IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Netupitant/palonosetron – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Netupitant/Palonosetron – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Oncology Centre, Berlin, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Lisa Schell
- Christiane Balg
- Lars Beckmann
- Gertrud Egger
- Andreas Gerber-Grote
- Ulrike Lampert
- Ulrike Seay
- Volker Vervölgyi

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[2] Due to legal data protection regulations, employees have the right not to be named.

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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FLIE	Functional Living Index – Emesis
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug netupitant/palonosetron. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 July 2015.

Research question

The aim of this report was to assess the added benefit of netupitant/palonosetron in adult patients for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy or with highly emetogenic cisplatin-based cancer chemotherapy in comparison with the appropriate comparator therapy (ACT).

Two research questions (A and B) resulted from this, for which the G-BA specified the ACTs presented in Table 2.

Table 2: Research questions of the benefit assessment of netupitant/palonosetron

Research question	Therapeutic indication	Appropriate comparator therapy[a]
A	Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy	Dual combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + **dexamethasone**
B	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy	Triple combination of serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + neurokinin-1 receptor antagonist (**aprepitant**, fosaprepitant) + **dexamethasone**
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

From the options specified by the G-BA, the company chose palonosetron + dexamethasone as ACT for research question A, and aprepitant + palonosetron + dexamethasone as ACT for research question B. The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results for research question A: prevention of nausea and vomiting in moderately emetogenic chemotherapy

The company presented one study of direct comparison (NETU-08-18) and one indirect comparison for research question A. Neither the study of direct comparison nor the indirect comparison was suitable for the derivation of the added benefit.

The NETU-08-18 study was a randomized, active-controlled, double-blind study sponsored by the company. Netupitant/palonosetron in combination with dexamethasone was compared with palonosetron in combination with dexamethasone in the study. The study was unsuitable for the derivation of the added benefit of netupitant/palonosetron because the patient population did not concur with the therapeutic indication: Patients receiving a combination chemotherapy of cyclophosphamide + doxorubicin or cyclophosphamide + epirubicin were included in the NETU-08-18 study. This kind of chemotherapy is rated as highly emetogenic in current guidelines. Moreover, the patients in the comparator group did not receive the treatment recommended for them. In the comparator arm of the study, a dual combination of serotonin antagonist and dexamethasone was used as comparator therapy. However, current guidelines recommend triple combination of serotonin receptor antagonist, steroid and neurokinin-1 receptor antagonist for the chemotherapy combination administered in the study.

The company used the NETU-08-18 study also for the netupitant/palonosetron side of the indirect comparison. Since the patient population, as described in the section above, did not comply with the therapeutic indication, this indirect comparison could also not be used for the benefit assessment. Moreover, the company itself did not use the indirect comparison for the derivation of the added benefit.

Hence no relevant data were available for the assessment of the added benefit of netupitant/palonosetron for the prevention of acute or delayed nausea and vomiting associated with moderately emetogenic chemotherapy. Hence there was no hint of an added benefit of netupitant/palonosetron in comparison with the ACT. An added benefit is therefore not proven.

Results for research question B: prevention of nausea and vomiting in highly emetogenic chemotherapy

One relevant study (NETU-10-29) was available for the benefit assessment.

Study characteristics

The NETU-10-29 study was a randomized, active-controlled, double-blind study sponsored by the company and conducted in 59 centres worldwide. Netupitant/palonosetron in combination with dexamethasone was compared with aprepitant + palonosetron + dexamethasone in the study.

Chemotherapy-naive adult patients receiving moderately emetogenic or highly emetogenic chemotherapy were included. The company presented analyses on the basis of the subpopulation of patients with highly emetogenic chemotherapy. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question B and were used for the benefit assessment.

The patients could receive the study medication for several chemotherapy cycles; the number of chemotherapy cycles per patient was not limited.

Patients in the relevant subpopulation in the intervention arm received a single dose of netupitant/palonosetron (300 mg/0.5 mg) in combination with 12 mg oral dexamethasone on day 1, before the start of the chemotherapy. The treatment was continued with 8 mg oral dexamethasone daily on days 2 to 4. Patients in the comparator arm received a single dose of 125 mg oral aprepitant in combination with 0.5 mg oral palonosetron and 12 mg oral dexamethasone on day 1, before the start of the chemotherapy. The treatment was continued with 80 mg oral aprepitant and 8 mg oral dexamethasone daily on days 2 to 3, and with 8 mg oral dexamethasone on day 4. The patients in both study arms received additional placebo to maintain blinding.

Risk of bias

The risk of bias at the study level was rated as low for the NETU-10-29 study, but as high at outcome level for all outcomes.

Data cut-off

The company presented analyses of the first chemotherapy cycle and analyses for the total study duration. Since patients receive several chemotherapy cycles it was particularly relevant for the benefit assessment whether an antiemetic effect is maintained across several chemotherapy cycles. Hence mainly the results for the total study duration were used for the derivation of the added benefit. The sole consideration of results on the first chemotherapy cycle was considered inadequate for the assessment of the added benefit, however.

Mortality

All-cause mortality

In the NETU-10-29 study, no statistically significant difference between the treatment groups was shown for the outcome “all-cause mortality”. There was no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

Morbidity

Nausea

There were no evaluable data for the outcome "nausea". There was no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

Vomiting

For the outcome "vomiting", only results for the first chemotherapy cycle were available. Hence there were no sufficient data on this outcome. There was therefore no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

A statistically significant difference in favour of netupitant/palonosetron in combination with dexamethasone was shown for the first chemotherapy cycle. The extent in this outcome of the outcome category "non-serious/non-severe symptoms/late complications" was no more than marginal, however. Hence there was no advantage of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone for the outcome "vomiting" even when only the first chemotherapy cycle was considered.

Health-related quality of life

Health-related quality of life was not investigated in the NETU-10-29 study. There was no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

Adverse events

Serious adverse events

In the NETU-10-29 study, no statistically significant difference between the treatment groups was shown for the outcome "serious adverse events (SAEs)". There was no hint of greater or lesser harm of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

In the NETU-10-29 study, no statistically significant difference between the treatment groups was shown for the outcome "discontinuation due to adverse events (AEs)". There was no hint of greater or lesser harm of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; greater or lesser harm is therefore not proven.

Diarrhoea

A statistically significant difference in favour of netupitant/palonosetron was shown for the outcome "diarrhoea". This AE does not result from the Summaries of Product Characteristics (SPCs) of aprepitant, palonosetron or dexamethasone. There were no important differences

between the chemotherapeutic regimens in the 2 treatment arms. It was therefore unlikely that the observed lesser harm was caused by the chemotherapies.

The risk of bias for this outcome was rated as high. Overall, this resulted in a hint of lesser harm from netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug netupitant/palonosetron in comparison with the ACT is assessed as follows:

Research question A (prevention of nausea and vomiting in moderately emetogenic chemotherapy)

An added benefit of netupitant/palonosetron for the prevention and treatment of nausea and vomiting in adult patients receiving moderately emetogenic chemotherapy versus the ACT is not proven.

Research question B (prevention of nausea and vomiting in highly emetogenic chemotherapy)

Overall, only a positive effect remains in the outcome category “non-serious/non-severe AEs” with the probability “hint” and the extent “considerable”.

It should be noted that the only positive effect in favour of netupitant/palonosetron was shown in the area of AEs. Proof of non-inferiority in other outcome categories is therefore additionally required for the derivation of an added benefit. No data for the outcome category “health-related quality of life” were available, however. Furthermore, for the outcomes in the category “morbidity”, no evaluable data or only results for the first chemotherapy cycle were available. The latter data alone are considered inadequate for the assessment of the added benefit. Against this background, no meaningful interpretation of the positive result in the area of AEs is possible. Overall, an added benefit of netupitant/palonosetron in comparison with the ACT for the prevention and treatment of nausea and vomiting is not proven for adult patients receiving highly emetogenic chemotherapy.

Table 3 presents a summary of the extent and probability of the added benefit of netupitant/palonosetron.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Table 3: Netupitant/palonosetron – extent and probability of added benefit

Research question	Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
A	Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy	Dual combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + **dexamethasone**	Added benefit not proven
B	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy	Triple combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + neurokinin-1 receptor antagonist (**aprepitant**, fosaprepitant) + **dexamethasone**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of netupitant/palonosetron in adult patients for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy or with highly emetogenic cisplatin-based cancer chemotherapy in comparison with the ACT.

Two research questions (A and B) resulted from this, for which the G-BA specified the ACTs presented in Table 4.

Table 4: Research questions of the benefit assessment of netupitant/palonosetron

Research question	Therapeutic indication	Appropriate comparator therapy[a]
A	Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy	Dual combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + **dexamethasone**
B	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy	Triple combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + neurokinin-1 receptor antagonist (**aprepitant**, fosaprepitant) + **dexamethasone**
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

For easier presentation and better readability, the report uses the following terms for the 2 therapeutic indications:

- prevention of nausea and vomiting in moderately emetogenic chemotherapy (research question A)
- prevention of nausea and vomiting in highly emetogenic cisplatin-based chemotherapy (research question B)

The G-BA specified a dual combination of serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, palonosetron) + dexamethasone as ACT for research question A. The G-BA further specified the ACT insofar as the dual combination was to be used before the chemotherapy on day 1 and the prevention after day 1 was to be continued either with the serotonin antagonist (except palonosetron), if applicable in combination with dexamethasone, or with dexamethasone mono (see Section 2.6.1 of the full dossier assessment). The company followed the specification of the G-BA and, from the options mentioned, chose palonosetron + dexamethasone as comparator therapy.

The G-BA specified a triple combination of serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, palonosetron) + neurokinin-1 receptor antagonist (aprepitant, fosaprepitant) + dexamethasone as ACT for research question B. The G-BA further specified the ACT insofar as the triple combination was to be used before the chemotherapy on day 1 and the prevention on days 2 to 3 with aprepitant and dexamethasone (if aprepitant on day 1) and on day 4 with dexamethasone (see Section 2.6.1 of the full dossier assessment). The company followed the specification of the G-BA and, from the options mentioned, chose aprepitant + palonosetron + dexamethasone as comparator therapy.

The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Research question A (prevention of nausea and vomiting in moderately emetogenic chemotherapy)

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on netupitant/palonosetron (status: 19 June 2015)
- bibliographical literature search on netupitant/palonosetron (last search on 18 June 2015)
- search in trial registries for studies on netupitant/palonosetron (last search on 19 June 2015)
- bibliographical literature search on the ACT (last search on 18 June 2015)
- search in trial registries for studies on the ACT (last search on 19 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on netupitant/palonosetron (last search on 11 August 2015)

No relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified studies for a direct and an indirect comparison.

Neither the direct nor the indirect comparison was adequate to derive conclusions on the added benefit of netupitant/palonosetron for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy in comparison with the ACT specified by the G-BA. The non-consideration of the direct comparison is justified below. For

the reasons of non-consideration of the indirect comparison, see Section 2.6.2.3.2 of the full dossier assessment.

Study pool of the company for the direct comparison

The company used one RCT (the NETU-08-18 study) for the direct comparison [3].

The NETU-08-18 study was a randomized, active-controlled, double-blind study sponsored by the company. Netupitant/palonosetron in combination with dexamethasone was compared with palonosetron in combination with dexamethasone in the study.

1455 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms. Chemotherapy-naive adult patients receiving a chemotherapy combination of cyclophosphamide + doxorubicin or cyclophosphamide + epirubicin were included.

The study duration was 2 to 5 weeks for each chemotherapy cycle. The number of chemotherapy cycles per patient was not limited.

Patient-relevant outcomes of the study were vomiting, nausea, significant nausea, AEs and health-related quality of life. The company's dossier only contained analyses of the first chemotherapy cycle for the patient-relevant outcomes. Health-related quality of life was recorded with the Functional Living Index - Emesis (FLIE) questionnaire [4,5], which measures the impact of nausea and vomiting during chemotherapy on patients' daily lives.

The study was unsuitable for the derivation of the added benefit of netupitant/palonosetron. This is justified below.

Patient population did not concur with the therapeutic indication (chemotherapy highly emetogenic instead of moderately emetogenic)

Patients receiving a combination chemotherapy of cyclophosphamide + doxorubicin or cyclophosphamide + epirubicin were included in the NETU-08-18 study. The company rated these combination chemotherapies as moderately emetogenic. However, they are rated as highly emetogenic in current guidelines [6-9] and therefore did not concur with the present therapeutic indication. Nonetheless, the European Medicines Agency (EMA) accepted the study as basis for the approval of netupitant/palonosetron in moderately emetogenic chemotherapy [10] under the condition that the fact that the approval of netupitant/palonosetron for the prevention of nausea and vomiting in moderately emetogenic chemotherapy was based on a study with highly emetogenic chemotherapy is addressed in the SPC of netupitant/palonosetron [11].

The study could also not be used for research question B (highly emetogenic chemotherapy) because a disadvantage of the control group could not be excluded. The comparator intervention in the study was a dual combination of serotonin antagonist and dexamethasone. This constitutes an appropriate treatment for moderately emetogenic chemotherapy. However, current guidelines recommend a triple combination of serotonin receptor antagonist, steroid

and neurokinin-1 receptor antagonist for a combination chemotherapy of cyclophosphamide + doxorubicin or cyclophosphamide + epirubicin [6,8,9]. Hence the patients in the comparator group of the NETU-08-18 study did not receive their recommended treatment.

Appropriate comparator therapy not adequately implemented

Moreover, the implementation of the ACT for moderately emetogenic chemotherapy was inadequate because dexamethasone was only allowed to be administered on day 1 of the chemotherapy.

As described in Section 2.6.1 of the full dossier assessment, the G-BA further specified the ACT insofar as the prevention after day 1 was to be continued either with the serotonin antagonist (except palonosetron), if applicable in combination with dexamethasone, or with dexamethasone mono under consideration of the information provided in the respective SPC, particularly regarding the duration of treatment (see Section 2.6.1 of the full dossier assessment). The SPC of dexamethasone [12] specifies for moderately emetogenic chemotherapy that the treatment is continued up to 3 days if required. Current guidelines [7-9] also recommend continued treatment with dexamethasone on days 2 to 3.

Unsuitable for therapeutic indication B

Highly emetogenic chemotherapy instead of moderately emetogenic chemotherapy was used in the NETU-08-18 study. However, the NETU-08-18 study can also not be used for the benefit assessment in the therapeutic indication of highly emetogenic chemotherapy for the following reasons:

Netupitant/palonosetron is only approved for highly emetogenic cisplatin-based chemotherapies. In the NETU-08-18 study however, combination chemotherapies of cyclophosphamide + doxorubicin or cyclophosphamide + epirubicin were administered. In addition, the comparator therapy of dual therapy with palonosetron and dexamethasone used in the study does not concur with the ACT of triple therapy of serotonin antagonist, neurokinin-1 receptor antagonist and dexamethasone specified by the G-BA for this therapeutic indication (see Section 2.6.1 of the full dossier assessment).

Summary

Overall, the NETU-08-18 study was unsuitable for the derivation of the added benefit of netupitant/palonosetron in moderately emetogenic chemotherapy.

The characteristics, the interventions and the results of the NETU-08-18 study for the indirect comparison are presented as additional information in Table 21, Table 22 and Table 24 in Appendix A of the full dossier assessment.

Study pool of the company for the indirect comparison

In addition to the direct comparison, the company conducted an adjusted indirect comparison of netupitant/palonosetron in combination with dexamethasone versus ondansetron (if

applicable in combination with dexamethasone). Palonosetron (if applicable in combination with dexamethasone) was used as common comparator.

The study pool of the company for the indirect comparison included 2 RCTs on the comparison of palonosetron (if applicable in combination with dexamethasone) with ondansetron (if applicable in combination with dexamethasone): PALO-99-03 [13] and Kaushal 2010 [14]. The company identified one RCT (the NETU-08-18 study [3]) for the comparison of netupitant/palonosetron in combination with dexamethasone and palonosetron in combination with dexamethasone, which it also used for the direct comparison.

The characteristics and interventions of the studies for the indirect comparison are presented in Table 27 and Table 28 in Appendix B of the full dossier assessment.

Since the company used the NETU-08-18 study for the indirect comparison on the netupitant/palonosetron side, which was assessed as inadequate already for the direct comparison, the indirect comparison presented by the company was not used for the benefit assessment (see Section 2.6.2.3.2 of the full dossier assessment). Furthermore, the company itself did not use the indirect comparison for the derivation of the added benefit, but presented it only as additional information.

2.3.2 Results on added benefit

No relevant data were available for the assessment of the added benefit of netupitant/palonosetron for the prevention of acute or delayed nausea and vomiting associated with moderately emetogenic chemotherapy. Hence there was no hint of an added benefit of netupitant/palonosetron in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since the company presented no relevant data for adult patients receiving netupitant/palonosetron for the prevention of acute or delayed nausea and vomiting associated with moderately emetogenic chemotherapy, an added benefit of netupitant/palonosetron is not proven.

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question B (prevention of nausea and vomiting in highly emetogenic cisplatin-based chemotherapy)

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on netupitant/palonosetron (status: 19 June 2015)
- bibliographical literature search on netupitant/palonosetron (last search on 18 June 2015)
- search in trial registries for studies on netupitant/palonosetron (last search on 19 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on netupitant/palonosetron (last search on 11 August 2015)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The study listed in Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NETU-10-29	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of netupitant/palonosetron corresponded to that of the company. Netupitant/palonosetron in combination with dexamethasone was directly compared with aprepitant + palonosetron + dexamethasone in the included NETU-10-29 study.

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NETU-10-29	RCT, double-blind, parallel	Chemotherapy-naive adult patients with moderately or highly emetogenic chemotherapy	Netupitant/palonosetron + dexamethasone (N = 309) Aprepitant + palonosetron + dexamethasone (N = 104) Relevant subpopulation thereof:[b] netupitant/palonosetron + dexamethasone (n = 74) aprepitant + palonosetron + dexamethasone (n = 26)	Single cycle and multiple cycles[c] In each chemotherapy cycle: screening: up to 14 days treatment: on day 1–4[b] follow-up: up to 21 (+2) days	59 centres in 10 countries (Bulgaria, Czech Republic, Germany, Hungary, India, Poland, Russia, Serbia, Ukraine, USA) 7/2011–9/2012	Primary: AEs Secondary: nausea, vomiting, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Patients with highly emetogenic chemotherapy.
c: The number of chemotherapy cycles per patient was not limited.
AE: adverse event; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study	Intervention	Comparison
NETU-10-29	Day 1: netupitant/palonosetron 300 mg/0.50 mg orally 60 min before administration of chemotherapy + placebo for aprepitant and palonosetron + dexamethasone 12 mg orally 30 min before administration of chemotherapy Day 2–3: dexamethasone 8 mg orally + placebo for aprepitant Day 4: dexamethasone 8 mg orally	Day 1: aprepitant 125 mg orally 60 min before administration of chemotherapy + palonosetron 0.5 mg orally 60 min before administration of chemotherapy + placebo for netupitant/palonosetron + dexamethasone 12 mg orally 30 min before administration of chemotherapy Day 2–3: aprepitant 80 mg orally + dexamethasone 8 mg orally Day 4: dexamethasone 8 mg orally
	Allowed chemotherapy:[a] ▪ day 1: any dosage of cisplatin, mechlorethamine, streptozocin, carmustine, dacarbazine or cyclophosphamide ≥1500 mg/m^2 ▪ day 2–5: no moderately or highly emetogenic chemotherapy allowed Allowed concomitant medication: ▪ rescue medication for treatment of established, refractory or persistent nausea, but not for prevention or to increase the effect of the study drugs ▪ disallowed rescue medication: neurokinin-1 receptor antagonists, serotonin receptor antagonists Prohibited concomitant medication: ▪ systemic corticosteroids: up to 72 hours before the start of the chemotherapy, on the day of the administration of the study medication and on the following days (exception: administration of systemic corticosteroids was allowed in the 48 hours before the start of the chemotherapy if this was required due to the chemotherapeutic regimen)	

a: The data refer to the subpopulation of patients with highly emetogenic chemotherapy.
RCT: randomized controlled trial; vs.: versus

Study design

The NETU-10-29 study was a randomized, active-controlled, double-blind study sponsored by the company and conducted in 59 centres worldwide. Netupitant/palonosetron in combination with dexamethasone was compared with aprepitant + palonosetron + dexamethasone in the study.

Chemotherapy-naive adult patients receiving moderately emetogenic or highly emetogenic chemotherapy were included. A total of 413 patients were randomly assigned in a ratio of 3:1 to the 2 treatment arms. Randomization was stratified by emetogenicity (highly or moderately emetogenic) of the chemotherapy and by sex. The subpopulation relevant for the benefit assessment who had highly emetogenic chemotherapy comprised n = 74 patients in the intervention arm and n = 26 patients in the comparator arm of the study. The company submitted analyses based on this relevant subpopulation of the NETU-10-29 study. The patients included in these analyses are an adequate representation of the subpopulation relevant for research question B and were used for the benefit assessment.

The patients could receive the study medication for several chemotherapy cycles; the number of chemotherapy cycles per patient was not limited. One treatment cycle lasted between 2 and 5 weeks.

Patient-relevant outcomes of the study were vomiting, nausea and AEs.

Characteristics of the interventions

Patients in the relevant subpopulation in the intervention arm received a single dose of netupitant/palonosetron (300 mg/0.5 mg) in combination with 12 mg oral dexamethasone on day 1, before the start of the chemotherapy. The treatment was continued with 8 mg oral dexamethasone daily on days 2 to 4. Patients in the relevant subpopulation in the comparator arm received a single dose of 125 mg oral aprepitant in combination with 0.5 mg oral palonosetron and 12 mg oral dexamethasone on day 1, before the start of the chemotherapy. The treatment was continued with 80 mg oral aprepitant and 8 mg oral dexamethasone daily on days 2 to 3, and with 8 mg oral dexamethasone on day 4. The patients in both study arms received additional placebo to maintain blinding.

In the NETU-10-29 study, 0.5 mg palonosetron was administered orally, although palonosetron in highly emetogenic chemotherapy is only approved as intravenous application in a dosage of 0.25 mg. This had no consequence for the benefit assessment, however (see Section 2.6.2.1 of the full dossier assessment).

Characteristics of the study population

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study Characteristics Category	**Netupitant/ palonosetron + dexamethasone N = 74**[a]	**Aprepitant + palonosetron + dexamethasone N = 26**[a]
NETU-10-29		
Age [years], mean (SD)	58 (10.0)	56 (13.2)
Sex [F/M], %	39/61	39/62
ECOG PS, n (%)		
0	41 (55.4)	13 (50.0)
1	32 (43.2)	12 (46.2)
2	1 (1.4)	1 (3.8)
BMI, mean (SD)	24.8 (4.9)	23.3 (4.0)
Ethnicity, n (%)		
White	65 (87.8)	22 (84.6)
Asian	9 (12.2)	4 (15.4)
Alcohol consumption, n (%)		
No	37 (50.0)	16 (61.5)
Occasionally	32 (43.2)	8 (30.8)
Regularly	5 (6.8)	2 (7.7)
Chemotherapy (first cycle)		
Carmustine	0 (0)	1 (4.0)
Cisplatin	72 (96.0)	23 (92.0)
Dacarbazine	3 (4.0)	1 (4.0)
Study discontinuations first cycle, n (%)	ND	ND
Treatment discontinuations first cycle, n (%)	ND	ND
Study discontinuations total, n (%)	ND	ND
Treatment discontinuations total, n (%)	ND	ND

a: Number of randomized patients in the full analysis set. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; N: number of randomized (or included) patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences between the treatment groups regarding age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and ethnicity. The mean age of the patients was 58 and 56 years. More men than women were included in both study arms with the distribution being comparable. The proportion of patients who consumed no alcohol was more than 10 percentage points higher in the comparator arm than in the netupitant/palonosetron arm. No analysis of the relevant subpopulation was available on the primary cancer diagnosis.

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
NETU-10-29	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - nausea
  - vomiting
- Health-related quality of life
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - diarrhoea (Preferred Term [PT])

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.6.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study	Outcomes						
	All-cause mortality	Nausea	Vomiting	Health-related quality of life	SAEs	Discontinuation due to AEs	Diarrhoea
NETU-10-29	Yes	No[a]	Yes[b]	No[c]	Yes	Yes	Yes

a: No evaluable data available; for reasons, see Section 2.6.2.4.3 of the full dossier assessment.
b: Data available only for the first chemotherapy cycle.
c: Outcome not recorded.
AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study	Study level	Outcomes						
		All-cause mortality	Nausea	Vomiting	Health-related quality of life	SAEs	Discontinuation due to AEs	Diarrhoea
NETU-10-29 (total study duration)	L	H[a]	-[b]	-[c]	-[d]	H[a]	H[a]	H[a]
NETU-10-29 (first cycle)[e]	L	H[a]	-[b]	H[a]	-[d]	H[a]	H[a]	-[c]

a: No data on missing values in the relevant subpopulation.
b: No evaluable data available.
c: No analyses available for this time period.
d: Outcome not recorded in the study.
e: The data on the first chemotherapy cycle are also presented, but on their own are not sufficient for the derivation of an added benefit (see Section 2.4.2.3).
AE: adverse event; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The assessment of the risk of bias at outcome level deviates from that of the company.

Deviating from the company, the outcomes “all-cause mortality”, “SAEs”, “discontinuation due to AEs” and “diarrhoea” were rated as potentially highly biased because of missing information on the proportions of missing values in the relevant subpopulation.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.6.2.4.2 of the full dossier assessment.

2.4.2.3 Results

Table 12 summarizes the results on the comparison of netupitant/palonosetron + dexamethasone with aprepitant + palonosetron + dexamethasone for the prevention of acute or delayed nausea and vomiting associated with highly emetogenic chemotherapy. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

The company presented analyses of the first chemotherapy cycle and analyses for the total study duration. Since patients receive several chemotherapy cycles it was particularly relevant for the benefit assessment whether an antiemetic effect is maintained across several chemotherapy cycles. Hence mainly the results for the total study duration were used for the derivation of the added benefit. If only results for the first chemotherapy cycle were available for individual outcomes, the corresponding results were also presented. The sole consideration of results on the first chemotherapy cycle was considered inadequate for the assessment of the added benefit, however. For the outcome “vomiting”, results were available for the total phase of the first chemotherapy cycle; the results of the acute and delayed phase are presented as additional information (see Section 2.6.2.4.3 of the full dossier assessment).

Table 12: Results (dichotomous outcomes) – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Study **Outcome category** **Outcome** Time point	**Netupitant/ palonosetron + dexamethasone**		**Aprepitant + palonosetron + dexamethasone**		**Netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
NETU-10-29					
Mortality					
All-cause mortality					
Total study duration	75	4 (5.3)	25	1 (4.0)	1.33 [0.16; 11.38][a] 0.870[b]
First cycle	75	0 (0.0)	25	0 (0.0)	NC
Morbidity					
Proportion of patients without nausea	No evaluable data				
Proportion of patients without vomiting					
Total study duration	ND				
First cycle					
Total phase[d]	74[c]	64 (86.5)	26[c]	16 (61.5)	1.40 [1.02; 1.92] 0.008[b]
Additional: acute phase[e]	74[c]	70 (94.6)	26[c]	25 (96.2)	0.98 [0.88; 1.10] 0.783[b]
Additional: delayed phase[f]	74[c]	65 (87.8)	26[c]	16 (61.5)	1.42 [1.03; 1.95] 0.005[b]
Health-related quality of life					
Outcome not recorded					

(continued)

Table 12: Results (dichotomous outcomes) – RCT, direct comparison: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone (continued)

Study Outcome category Outcome Time point	Netupitant/ palonosetron + dexamethasone		Aprepitant + palonosetron + dexamethasone		Netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Adverse events					
AEs[g]					
Total study duration	75	64 (85.3)	25	22 (88.0)	
First cycle	75	47 (62.7)	25	13 (52.0)	
SAEs[g]					
Total study duration	75	12 (16.0)	25	8 (32.0)	0.50 [0.23; 1.08][a] 0.107[b]
First cycle	75	2 (2.7)	25	2 (8.0)	0.34 [0.05; 2.25] 0.290[b]
Discontinuation due to AEs[g]					
Total study duration	75	7 (9.3)	25	4 (16.0)	0.58 [0.19; 1.83][a] 0.388[b]
First cycle	75	1 (1.3)	25	1 (4.0)	0.33 [0.02; 5.09] 0.447[b]
Diarrhoea					
Total study duration	75	5 (6.7)	25	7 (28.0)	0.24 [0.08; 0.68][a] 0.007[b]
First cycle				ND	

a: Institute's calculation.
b: Institute's calculation, unconditional exact test (CSZ method according to [15]).
c: Data of the full analysis set.
d: Comprises the first 120 h of the chemotherapy cycle.
e: Comprises the first 24 h of the chemotherapy cycle.
f: Comprises the time from 25 h to 120 h of the chemotherapy cycle.
g: The data on AEs, SAEs, and discontinuation due to AEs contain no events with the PTs "vomiting" and "nausea".

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

All-cause mortality

In the NETU-10-29 study, no statistically significant difference between the treatment groups was shown for the outcome "all-cause mortality". There was no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Nausea

There were no evaluable data for the outcome "nausea". There was no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

The company used the outcome (operationalized as significant nausea) in its assessment, but also derived no added benefit.

Vomiting

For the outcome "vomiting", only results for the first chemotherapy cycle were available (see Section 2.6.2.4.3 of the full dossier assessment). Hence there were no sufficient data on this outcome. There was therefore no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

A statistically significant difference in favour of netupitant/palonosetron was shown for the first chemotherapy cycle. The extent in this outcome of the outcome category "non-serious/non-severe symptoms/late complications" was no more than marginal, however. Hence there was no advantage of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone for the outcome "vomiting" even when only the first chemotherapy cycle was considered.

This assessment deviates from that of the company, which derived a considerable added benefit for this outcome.

Health-related quality of life

Health-related quality of life was not investigated in the NETU-10-29 study. There was no hint of an added benefit of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Adverse events

The AEs that most commonly occurred in the relevant subpopulation of the NETU-10-29 study are presented in Appendix C of the full dossier assessment. There were no lists of common SAEs and discontinuations due to AEs for the relevant subpopulation.

Serious adverse events

In the NETU-10-29 study, no statistically significant difference between the treatment groups was shown for the outcome "SAEs". There was no hint of greater or lesser harm of

netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events

In the NETU-10-29 study, no statistically significant difference between the treatment groups was shown for the outcome "discontinuation due to AEs". There was no hint of greater or lesser harm of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Diarrhoea

A statistically significant difference in favour of netupitant/palonosetron was shown for the outcome "diarrhoea". The risk of bias for this outcome was rated as high. Such an AE does not result from the SPCs of aprepitant [16], palonosetron [17] or dexamethasone [12]. There were no important differences between the chemotherapeutic regimens in the 2 treatment arms. It was therefore unlikely that the observed lesser harm was caused by the chemotherapies.

Overall, this resulted in a hint of lesser harm from netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone.

The company did not use the outcome "diarrhoea" in its assessment.

2.4.2.4 Subgroups and other effect modifiers

Selected subgroups were to be investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company's dossier contained no subgroup analyses (see Section 2.6.2.4.3 of the full dossier assessment). Hence no subgroup results are presented.

2.4.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in section 2.4.2 resulted in a hint of lesser harm of netupitant/palonosetron in comparison with aprepitant + palonosetron + dexamethasone for the outcome “diarrhoea” in adult patients who receive netupitant/palonosetron for the prevention of acute or delayed nausea and vomiting associated with highly emetogenic chemotherapy.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone

Outcome category **Outcome**	**Netupitant/palonosetron + dexamethasone vs. aprepitant + palonosetron + dexamethasone** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	5.3% vs. 4.0% RR: 1.33 [0.16; 11.38][c] p = 0.870[d]	Added benefit not proven
Morbidity		
Proportion of patients without nausea	No evaluable data	
Proportion of patients without vomiting[e]	No data for the consideration of several cycles	Added benefit not proven
Health-related quality of life		
	Outcome not recorded	
Adverse events		
SAEs	16.0% vs. 32.0% RR: 0.50 [0.23; 1.08][c] p = 0.107[d]	Greater/lesser harm not proven
Discontinuation due to AEs	9.3% vs. 16.0% RR: 0.58 [0.19; 1.83][c] p = 0.388[d]	Greater/lesser harm not proven
Diarrhoea	6.7% vs. 28.0% RR: 0.24 [0.08; 0.68][c] p = 0.007[d] probability: “hint”	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm, extent: “considerable”

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute’s calculation.
d: Institute’s calculation, unconditional exact test (CSZ method according to [15]).
e: Only results on the first chemotherapy cycle are available.
f: Institute’s calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of netupitant/palonosetron + dexamethasone compared with aprepitant + palonosetron + dexamethasone

Positive effects	Negative effects
Hint of lesser harm – extent: "considerable" (non-serious/non-severe symptoms: diarrhoea)	-

Overall, only a positive effect remains in the outcome category "non-serious/non-severe AEs" with the probability "hint" and the extent "considerable".

It should be noted that the only positive effect in favour of netupitant/palonosetron was shown in the area of AEs. Proof of non-inferiority in other outcome categories is therefore additionally required for the derivation of an added benefit. No data for the outcome category "health-related quality of life" were available, however. Furthermore, for the outcomes in the category "morbidity", no evaluable data or only results for the first chemotherapy cycle were available. The latter data alone are considered inadequate for the assessment of the added benefit. Against this background, no meaningful interpretation of the positive result in the area of AEs is possible. Overall, an added benefit of netupitant/palonosetron in comparison with the ACT for the prevention and treatment of nausea and vomiting is not proven for adult patients receiving highly emetogenic chemotherapy.

2.4.4 List of included studies

NETU-10-29

Gralla RJ, Bosnjak SM, Hontsa A, Balser C, Rizzi G, Rossi G et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 2014; 25(7): 1333-1339.

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Helsinn Healthcare. A phase III, multicenter, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles [online]. In: EU Clinical Trials Register. [Accessed: 19 June 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-023297-39.

Helsinn Healthcare. A safety study of oral netupitant and palonosetron for the prevention of nausea and vomiting: study results [online]. In: ClinicalTrials.gov. 6 November 2014 [accessed: 18 June 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01376297.

Helsinn Healthcare. A phase III, multicenter, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles: study NETU-10-29; clinical study report [unpublished]. 2013.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of netupitant/palonosetron in comparison with the ACT is summarized in Table 15

Table 15: Netupitant/palonosetron – extent and probability of added benefit

Research question	Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
A	Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy	Dual combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + **dexamethasone**	Added benefit not proven
B	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy	Triple combination of: serotonin antagonist (ondansetron, granisetron, tropisetron, dolasetron, **palonosetron**) + neurokinin-1 receptor antagonist (**aprepitant**, fosaprepitant) + **dexamethasone**	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

In summary, an added benefit of netupitant/palonosetron for the prevention and treatment of nausea and vomiting in comparison with the ACT is not proven for adult patients who receive moderately emetogenic chemotherapy (therapeutic indication A) or for adult patients who receive highly emetogenic cisplatin-based chemotherapy (therapeutic indication B).

This overall assessment deviates from that of the company, which derived an indication of considerable added benefit for research question A, and a hint of considerable added benefit for research question B.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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