 8 mg a day on days 2 to 4 for highly emetogenic chemotherapy). In the netupitant/palonosetron group 308 people had a total of 1446 cycles of moderately or highly emetogenic chemotherapy. In the palonosetron plus aprepitant group 104 participants were treated for a total of 515 cycles.

- Outcomes: this study assessed the safety of netupitant/palonosetron over multiple cycles. Safety was assessed primarily by treatment emergent adverse events (defined as those occurring after the first dose of study drug). Clinical laboratory evaluations, physical examinations, ECG recordings and vital signs were also assessed. No formal comparison between the 2 groups was conducted.

**Table 2 Summary of safety data from Gralla et al. 2014**

	Netupitant/ palonosetron	Aprepitant plus palonosetron	Analysis
Randomised	n=309	n=104	No statistical analysis presented for any of the safety outcomes
<b>Safety<sup>a</sup></b>	n=308	n=104	
Any treatment emergent <sup>b</sup> adverse event during cycle 1	64.6% (199/308)	61.5% (64/104)	
Treatment related <sup>c</sup> adverse event leading to discontinuation in cycle 1	0.3% (1/308)	0	
Any treatment emergent adverse event during multiple cycles	86.0% (265/308)	91.3% (95/104)	
Serious treatment emergent adverse event during multiple cycles	16.2% (50/308)	18.3% (19/104)	

Treatment related adverse event leading to discontinuation during multiple cycles	0.3% (1/308)	0
Total deaths during multiple cycles <sup>d</sup>	5.2% (16/308)	1.0% (1/104)
Treatment related constipation during multiple cycles	3.6% (11/308)	1.0% (1/104)
Treatment related dyspepsia during multiple cycles	0.3% (1/308)	1.0% (1/104)
Treatment related eructation during multiple cycles	0.3% (1/308)	1.0% (1/104)
Treatment related headache during multiple cycles	1.0% (3/308)	1.0% (1/104)

<sup>a</sup> The safety analysis population consisted of all participants who received study treatment and had at least 1 safety assessment after treatment administration. 308 participants were treated with netupitant/palonosetron for a total of 1446 cycles and 104 were treated with aprepitant plus palonosetron for a total of 515 cycles. In total, 98% of participants completed cycle 1, 75% completed at least 4 cycles and 40% completed 6 cycles.

<sup>b</sup> Treatment emergent adverse events were defined as those occurring after the first dose of study drug.

<sup>c</sup> Adverse events were considered to be treatment-related if the relationship to study drug was assessed as definite, probable, possible, unassessable or missing.

<sup>d</sup> The most common cause of death was disease progression. None of these deaths were attributed to the study drug by the study investigators.

## Clinical effectiveness

Netupitant/palonosetron has been compared with palonosetron in a phase 3 RCT in adults (the majority of whom were women with breast cancer) receiving cyclophosphamide with either doxorubicin or epirubicin (Aapro et al. 2014). Either netupitant/palonosetron or palonosetron, both in combination with dexamethasone, were given on the day of chemotherapy. Statistically significantly more participants in the netupitant/palonosetron

group achieved the primary outcome of complete response (defined as no emesis and no rescue medication) during the delayed phase of cycle 1 of chemotherapy (76.9% compared with 69.5%; OR 1.48, 95% CI 1.16 to 1.87,  $p=0.001$ ). The European public assessment report (EPAR) for netupitant/palonosetron capsules considered this difference in the percentage of participants with a complete response to be a clinically relevant difference. There were also statistically significantly more participants who had a complete response in the acute phase of cycle 1 in the netupitant/palonosetron group compared with the palonosetron group, although the difference was small (see table 1 for details). There were statistically significantly more participants in the netupitant/palonosetron group who had no significant nausea or complete protection during the delayed phase of cycle 1. However, there was no statistically significant difference between the 2 groups for these outcomes for the acute phase of cycle 1 (see table 1 for details). The FLIE questionnaire was used to assess the impact of nausea and vomiting on participants' daily lives. Statistically significantly more participants in the netupitant/palonosetron group had no impact on daily living (defined as an FLIE score greater than 108) during the overall phase of cycle 1 (78.5% compared with 72.1%,  $p=0.005$ ).

Participants in Apro et al. (2014) had the option of continuing in a multiple-cycle extension phase after the first cycle of chemotherapy, receiving the same treatment as they were assigned in cycle 1. This extension phase included 635 and 651 participants from the netupitant/palonosetron and palonosetron groups respectively; however results from this extension phase were not presented. The EPAR for netupitant/palonosetron capsules commented that during this extension phase the complete response rates were consistently higher with netupitant/palonosetron compared with palonosetron in each phase and each cycle up to cycle 6. Similarly the percentage of participants with no significant nausea was higher in the netupitant/palonosetron group than the palonosetron group in each phase and each cycle up to cycle 6. Further details are given in a review article by Hesketh et al. 2015.

Netupitant/palonosetron has also been compared with palonosetron (both in combination with dexamethasone) in a phase 2 dose-ranging study (Hesketh et al. 2014) in adults due to receive their first course of highly emetogenic cisplatin-based chemotherapy. Approximately 43% of the population were women and the median age was 55 years. The group had a variety of cancer types (including lung or respiratory cancer, head and neck cancer, ovarian cancer and other urogenital cancers). Netupitant/palonosetron at 3 different doses (100 mg/500 microgram, 200 mg/500 microgram and 300 mg/500 microgram) were compared with palonosetron 500 microgram. Netupitant/palonosetron at 1 of the 3 different doses or palonosetron was given on the day of

chemotherapy (day 1) and for all groups dexamethasone was given on days 1 to 4. For the licensed dose of netupitant/palonosetron 300 mg/500 microgram, statistically significantly more people achieved the primary outcome of complete response during the overall phase of cycle 1 compared with palonosetron (89.6% [121/135] compared with 76.5% [104/136];  $p=0.004$ ).

In both Aapro et al. (2014) and Hesketh et al. (2014) netupitant/palonosetron was compared with palonosetron. There are no data from a published RCT with a predefined analysis comparing netupitant/palonosetron with other 5-HT<sub>3</sub> receptor antagonists and neurokinin-1 receptor antagonists given in combination. Hesketh et al. (2014) included an exploratory arm where participants received oral aprepitant plus intravenous ondansetron on day 1 and then aprepitant on days 2 and 3. In this exploratory arm 86.6% (116/134) of participants achieved the primary outcome of complete response during the overall phase of cycle 1 (as stated above 89.6% achieved this outcome in the netupitant/palonosetron group in this study). However the study was not powered for or analysed for comparisons between this exploratory arm and netupitant/palonosetron (see evidence strengths and limitations).

## Safety and tolerability

In [Aapro et al. 2014](#) 76% (551/726) of participants in the netupitant/palonosetron group reported at least 1 treatment-emergent adverse event compared with 69.9% (507/725) in the palonosetron group (no statistical analysis provided). The frequency of serious adverse events was similar between the 2 groups (see table 1 for details). The most frequently reported treatment-related adverse events were headache and constipation and these occurred at a similar frequency in each group (no statistical analysis provided; see table 1 for details). Changes from baseline in 12-lead ECGs were reported to be similar between treatment groups at each time point.

The percentages of treatment emergent adverse events, serious treatment emergent adverse events and treatment related adverse events leading to discontinuation for netupitant/palonosetron and aprepitant plus palonosetron from [Gralla et al. 2014](#) are reported in table 2 (no statistical analysis was provided). There was no indication of increasing adverse events over multiple cycles. The percentage of participants with adverse events over multiple cycles considered by the investigators to be treatment related was 10.1% (31/308) in the netupitant/palonosetron group and 5.8% (6/104) in the aprepitant plus palonosetron group. The most common treatment-related adverse events were constipation, dyspepsia, eructation and headache. Constipation occurred more

frequently in the netupitant/palonosetron group, although no statistical analysis is provided (see table 2 for details). A similar percentage of participants in both groups had serious treatment emergent adverse events during multiple cycles (see table 2). The study investigators considered 2 of the serious adverse events that occurred in the netupitant/palonosetron group to be treatment related; acute psychosis in cycle 1 and ventricular systole in cycle 6. ECG changes from baseline, 5 and 24 hours after dose were reported to be similar between the groups, with any corrected QT interval prolongation being transient and returning to baseline measurements within 120 hours after dose across all cycles. The percentage of people who developed ECG abnormalities was reported to be comparable for the treatment groups throughout the study. The most frequently reported abnormalities were flat T waves (16.9% and 13.5% in the netupitant/palonosetron and aprepitant plus palonosetron groups respectively) and ST depression (11.7% and 16.3% respectively).

The [EPAR](#) for netupitant/palonosetron capsules states that across the study programme the frequencies of participants reporting treatment-emergent adverse events for cycle 1 were similar for netupitant/palonosetron (all doses combined), palonosetron and comparator groups (which included placebo), except for skin and subcutaneous tissue disorders and blood and lymphatic system disorders. Skin and subcutaneous tissue disorders were reported less frequently in the total comparator group (7.1%, 17/238) than in the total netupitant/palonosetron group (22.3%, 321/1442) and total palonosetron groups (17.9%, 286/1600). Blood and lymphatic system disorders were reported less frequently in the total comparator group (13.9%, 33/238) than in the total netupitant/palonosetron group (24.5%, 353/1442) and total palonosetron groups (20.6%, 330/1600).

The EPAR states that a total of 1538 people received netupitant/palonosetron at the licensed dose during the clinical study programme, with 1169 people with cancer having at least 1 dose while participating in a phase 2 or 3 study and 317 people having 6 or more cycles of treatment. Overall, the EPAR concluded that netupitant/palonosetron was well tolerated with many adverse reactions likely to be associated with either the underlying condition or associated cytotoxic treatments. Similarly serious adverse events and deaths reflect the patient population and current treatment.

As stated in the EPAR cases of severe constipation and complications due to constipation were seen during the clinical trial programme and information on this has been included in the SPC ([Akynzeo](#)). In-line with the other 5-HT<sub>3</sub> receptor antagonists the SPC also includes warnings and precautions on the risk of serotonin syndrome and QT prolongation. Netupitant/palonosetron is contraindicated in pregnancy (animal studies of netupitant

have shown reproductive and teratogenic toxicity). Netupitant is a moderate inhibitor of CYP3A4, therefore the SPC includes information on potential interactions. The SPC lists headache, constipation and fatigue as common adverse reactions (occurring in 1 in 100 or more to less than 1 in 10 people).

See the [SPC](#) for further information on contraindications, warnings and precautions, potential interactions and adverse effects of netupitant/palonosetron.

## Evidence strengths and limitations

There are no data from a published RCT with a predefined analysis comparing netupitant/palonosetron with a recommended antiemetic treatment regimen for anthracycline plus cyclophosphamide based or highly emetogenic chemotherapy. For example, the regimen recommended by the [MASCC/ESMO antiemetic guidelines](#) includes a combination of a 5-HT<sub>3</sub> receptor antagonist and aprepitant on the day of chemotherapy (day 1) followed by aprepitant post chemotherapy on days 2 and 3. In [Aapro et al. 2014](#) netupitant/palonosetron was compared with palonosetron. [Hesketh et al. 2014](#) included an exploratory arm where participants received aprepitant plus ondansetron on day 1 and then aprepitant on days 2 and 3. However, the study was not powered for or analysed for comparisons between this exploratory arm and netupitant/palonosetron. The safety study [Gralla et al. 2014](#) also had a control group who received palonosetron on day 1 and aprepitant on days 1 to 3 but no formal comparison between this group and the netupitant/palonosetron group was conducted.

The [EPAR](#) for netupitant/palonosetron capsules states that the patient population recruited to the clinical trials was appropriate and generally representative of those receiving such chemotherapy regimens. In [Aapro et al. \(2014\)](#) baseline characteristics such as age, ethnicity and chemotherapy regimen appeared balanced between the groups. [Gralla et al. \(2014\)](#) appeared to be balanced between the groups for gender and age and chemotherapy regimen (moderately or highly emetogenic). However, there were some differences between the groups for cancer type and extent of cancer (primary, metastatic or local recurrence).

The EPAR highlighted that in [Aapro et al. \(2014\)](#) an anthracycline plus cyclophosphamide regimen was chosen to support the moderately emetogenic chemotherapy indication. It further adds that individual patient risk factors (the majority of people in the study were women with breast cancer, median age 54 years) may have put this group at an increased risk of chemotherapy induced nausea vomiting over what anthracycline plus

cyclophosphamide chemotherapy alone would suggest. The EPAR states that anthracycline plus cyclophosphamide chemotherapy has been seen as the gold standard in previous trials of antiemetic treatment as being a worst-case representation of a moderately emetogenic chemotherapy regimen. In addition, [ASCO antiemetic guidelines](#) and the [NCCN antiemesis guideline](#) (2015) classify anthracycline plus cyclophosphamide based chemotherapy as highly emetogenic. Hesketh et al. (2014) was conducted in people receiving highly emetogenic cisplatin-based chemotherapy and Gralla et al. (2014) was conducted in people receiving moderately or highly emetogenic chemotherapy. However, Hesketh et al. (2014) was a phase 2 dose ranging study and Gralla et al. (2014) was a safety study where no formal comparisons were made between groups. Consequently, comparative RCT data for the licensed dose mainly comes from Aapro et al. (2014). There is limited comparative RCT data in people receiving other chemotherapy regimens or with other cancer types, or in alternative populations such as an older or male population. Data from Aapro et al. (2014) was only presented for the first cycle of chemotherapy although this study did have a multiple-cycle extension phase.

Aapro et al. (2014), Gralla et al. (2014) and Hesketh et al. (2014) all included participants scheduled to receive a single day of moderately or highly emetogenic chemotherapy treatment per cycle. People scheduled to receive multiple days of moderate or highly emetogenic chemotherapy were excluded from the studies. Consequently these studies provide no data on the use of netupitant/palonosetron to prevent nausea and vomiting in people receiving multiple day chemotherapy regimens.

## Context

### Alternative treatments

Netupitant/palonosetron capsules ([Akynzeo](#)) are the first combination preparation to contain both a 5-HT<sub>3</sub> receptor antagonist (palonosetron) and a neurokinin-1 receptor antagonist (netupitant). Palonosetron is already available as a single-component preparation (available in oral and injectable formulations). Two other single-component 5-HT<sub>3</sub> receptor antagonists are also available in the UK: ondansetron (available in oral, injectable and rectal formulations) and granisetron (available in oral, injectable and transdermal formulations). Two single-component neurokinin-1 receptor antagonists are available in the UK: aprepitant capsules and intravenous fosaprepitant (a pro-drug of aprepitant). Licensed dosage regimens vary between the individual products (see [summaries of product characteristics](#)).

For anthracycline plus cyclophosphamide based or highly emetogenic chemotherapy the [MASCC/ESMO antiemetic guidelines](#) (2010) recommend a combination of a 5-HT<sub>3</sub> receptor antagonist and aprepitant on the day of chemotherapy (day 1) followed by aprepitant post chemotherapy on days 2 and 3 (with dexamethasone on either days 1 to 4 for highly emetogenic chemotherapy or day 1 only for anthracycline plus cyclophosphamide based chemotherapy). However, local UK treatment protocols may vary. Example costs of alternative treatments based on the MASCC/ESMO antiemetic guidelines are given in the table below.

## Costs of alternative treatments

Drug	Example dosage <sup>a</sup>	Estimated cost for 1 cycle (excluding VAT) <sup>b</sup>
Netupitant/ palonosetron 300 mg/ 500 microgram capsules	One capsule 1 hour before the start of chemotherapy	£69.00 <sup>c</sup>
Granisetron tablets	2 mg 1 hour before the start of chemotherapy	£7.45 <sup>e</sup>
Intravenous granisetron	1 mg (as a slow intravenous injection or as an infusion) 5 minutes before the start of chemotherapy	£1.60 <sup>d</sup>
Ondansetron tablets	16 mg on day of chemotherapy	£0.56 <sup>e</sup>
Intravenous ondansetron	8 mg as a slow intravenous injection immediately before chemotherapy or as an intravenous infusion given over at least 15 minutes	£11.99 <sup>c</sup>
Palonosetron 500 microgram capsules	500 micrograms 1 hour before the start of chemotherapy	£55.89 <sup>c</sup>

Intravenous palonosetron	250 micrograms as an intravenous injection (injected over 30 seconds) 30 minutes before the start of chemotherapy	£55.89 <sup>c</sup>
Aprepitant capsules	125 mg 1 hour before the start of chemotherapy (day 1) and then 80 mg once a day on days 2 and 3	£47.42 <sup>c</sup>
Intravenous fosaprepitant <sup>f</sup>	150 mg as an intravenous infusion (over 20 to 30 minutes) approximately 30 minutes before chemotherapy	£47.42 <sup>c</sup>

<sup>a</sup> Doses shown are example doses based on guidelines and do not represent the full range that can be used and do not imply therapeutic equivalence. For prescribing information please refer to the relevant [summary of product characteristics](#).

<sup>b</sup> Costs do not include cost of dexamethasone

<sup>c</sup> Prices based on [MIMS](#) January 2016.

<sup>d</sup> Price based on [BNF](#) January 2016.

<sup>e</sup> Prices based on [Drug Tariff](#) February 2016.

<sup>f</sup> If intravenous fosaprepitant is given as the neurokinin-1 receptor antagonist this is given as a single dose prior to chemotherapy on day 1 of cycle only.

## Estimated impact for the NHS

### Likely place in therapy

Netupitant/palonosetron ([Akynzeo](#)) is licensed in adults for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy or moderately emetogenic cancer chemotherapy. It is given as a single dose approximately 1 hour before the start of each chemotherapy cycle.

As discussed in the [evidence strengths and limitations section](#) comparative randomised controlled trial data for the licensed dose mainly comes from a study conducted in women with breast cancer receiving an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide chemotherapy regimen. Netupitant/palonosetron has been compared with palonosetron (both in combination with dexamethasone) and has shown advantages mainly for the prevention of delayed nausea and vomiting. However, there are limited data

comparing it with other 5-HT<sub>3</sub> receptor antagonists and neurokinin-1 receptor antagonists given in combination.

Guidelines such as the [MASCC/ESMO antiemetic guidelines](#) (2010) recommend regimens including both a 5-HT<sub>3</sub> receptor antagonist and a neurokinin-1 receptor antagonist for the prevention of nausea and vomiting in people receiving highly emetogenic or anthracycline plus cyclophosphamide based chemotherapy regimens. Netupitant/palonosetron capsules are given as a single dose prior to each chemotherapy cycle, which may simplify the treatment regimen and be preferable to some people.

Netupitant/palonosetron costs £69.00 for each chemotherapy cycle. Costs for other 5-HT<sub>3</sub> receptor antagonist and neurokinin-1 receptor antagonist treatment regimens range from approximately £48 to £103 for each chemotherapy cycle.

## Estimated usage

The manufacturer estimates that approximately 17,057 adults in England and Wales would be expected to be receiving highly emetogenic cisplatin-based chemotherapy annually. Based on these figures, the manufacturers have estimated that netupitant/palonosetron would have a maximal uptake of 45% after 5 years and therefore an estimated maximum usage in 7,675 adults in England and Wales. The manufacturer could provide no data on the estimated uptake of netupitant/palonosetron in adults receiving anthracycline plus cyclophosphamide based or moderately emetogenic cancer chemotherapy.

## Relevance to NICE guidance programmes

Netupitant/palonosetron for the prevention of chemotherapy induced nausea and vomiting is not appropriate for referral for a NICE technology appraisal and it is not currently planned into any work programme.

There is no published NICE guidance on the treatment of chemotherapy induced nausea and vomiting.

## References

Aapro M, Rugo H, Rossi G et al. (2014) [A randomised phase III study evaluating the efficacy and safety of NEPA, a fixed dose combination of netupitant and palonosetron, for](#)

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## Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

### Expert advisers

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## Declarations of interest

Joanne McCaughey declared that she attended a weekend education session in Berlin with Leo Pharmaceuticals in 2011/2 and was sponsored by AstraZeneca to go to BOPA in October 2011.

Pinkie Chambers declared attendance as a speaker at a Chugai sponsored event in October 2015. The presentation detailed a piece of research involved in developing an acute oncology data base. The company offered an honorarium which was declined.

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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