IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-26

Rolapitant (prevention of nausea and vomiting in chemotherapy) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Rolapitant (Prävention von Übelkeit und Erbrechen bei Chemotherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 August 2017). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
5-HT3	5-hydroxytryptamine
AC	anthracycline-cyclophosphamide combination
ACT	appropriate comparator therapy
AE	adverse event
AUC	area under the curve
CSR	clinical study report
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)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 rolapitant. 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 1 June 2017.

Research question

The aim of this report was to assess the added benefit of rolapitant for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults.

Rolapitant is administered in combination with a 5-hydroxytryptamine (5-HT3) receptor antagonist and dexamethasone.

The G-BA distinguished between different patient groups in its specification of the appropriate comparator therapy (ACT). This resulted in 3 research questions for the assessment. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of rolapitant

Research question	Subindication	ACT[a]
1	Prevention of delayed nausea and vomiting after ▪ highly emetogenic chemotherapy	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4; aprepitant is additionally given on days 2 to 3 (if aprepitant on day 1; not applicable to fosaprepitant on day 1).
2a	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy	Dual combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + dexamethasone The dual combination is administered on day 1 before chemotherapy. After day 1, prevention is continued either with the serotonin antagonist (except palonosetron), if appropriate in combination with dexamethasone, or with dexamethasone monotherapy.
2b	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy with carboplatin	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4 or with aprepitant on days 2 to 3 (if aprepitant on day 1).

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**.
b: Referred to as "5-HT3 receptor antagonist" in the assessment.
5-HT3: 5-hydroxytryptamine; G-BA: Federal Joint Committee; NK-1: neurokinin-1

Results

Research question 1: highly emetogenic chemotherapy

The company included the studies TS-P04832, TS-P04833 and TS-P04834 for the assessment of the added benefit of rolapitant in highly emetogenic chemotherapy. However, none of the 3 studies was relevant for the present research question because the ACT specified by the G-BA was not implemented.

The studies TS-P04832 and TS-P04833 included patients receiving cisplatin-based chemotherapy. Guidelines rate cisplatin as highly emetogenic.

Both studies compared the combination of rolapitant + granisetron + dexamethasone with a dual combination of granisetron + dexamethasone (+ placebo) on day 1 before starting chemotherapy, in each case followed by dexamethasone on days 2 to 4. This comparison does not concur with the ACT specified by the G-BA. In this therapeutic indication, the G-BA mandated the comparison of a combination treatment with rolapitant versus a triple combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by dexamethasone and aprepitant if appropriate. The studies TS-P04832 and TS-P04833 were therefore not relevant for the present benefit assessment.

The company additionally included a subpopulation of study TS-P04834. This subpopulation included patients receiving an anthracycline-cyclophosphamide (AC)-based chemotherapy. Once again, the ACT specified by the G-BA was not implemented. In this case, the ACT was also a triple combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by dexamethasone and aprepitant if appropriate. However, the study TS-P04834 compared rolapitant + granisetron + dexamethasone with a dual combination of granisetron and dexamethasone, in each case followed by granisetron on days 2 to 3. The subpopulation of patients treated with AC-based chemotherapy was therefore also not relevant for the benefit assessment.

No relevant data were available for research question 1. Hence, there was no hint of an added benefit of rolapitant in comparison with the ACT in patients treated with highly emetogenic chemotherapy. An added benefit for this research question is not proven.

Research question 2a: moderately emetogenic chemotherapy

Study pool and study characteristics

The company included a subpopulation of study TS-P04834 for the assessment of the added benefit of rolapitant in moderately emetogenic chemotherapy. The TS-P04834 study was a randomized controlled trial (RCT) with chemotherapy-naive patients. A subpopulation of this study received moderately emetogenic chemotherapy and was therefore relevant for research question 2a.

Study TS-P04834 was double-blind and included 1369 patients; the relevant subpopulation included 228 patients. In the TS-P04834 study, rolapitant was administered together with

dexamethasone and the 5-HT3 receptor antagonist granisetron before initiation of the chemotherapy. Patients in the comparator arm of the study received dexamethasone and granisetron (+ placebo). In both arms, treatment was continued with granisetron on days 2 and 3.

Observation of all study participants was planned for the first cycle of their chemotherapy. Treatment and observation could then be continued for a maximum of 5 further cycles if the patients consented and the responsible investigator considered there to be no reasons against continued treatment. Blinding of study participants and treating staff was maintained.

There was no information for the present subpopulation about the reasons why patients discontinued the study. The number of patients who were included in the subsequent cycles could be inferred from the information in the dossier, however. About 20% of the relevant subpopulation dropped out of the study after the first cycle. It cannot be excluded that this percentage included mostly patients who had already suffered from severe nausea and vomiting in the first cycle and who therefore would have had a high risk of nausea and vomiting also in the subsequent cycles. This is also suggested by the data on the outcomes "nausea" and "vomiting". In the relevant subpopulation, the proportions of patients (in relation to the number of those who were still under observation in the respective cycle) with at least 1 event were largest in the first chemotherapy cycle for both outcomes (vomiting: 19% versus 34%; nausea: 51% versus 56%). The respective event rates were notably lower in the subsequent cycles (cycle 2 – vomiting: 8% versus 10%; nausea: 13% versus 17%). On the basis of the available information, it can therefore not be excluded that there was a large extent of informative censorings starting with the second cycle. As a result, the data on all outcomes for the cycles 2 to 6 are not interpretable.

Since patients usually receive several chemotherapy cycles, it is particularly relevant for the benefit assessment whether an antiemetic effect is maintained across several cycles. The sole consideration of results on the first cycle is therefore inadequate for the assessment of the added benefit.

Overall, no conclusion on the added benefit of rolapitant in comparison with the ACT in moderately emetogenic chemotherapy can be drawn on the basis of the available data from the TS-P04834 study.

An added benefit of rolapitant + granisetron + dexamethasone in comparison with placebo + granisetron + dexamethasone for patients with moderately emetogenic chemotherapy is therefore not proven.

Research question 2b: moderately emetogenic chemotherapy with carboplatin

For the assessment of the added benefit in this research question, the company included patients of the TS-P04834 study who received carboplatin-containing chemotherapy. The

subpopulation of the study was not relevant for the derivation of an added benefit in the present research question, however, because the ACT was not implemented.

The ACT for carboplatin-containing chemotherapy was a triple combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by dexamethasone or aprepitant. However, all patients in the comparator arm of the TS-P04834 study were treated with a dual combination of granisetron and dexamethasone (+ placebo), followed by granisetron on days 2 to 3.

Overall, no relevant data were available for research question 2b. Hence, there was no hint of an added benefit of rolapitant in comparison with the ACT in patients treated with carboplatin-containing chemotherapy. An added benefit for this research question is not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the probability and the extent of the added benefit of the drug rolapitant compared with the ACT is assessed as follows:

An added benefit of rolapitant is not proven for patients receiving highly or moderately emetogenic chemotherapy or carboplatin-containing chemotherapy.

Table 3 presents a summary of the probability and extent of the added benefit of rolapitant.

[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: Rolapitant – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Prevention of delayed nausea and vomiting after ▪ highly emetogenic chemotherapy	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4; aprepitant is additionally given on days 2 to 3 (if aprepitant on day 1; not applicable to fosaprepitant on day 1).	Added benefit not proven
2a	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy	Dual combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + dexamethasone The dual combination is administered on day 1 before chemotherapy. After day 1, prevention is continued either with the 5-HT3 receptor antagonist (except palonosetron), if appropriate in combination with dexamethasone, or with dexamethasone monotherapy.	Added benefit not proven
2b	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy with carboplatin	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4 or with aprepitant on days 2 to 3 (if aprepitant on day 1).	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**.
b: Referred to as "5-HT3 receptor antagonist" in the assessment.
5-HT3: 5-hydroxytryptamine; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NK-1: neurokinin-1

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of rolapitant for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults.

Rolapitant is administered in combination with a 5-HT3 receptor antagonist and dexamethasone.

The G-BA distinguished between different patient groups in its specification of the ACT. This resulted in 3 research questions for the assessment. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of rolapitant

Research question	Subindication	ACT[a]
1	Prevention of delayed nausea and vomiting after ▪ highly emetogenic chemotherapy	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4; aprepitant is additionally given on days 2 to 3 (if aprepitant on day 1; not applicable to fosaprepitant on day 1).
2a	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy	Dual combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + dexamethasone The dual combination is administered on day 1 before chemotherapy. After day 1, prevention is continued either with the serotonin antagonist (except palonosetron), if appropriate in combination with dexamethasone, or with dexamethasone monotherapy.
2b	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy with carboplatin	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4 or with aprepitant on days 2 to 3 (if aprepitant on day 1).

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**.
b: Referred to as "5-HT3 receptor antagonist" in the assessment.
5-HT3: 5-hydroxytryptamine; G-BA: Federal Joint Committee; NK-1: neurokinin-1

In research questions 1 and 2b, the company deviated from the G-BA's specifications and was also not consistent in the information it provided (see Sections 2.7.1 and 2.7.2.1 of the full dossier assessment). According to the company's information on the chosen comparator therapy in Module 3 A and Module 3 B of its dossier, the company deviated from the G-BA's specification as follows:

- Research question 1: The company distinguished between AC-based chemotherapies and other highly emetogenic chemotherapies. For AC-based chemotherapies, the company deviated from the G-BA's specification by choosing a 5-HT3 receptor antagonist instead of treatment with dexamethasone (+ aprepitant if appropriate) on days 2 to 4.
- Research question 2b: For carboplatin-based chemotherapies, the G-BA specified a triple combination on day 1, followed by either aprepitant or dexamethasone. The company, however, planned to use a 5-HT3 receptor antagonist from day 2.

In addition, for both research questions, the company included studies in which neither the ACT specified by the G-BA nor the comparator therapy chosen by the company was implemented (see also Sections 2.7.2.1 and 2.7.2.3.2 of the full dossier assessment).

The approach of the company was not followed. The present benefit assessment was based on the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Research question 1: highly 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 list on rolapitant (status: 19 April 2017)
- bibliographical literature search on rolapitant (last search on 19 April 2017)
- search in trial registries for studies on rolapitant (last search on 19 April 2017)

To check the completeness of the study pool:

- search in trial registries for studies on rolapitant (last search on 20 June 2017)

Study pool of the company

The company included the studies TS-P04832, TS-P04833 and TS-P04834[5] for the assessment of the added benefit of rolapitant in highly emetogenic chemotherapy. However, none of the 3 studies was relevant for the present research question because the ACT specified by the G-BA was not implemented.

The studies TS-P04832 and TS-P04833 [3] included patients receiving cisplatin-based chemotherapy. Guidelines rate cisplatin as highly emetogenic [4-6].

Both studies compared the combination of rolapitant + granisetron + dexamethasone with a dual combination of granisetron + dexamethasone (+ placebo) on day 1 before starting chemotherapy, in each case followed by dexamethasone on days 2 to 4. This comparison does not concur with the ACT specified by the G-BA. For this indication, the G-BA mandated the comparison of a combination treatment with rolapitant versus a triple combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by dexamethasone and aprepitant if appropriate (see Section 2.2). The studies TS-P04832 and TS-P04833 were therefore not relevant for the present benefit assessment.

The company additionally included a subpopulation of study TS-P04834 for the assessment of the added benefit of rolapitant in highly emetogenic chemotherapy. This subpopulation included patients receiving an AC-based chemotherapy. According to current guidelines, this drug combination is rated as highly emetogenic in breast cancer patients [4-6]. The analysis of the patient characteristics for the AC population of study TS-P04834 shows that 97% of this population were breast cancer patients. The patient population considered would therefore be relevant for the benefit assessment.

[5] A list of references for study TS-P04834 can be found in Section 2.4.5.

The ACT specified by the G-BA was also not implemented in the TS-P04834 study. The G-BA did not distinguish between AC-based chemotherapy and other highly emetogenic chemotherapies. In this case, the ACT was therefore also a triple combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by dexamethasone and aprepitant if appropriate. However, the study TS-P04834 compared rolapitant + granisetron + dexamethasone (+ placebo) with a dual combination of granisetron and dexamethasone (+ placebo), in each case followed by granisetron on days 2 to 3. The subpopulation of patients treated with AC-based chemotherapy was therefore also not relevant for the benefit assessment.

In summary, no relevant data were available for research question 1.

2.3.2 Results on added benefit

The company presented no relevant data for research question 1. Hence, there was no hint of an added benefit of rolapitant in comparison with the ACT in patients treated with highly emetogenic chemotherapy. An added benefit for this research question is not proven.

2.3.3 Probability and extent of added benefit

The company presented no relevant data for the assessment of the added benefit of rolapitant in patients receiving highly emetogenic chemotherapy. An added benefit for these patients is therefore not proven.

This assessment deviates from that of the company. The company derived proof of a non-quantifiable added benefit of rolapitant for patients receiving highly emetogenic cisplatin-based chemotherapy and an indication of a non-quantifiable added benefit for patients receiving an AC-based chemotherapy.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for this research question.

2.4 Research question 2a: moderately emetogenic 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 rolapitant (status: 19 April 2017)
- bibliographical literature search on rolapitant (last search on 19 April 2017)
- search in trial registries for studies on rolapitant (last search on 19 April 2017)

To check the completeness of the study pool:

- search in trial registries for studies on rolapitant (last search on 20 June 2017)

The check identified no additional relevant study.

2.4.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
TS-P04834	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

Section 2.4.5 contains a reference list for the study 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: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TS-P04834	RCT, double-blind, parallel	Chemotherapy-naive[b] adults receiving chemotherapy ▪ Karnofsky performance score ≥ 60 ▪ life expectancy of ≥ 4 months	Rolapitant + granisetron + dexamethasone (N = 684) placebo + granisetron + dexamethasone (N = 685) Relevant subpopulation thereof[c]: rolapitant + granisetron + dexamethasone (n = 130) placebo + granisetron + dexamethasone (n = 98)	Screening: up to 30 days Treatment per chemotherapy cycle: on days 1–3; for up to 6 chemotherapy cycles Observation: until 29 days after initiation of cycle (30 days after the last chemotherapy)	175 centres in Europe, Asia, Central and South America, South Africa, USA 03/2012–2/2014	Primary: rate of complete response Secondary: vomiting, nausea, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for the present benefit assessment.
b: "Chemotherapy-naive" refers to highly and moderately emetogenic chemotherapies.
c: Patients receiving moderately emetogenic chemotherapy (no carboplatin, no AC-based chemotherapy).

AC: anthracycline and cyclophosphamide; AE: adverse event; N: number of randomized patients; n: relevant subpopulation according to information in Module 4 A; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy)

Study	Intervention	Comparison
TS-P04834	Day 1: rolapitant 180 mg orally, 1 to 2 hours before administration of chemotherapy + granisetron 2 mg orally, 30 minutes before administration of chemotherapy + dexamethasone 20 mg[a] orally, 30 minutes before administration of chemotherapy Days 2–3: granisetron 2 mg orally	Day 1: placebo, orally, 1 to 2 hours before administration of chemotherapy + granisetron 2 mg orally, 30 minutes before administration of chemotherapy + dexamethasone 20 mg[a] orally, 30 minutes before administration of chemotherapy Days 2–3: granisetron 2 mg orally
	Allowed chemotherapy[b]: ▪ cyclophosphamide (< 1500 mg/m²), doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, cytarabine IV (> 1 g/m²) Allowed concomitant medication: ▪ rescue medication for existing nausea and vomiting: 5-HT3 receptor antagonists (after 24 hours or later), phenothiazines, benzamides, corticosteroids, benzodiazepines, sedative antihistamines Prohibited concomitant medication: ▪ within 48 hours before initiation of treatment: 5-HT3 antagonists, phenothiazines, benzamides, domperidone, cannabinoids, NK1 antagonist, benzodiazepines ▪ from day -2 to day 6: chemotherapeutic agents with an emetogenicity level of 3 or above on the Hesketh Scale, except for the chemotherapeutic agent administered on day 1 of the cycle ▪ within 72 hours before day 1: systemic corticosteroids or sedative antihistamines, except as premedication for chemotherapy (e.g. taxanes); exception: inhaled or topical steroids for respiratory or skin conditions	

a: Patients receiving taxanes as chemotherapy were given dexamethasone in accordance with the SPC.
b: The data refer to the subpopulation of patients with moderately emetogenic chemotherapy who did not receive carboplatin.
IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study TS-P04834 was an RCT in chemotherapy-naive patients scheduled to receive chemotherapy and therefore requiring prevention for vomiting and nausea. Other inclusion criteria were a Karnofsky performance score of ≥ 60 and a predicted life expectancy of ≥ 4 months. The goal of the study was to compare the drug combination of rolapitant + granisetron + dexamethasone with the dual combination of granisetron and dexamethasone.

Only the subpopulation of the study with moderately emetogenic chemotherapy was used for the present research question. All patients treated with AC-based chemotherapy were not included in this subpopulation. According to current guidelines, AC-based chemotherapies are

highly emetogenic chemotherapies (see Section 2.3). This research question also does not address patients receiving carboplatin-containing chemotherapy because the G-BA specified a different ACT for them, which was not implemented in the study. These subpopulations are addressed by research questions 1 and 2b. In the framework of the research question considered here, all information on the study population and on study results refer to the relevant subpopulation.

Study TS-P04834 was double-blind and included 1369 patients; the relevant subpopulation included 228 patients. Observation of all study participants was planned for the first cycle of their chemotherapy. Treatment and observation could then be continued for a maximum of 5 further cycles if the patients consented and the responsible investigator considered them suitable candidates.

In the TS-P04834 study, rolapitant was administered together with dexamethasone and the 5-HT3 receptor antagonist granisetron before initiation of the chemotherapy. Patients in the comparator arm of the study received dexamethasone and granisetron (+ placebo). In both arms, treatment was continued with granisetron on days 2 and 3.

Rolapitant is approved as part of a combination therapy. For moderately emetogenic chemotherapy, the SPC for rolapitant recommends a triple combination with a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by continued treatment with the 5-HT3 receptor antagonist as monotherapy on days 2 to 4 [7]. In the study, the 5-HT3 receptor antagonist granisetron was only administered for a total of 3 days, however. This deviation was not rated to be so serious as to raise doubts about the relevance of the study, however (see Section 2.7.2.4.1 of the full dossier assessment).

Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy)

Study **Outcome category** **Outcome**	**Planned follow-up**
TS-P04834	
Mortality	
All-cause mortality	Until 30 days after the end of study participation
Morbidity	
Vomiting	Until 120 hours after administration of chemotherapy (acute and delayed phase), all cycles
Nausea	Until 120 hours after administration of chemotherapy (acute and delayed phase), all cycles
Side effects	
All outcomes in the category "side effects"	Until 30 days after the end of study participation
RCT: randomized controlled trial; vs.: versus	

The observation period of the outcomes in the TS-P04834 study depended on the duration of participation. Vomiting and nausea were continuously recorded in each cycle until 120 hours after administration of chemotherapy, and adverse events (AEs) were continuously recorded until 30 days after the last study visit. See Section 2.7.2.4.3 of the full dossier assessment for detailed information on the recording of outcomes.

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy)

Study Characteristics Category	**Rolapitant + granisetron + dexamethasone**	**Placebo + granisetron + dexamethasone**
TS-P04834	N[a] = 130	N[a] = 98
Age [years], mean (SD)	60 (11.9)	59 (12.4)
Sex [F/M], %	73/27	69/31
Body weight [kg] mean (SD)	72.7 (17.7)	74.5 (20.4)
Ethnicity, n (%)		
Caucasian	103 (79.2)	73 (74.5)
Asian	16 (12.3)	18 (18.4)
Other[b]	11 (8.5)	7 (7.1)
Region, n (%)		
North America	66 (50.8)	41 (41.8)
Central and South America	4 (3.1)	1 (1.0)
Europe	45 (34.6)	38 (38.8)
Eastern Europe	26 (20.0[b])	19 (19.4[b])
Central Europe	15 (11.5[b])	13 (13.3[b])
Western Europe	4 (3.1[b])	6 (6.1[b])
Asia/South Africa	15 (11.5)	18 (18.4)
Alcohol consumption (drinks/week), n (%)		
0	107 (82.3)	78 (79.6)
> 0 to ≤ 5	19 (14.6)	13 (13.3)
> 5 to ≤ 10	1 (0.8)	3 (3.1)
> 10	3 (2.3)	4 (4.1)
Primary tumour site, n (%)		
Breast	63 (48.5)	47 (48.0)
Colon/rectum	38 (29.2)	26 (26.5)
Other[b]	29 (22.3)	25 (25.5)
Type of chemotherapy, n (%)[c]		
Cyclophosphamide	64 (49.2)[d]	44 (44.9)[d]
Irinotecan	39 (30.0)[d]	32 (32.7)[d]
Pemetrexed	14 (10.8)[d]	29 (29.6)[d]
Oxaliplatin	19 (14.6)[d]	15 (15.3)[d]
Doxorubicin	13 (10.0)[d]	14 (14.3)[d]
Epirubicin	6 (4.6)[d]	5 (5.1)[d]
Ifosfamide	2 (1.5)[d]	1 (1.0)[d]
Cisplatin (< 50 mg/m²)	0 (0.0)[d]	1 (1.0)[d]
Mitoxantrone	1 (0.8)[d]	0 (0.0)[d]

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy) (continued)

Study Characteristics Category	Rolapitant + granisetron + dexamethasone	Placebo + granisetron + dexamethasone
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: No delineation of individual subpopulations in the CSR; the numbers refer to the number of patients receiving moderately emetogenic chemotherapy, but not carboplatin or a combination of anthracycline and cyclophosphamide (intervention N = 124, control N = 94).
d: Referring to N = 130 vs. 98; multiple answers possible; percentage calculated by the Institute.
AE: adverse event; CSR: clinical study report; F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The study was randomized in a ratio of 1:1, but patients were unevenly distributed between the treatment arms of the analysed subpopulation. There were 130 patients in the rolapitant group, but only 98 patients in the comparator group. Since the type of chemotherapy was no stratification factor in the randomization, this deviation was presumably due to chance. The most important patient characteristics were comparable between the groups also in the subpopulation. The mean age of the participants was about 60 years. Most patients included were women (about 71%). About 80% of the patients reported that they did not consume alcohol.

A majority of about 77% of the patients were of Caucasian origin. Almost half of the participants were treated in North American centres (51% versus 42%). Another 37% of the participants were treated in centres in Europe.

Almost half of the subpopulation considered were women with primary tumour in the breast. The second most common entity were tumours in the colon or rectum, which occurred in almost 30% of the patients.

The most common cytostatic agent, which was used in almost 50% of the cases, was cyclophosphamide, followed by irinotecan, pemetrexed, oxaliplatin and doxorubicin, with the proportions differing greatly between the treatment groups particularly for pemetrexed (11% versus 30%). Pemetrexed is a cytostatic agent with low emetogenicity. It can be assumed that pemetrexed is mainly administered in combination with other moderately emetogenic drugs.

In its description of the patient characteristics, the company stated that 11% of the patients in the rolapitant group and 13% of the patients in the comparator group had not received any concomitant emetogenic chemotherapy. It is unclear what the company meant by this because

treatment with emetogenic chemotherapy had been an inclusion criterion of the study. In addition, the company's information was inconsistent and differed between the text and the table. According to the information provided in the clinical study report (CSR), there were only 3 patients in the total study population who did not receive emetogenic chemotherapy. It was not clear from the information provided by the company which other concomitant treatments were meant.

For the relevant subpopulation of the study, the company did not provide any information on patients who discontinued the study or the treatment.

Table 10 shows the number of patients who were included in the analysis in each chemotherapy cycle.

Table 10: Number of patients under observation – RCT, direct comparison: rolapitant + granisetron + dexamethasone vs. placebo + granisetron + dexamethasone (moderately emetogenic chemotherapy)

Study **Chemotherapy cycle**	**Rolapitant + granisetron + dexamethasone** **N (%)**	**Placebo + granisetron + dexamethasone** **N (%)**
TS-P04834	**N = 130[a]**	**N = 98[a]**
Cycle 1	130 (100)[a]	98 (100)[a]
Cycle 2	105 (81)[b]	77 (79)[b]
Cycle 3	92 (71)[b]	73 (74)[b]
Cycle 4	85 (65)[b]	69 (70)[b]
Cycle 5	46 (35)[b]	38 (39)[b]
Cycle 6	43 (33)[b]	35 (36)[b]

a: mITT population: all patients who received at least 1 dose of the study medication.
b: mITT population for subsequent cycles: all patients who received at least 1 dose of the study medication in the respective cycle.
mITT population: modified intention-to-treat population; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

The number of patients under observation decreased over several chemotherapy cycles. In the sixth cycle, only about 1 third of the patients were still in the analysis. The company did not mention the reasons for discontinuation for the relevant subpopulation in Module 4 A of the dossier. It can be inferred from the CSR that about half of the patients in the total population who discontinued the study dropped out before the sixth cycle because their chemotherapy had ended or a different treatment had been initiated. It is unknown to what extent the reasons for discontinuation can be transferred to the subpopulation considered.

2.4.2 Risk of bias

Overall, the data of the TS-P04834 study were not usable for the present assessment. The reason for this is that too many patients had discontinued the study starting from the second

cycle so that the results were considered not interpretable. This is explained below. The data of the first cycle alone are not sufficient for the derivation of an added benefit.

The TS-P04834 study was designed to observe all patients during the first chemotherapy cycle. Study participants could be observed beyond the first cycle if they consented and the investigator considered there to be no reasons against continued treatment. Blinding of study participants and treating staff was maintained.

There was no information for the present subpopulation about the reasons why patients discontinued the study. The number of patients who were included in the subsequent cycles could be inferred from the information in the dossier, however. As shown in Table 10, about 20% of the patients dropped out of the study during and after the first cycle. It cannot be excluded that this percentage included mostly patients who had already suffered from severe nausea and vomiting in the first cycle and who therefore would have had a high risk of nausea and vomiting also in the subsequent cycles. This is also suggested by the data on the outcomes “nausea” and “vomiting”. In the relevant subpopulation, the proportions of patients (in relation to the number of those who were still under observation in the respective cycle) with at least 1 event were largest in the first chemotherapy cycle for both outcomes (vomiting: 19% versus 34%; nausea: 51% versus 56%). The respective event rates were notably lower in the subsequent cycles (cycle 2 – vomiting: 8% versus 10%; nausea: 13% versus 17%, see Appendix A of the full dossier assessment). On the basis of the available information, it can therefore not be excluded that there was a large extent of informative censorings starting with the second cycle. As a result, the data on all outcomes for the cycles 2 to 6 are not interpretable.

Since patients usually receive several chemotherapy cycles, it is particularly relevant for the benefit assessment whether an antiemetic effect is maintained across several cycles. The sole consideration of results on the first cycle is therefore inadequate for the assessment of the added benefit. This was also determined by the G-BA in the decision on the benefit assessment procedure of netupitant/palonosetron [8].

Overall, no conclusion on the added benefit of rolapitant in comparison with the ACT in moderately emetogenic chemotherapy can be drawn on the basis of the available data from the TS-P04834 study.

2.4.3 Results on added benefit

In its dossier, the company presented no usable data for the assessment of the added benefit of rolapitant for research question 2a. This resulted in no hint of an added benefit of rolapitant in comparison with the ACT; an added benefit is therefore not proven.

The results of the study are presented as additional information in Appendix A, Appendix B and Appendix C of the full dossier assessment. The patient relevance of the outcomes recorded is presented in Section 2.7.2.4.3 of the full dossier assessment.

2.4.4 Probability and extent of added benefit

The results of the TS-P04834 study were considered not interpretable (see Section 2.4.2). It cannot be excluded that there was selective exclusion of patients after the first chemotherapy cycle. The results of cycles 2 to 6 were therefore not meaningfully interpretable. An assessment based on the first cycle alone is insufficient for the derivation of the added benefit of rolapitant, however, because chemotherapy is usually administered for several cycles.

An added benefit of rolapitant + granisetron + dexamethasone in comparison with placebo + granisetron + dexamethasone for patients with moderately emetogenic chemotherapy is therefore not proven.

This assessment deviates from that of the company, which derived an indication of a minor added benefit for patients receiving moderately emetogenic chemotherapy (except carboplatin).

The company mainly justified its assessment with the analyses of outcomes that were only recorded during the first chemotherapy cycle and some of which were not patient-relevant (complete response, no vomiting, time to first vomiting or use of rescue medication, complete protection, health-related quality of life [recorded with the Functional Living Index – Emesis (FLIE) questionnaire]).

The G-BA decides on the added benefit.

2.4.5 List of included studies

TS-P04834

Hesketh PJ, Schnadig ID, Schwartzberg LS, Modiano MR, Jordan K, Arora S et al. Efficacy of the neurokinin-1 receptor antagonist rolapitant in preventing nausea and vomiting in patients receiving carboplatin-based chemotherapy. Cancer 2016; 122(15): 2418-2425.

Schwartzberg LS, Modiano MR, Rapoport BL, Chasen MR, Gridelli C, Urban L et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol 2015; 16(9): 1071-1078.

Tesaro. Ph 3 safety/efficacy study of rolapitant for prevention of CINV in subjects receiving moderately emetogenic chemotherapy: full text view [online]. In: ClinicalTrials.gov. 02.02.2016 [Accessed: 22.06.2017]. URL: https://ClinicalTrials.gov/show/NCT01500226.

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Tesaro. A phase 3, multicenter, randomized, double-blind, active-controlled study of the safety and efficacy of rolapitant for the prevention of chemotherapy- induced nausea and vomiting (CINV) in subjects receiving moderately emetogenic chemotherapy (MEC) [online]. In: EU Clinical Trials Register. [Accessed: 22.06.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-022746-24.

Tesaro. A phase 3, multicenter, randomized, double-blind, active-controlled study of the safety and efficacy of rolapitant for the prevention of chemotherapy- induced nausea and vomiting (CINV) in subjects receiving moderately emetogenic chemotherapy (MEC) [online]. In: Clinical Trials Peruvian Registry. [Accessed: 22.06.2017]. URL: http://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=056-12.

Tesaro. A phase 3, multicenter, randomized, double-blind, active-controlled study of the safety and efficacy of rolapitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in subjects receiving moderately emetogenic chemotherapy (MEC): study TS-P04834; Zusatzanalysen [unpublished]. 2017.

Tesaro. A phase 3, multicenter, randomized, double-blind, active-controlled study of the safety and efficacy of rolapitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in subjects receiving moderately emetogenic chemotherapy (MEC): study TS-P04834; clinical study report [unpublished]. 2014.

2.5 Research question 2b: moderately emetogenic chemotherapy with carboplatin

2.5.1 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 rolapitant (status: 19 April 2017)
- bibliographical literature search on rolapitant (last search on 19 April 2017)
- search in trial registries for studies on rolapitant (last search on 19 April 2017)

To check the completeness of the study pool:

- search in trial registries for studies on rolapitant (last search on 20 June 2017)

Study pool of the company

For the assessment of the added benefit in this research question, the company included patients of the TS-P04834 study who received carboplatin-containing chemotherapy. The subpopulation of the study was not relevant for the derivation of an added benefit in the present research question, however, because the ACT was not implemented.

The ACT for carboplatin-containing chemotherapy was a triple combination of an NK-1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone on day 1, followed by dexamethasone or aprepitant (see Section 2.2). However, all patients in the comparator arm of the TS-P04834 study were treated with a dual combination of granisetron and dexamethasone (+ placebo), followed by granisetron on days 2 to 3 (a detailed description of the TS-P04834 study can be found in Section 2.4.1).

The company noted that, according to current German guidelines, more intense prevention than in other moderately emetogenic chemotherapy was only indicated for a carboplatin concentration of AUC (area under the curve) ≥ 4 because randomized studies were only available for this subindication [9]. However, the company itself described that this criterion was fulfilled for the present carboplatin subpopulation and that intensified prevention was indicated for the patients. According to the company, the mean AUC of carboplatin in both study arms was 5.1. In addition, the G-BA did not distinguish the ACT by carboplatin dosage. The MASCC and ESMO guideline [6] also recommends additional prevention with an NK-1 receptor antagonist, irrespective of the dose used.

Correspondingly, the data of the carboplatin subpopulation were not relevant and there were overall no relevant data for research question 2b.

2.5.2 Results on added benefit

The company presented no relevant data for research question 2b. Hence, there was no hint of an added benefit of rolapitant in comparison with the ACT in patients treated with carboplatin-containing chemotherapy. An added benefit for this research question is not proven.

2.5.3 Probability and extent of added benefit

The company presented no relevant data for the assessment of the added benefit of rolapitant in patients receiving carboplatin-containing chemotherapy. An added benefit for these patients is therefore not proven.

This assessment deviates from that of the company. The company derived an indication of a non-quantifiable added benefit of rolapitant for patients receiving carboplatin-containing chemotherapy.

2.5.4 List of included studies

Not applicable as the company presented no relevant data for this research question.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of rolapitant in comparison with the ACT is summarized in Table 11.

Table 11: Rolapitant – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Prevention of delayed nausea and vomiting after ▪ highly emetogenic chemotherapy	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4; aprepitant is additionally given on days 2 to 3 (if aprepitant on day 1; not applicable to fosaprepitant on day 1).	Added benefit not proven
2a	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy	Dual combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + dexamethasone The dual combination is administered on day 1 before chemotherapy. After day 1, prevention is continued either with the 5-HT3 receptor antagonist (except palonosetron), if appropriate in combination with dexamethasone, or with dexamethasone monotherapy.	Added benefit not proven
2b	Prevention of delayed nausea and vomiting after ▪ moderately emetogenic chemotherapy with carboplatin	Triple combination of: serotonin antagonist[b] (ondansetron or **granisetron** or tropisetron or palonosetron) + NK-1 receptor antagonist (aprepitant or **fosaprepitant**) + dexamethasone The triple combination is administered on day 1 before chemotherapy. Prevention is continued with dexamethasone on days 2 to 4 or with aprepitant on days 2 to 3 (if aprepitant on day 1).	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**.
b: Referred to as "5-HT3 receptor antagonist" in the assessment.
5-HT3: 5-hydroxytryptamine; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NK-1: neurokinin-1

An added benefit of rolapitant is not proven for patients receiving highly or moderately emetogenic chemotherapy (with or without carboplatin).

This assessment deviates from that of the company. For research question 1, the company derived proof of a non-quantifiable added benefit (cisplatin-containing highly-emetogenic chemotherapy) and an indication of a non-quantifiable added benefit (AC-based chemotherapy). The company derived an indication of a minor added benefit for research question 2a and an indication of a non-quantifiable added benefit for research question 2b.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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