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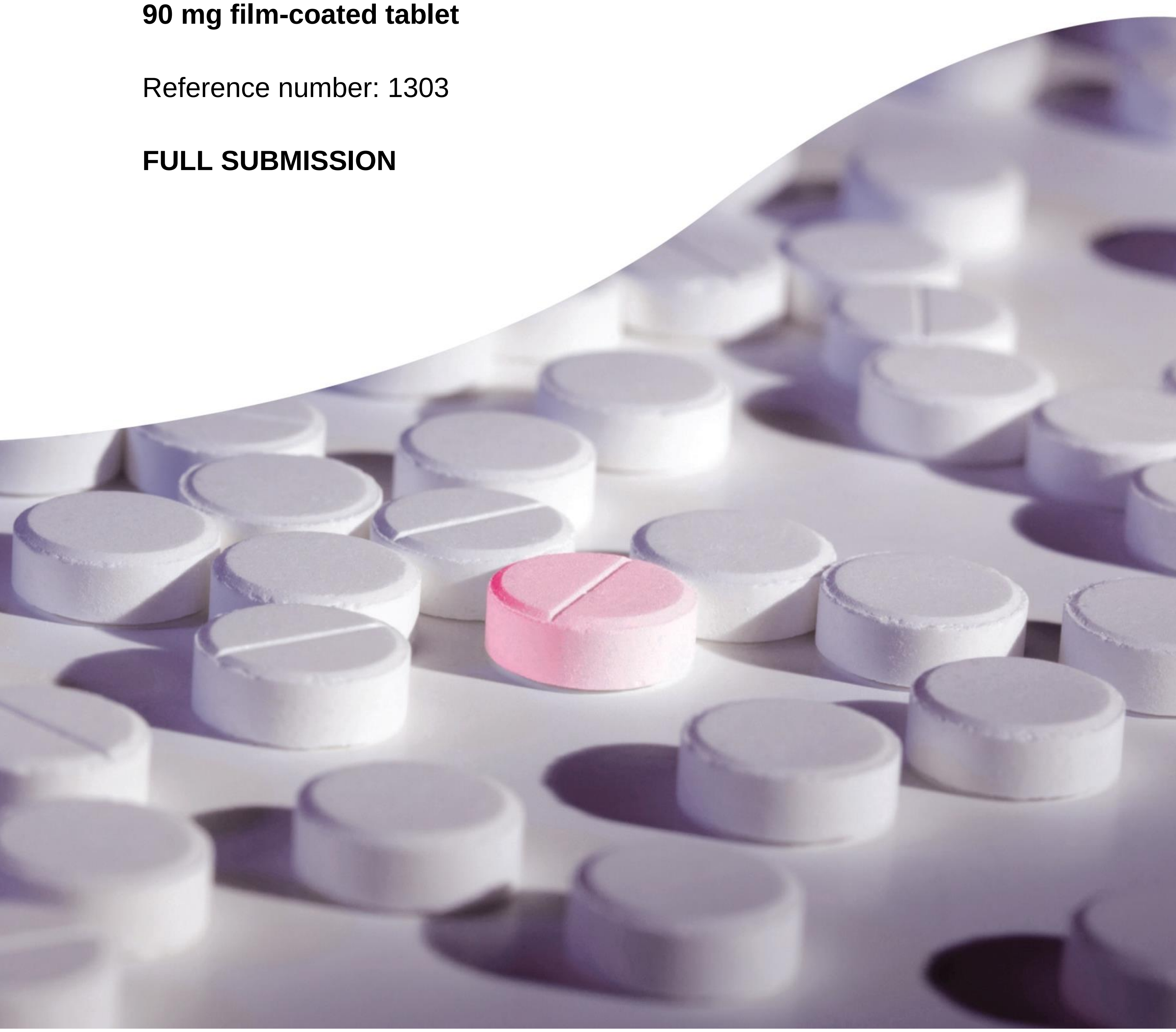
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Rolapitant (Varuby®)
90 mg film-coated tablet

Reference number: 1303

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Rolapitant (Varuby®) 90 mg film-coated tablet. Reference number: 1303. January 2018.

AWMSG Secretariat Assessment Report
Rolapitant (Varuby®▼) 90 mg film-coated tablet

This assessment report is based on evidence submitted by Tesaro UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Rolapitant (Varuby®▼) for the prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Varuby is given as part of combination therapy[2]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Dosing	Rolapitant is given as part of a regimen that includes dexamethasone and a 5-HT_3 receptor antagonist. 180 mg (two tablets) should be given within two hours before initiation of each chemotherapy cycle, but at no less than two-week intervals. Refer to the Summary of Product Characteristics for further dosing information[2].
Marketing authorisation date	20 April 2017[3]

2.0 DECISION CONTEXT

2.1 Background

Chemotherapy-induced nausea and vomiting (CINV) plays a significant role in cancer patients' morbidity, and is associated with significant clinical, social and economic burden[3]. It can interfere with treatment adherence as well as have a negative impact on quality of life and daily functioning, leading to increased healthcare costs[3].

Chemotherapy regimens can be classified based on their emetogenic potential: highly emetic (> 90% risk of emesis), moderately emetic (30–90% risk of emesis), low emetogenicity (10–30% risk of emesis) and minimally emetic (< 10% risk of emesis)[3,4]. Nausea and vomiting can be either acute (≤ 24 hours after chemotherapy) or delayed (> 24 hours after chemotherapy, usually 2–5 days following initiation of chemotherapy)[3]. Despite the availability of effective prevention therapies, some patients still suffer with CINV, particularly during the delayed phase of chemotherapy[3].

Delayed emesis involves the production of substance P, which binds to neurokinin-1 receptors in the vomiting centre of the brain, leading to nausea and vomiting[3]. Rolapitant is a potent, selective, competitive neurokinin-1 receptor antagonist (NK_1RA) with no known activity at other pharmacological targets. It is given as part of a regimen that includes a 5-HT_3 receptor antagonist and dexamethasone (double therapy)[3].

The company has requested that the All Wales Medicines Strategy Group (AWMSG) consider rolapitant for use in the following subpopulations:

- Cisplatin-based highly emetogenic chemotherapy (HEC) as a first-line option.
- Carboplatin-based moderately emetogenic chemotherapy (MEC), in line with international guidelines[4], where patients currently only receive double therapy. The company suggest focusing on this subpopulation in order to reduce the budget impact on NHS Wales.

The Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) antiemetic guideline recommends that people receiving HEC are given an NK_1RA and double therapy before chemotherapy[4], which is in line with Welsh guidelines[5,6]. For people receiving carboplatin-based MEC, the MASCC/ESMO guideline recommends an NK_1RA plus double therapy[4]; currently for all MEC regimens, Velindre Trust and Betsi Cadwaladr Health Board guidelines recommend double therapy only[5,6].

2.2 Comparators

The main comparators included in the company submission are:

- aprepitant (in combination with double therapy) for cisplatin-based HEC
- placebo (in combination with double therapy) for carboplatin-based MEC.

Aprepitant was used as a comparator in the network meta-analysis (NMA) and health economics model only; the pivotal clinical studies were versus placebo.

2.3 Guidance and related advice

- American Society of Clinical Oncology (ASCO). Antiemetics (2017)[7].
- National Comprehensive Cancer Network. Insights: Antiemesis guidelines, Version 2 (2017)[8].
- Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO). Antiemetic Guideline (2016)[4].

AWMSG has previously issued a recommendation for the use of netupitant/palonosetron (NEPA; Akynzeo®) in 2016[9]. Aprepitant (Emend®) has not been appraised previously by AWMSG for use in adults due to meeting AWMSG exclusion criteria (granted marketing authorisation prior to 1 October 2010[10]).

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The All Wales Therapeutics and Toxicology Centre (AWTTC) critiqued three phase III studies: in two of the studies patients received HEC (HEC-1 and HEC-2)[11], and in the other study patients received MEC (NCT01500226)[12]. All three studies were placebo-controlled and did not include an NK_1RA as a comparator. The company submission includes a post-hoc analysis of the MEC study for patients who received carboplatin-based therapy[13]. An NMA was conducted to compare rolapitant versus other NK_1RAs[1]. The company submission also highlights a phase II dose-finding study[14], which will not be discussed in detail here, but was included in the NMA.

3.1 HEC-1 and HEC-2

HEC-1 and HEC-2 were two multicentre, randomised, double-blind phase III studies designed to assess the efficacy and safety of 180 mg rolapitant for prevention of CINV with cisplatin-based HEC[11]. The studies were carried out at 155 cancer centres in 26 countries, including the US and Europe[11]. Both studies shared common design features, including the same inclusion and exclusion criteria, rolapitant dosing regimen, comparator regimen, primary and secondary endpoints, and statistical methodology. The studies included patients aged ≥ 18 years old, with a wide range of solid tumours and a predicted life expectancy of four months or longer. Patients did not have to be treatment-naive but were scheduled to receive their first course of cisplatin-based chemotherapy[3,11].

Patients (combined population of both studies, n = 1,087) were randomised 1:1 to have either 180 mg rolapitant or placebo 1–2 hours before receiving HEC (day 1)[11]. Both the rolapitant and placebo groups also received intravenous granisetron (10 micrograms/kg) plus oral dexamethasone (20 mg) approximately 30 minutes before HEC, and 8 mg oral dexamethasone twice-daily after HEC (days 2–4)[11]. At the end of cycle 1, eligible patients could continue the same therapy regimen for up to five additional cycles. Every cycle was a minimum of 14 days[11]. Patients could be prescribed rescue medications at any time when medically indicated, or withdraw from the study and receive aprepitant with subsequent chemotherapy cycles[11].

The primary endpoint was the proportion of patients achieving a complete response in the delayed phase (> 24–120 hours after chemotherapy) in cycle 1 (n = 1,070)[11]. A complete response was defined as no emesis or use of rescue medication (with or without nausea)[11]. Patients recorded all events of vomiting and use of rescue medication in a daily diary during the 120 hour study period[11]. In HEC-1, HEC-2 and the pooled data, the rolapitant group had a significantly greater proportion of complete responders in the delayed phase compared with placebo (Table 1)[11]. Secondary endpoints included complete response in the overall phase (0–120 hours), where the rolapitant group had significantly greater complete response than placebo in the pooled analysis.

Table 1. Primary and secondary endpoints for HEC-1 and HEC-2[11]

	Complete response*		OR (95% CI)	p-value†
	Rolapitant	Placebo		
Primary endpoint: Delayed phase (> 24–120 hours after chemotherapy)				
HEC-1	192/264 (73%)	153/262 (58%)	1.9 (1.3 to 2.7)	0.0006
HEC-2	190/271 (70%)	169/273 (62%)	1.4 (1.0 to 2.1)	0.0426
Pooled HEC-1/HEC-2	382/535 (71%)	322/535 (60%)	1.6 (1.3 to 2.1)	0.0001
Secondary endpoint: Complete response during the overall phase (0–120 hours)				
Pooled HEC-1/HEC-2	368/535 (69%)	313/535 (59%)	1.6 (1.2 to 2.0)	0.0005

*Complete response is defined as no emesis and no rescue medication.
†Unadjusted p-values
CI: confidence intervals; OR: odds ratio.

On day six of cycle 1, patients completed the Functional Living Index-Emesis (FLIE) questionnaire, which was used to measure the effect of CINV on daily life[11]. The proportion of patients who reported no effect on daily life (defined as a FLIE score of more than 108) did not differ between rolapitant and placebo groups in the pooled studies[11]. However, the rolapitant group did have a significantly improved FLIE score versus placebo overall (114.5 versus 109.3, p < 0.001)[1].

3.2 MEC study (NCT01500226)

The MEC study was a multicentre, randomised, double-blind trial phase III study designed to assess the efficacy and safety of 180 mg rolapitant for prevention of CINV with MEC[12]. The study was carried out at 170 study sites in 23 countries, including the US and Europe. Inclusion criteria were similar to the HEC studies, with the exception that patients were ineligible if they had previously received chemotherapy. Patients were scheduled to receive their first course of MEC, including one or more of the following agents: intravenous cyclophosphamide, doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or intravenous cytarabine[12].

Patients (n = 1,369) were randomised 1:1 to receive either 180 mg rolapitant or placebo 1–2 hours before chemotherapy (day 1)[12]. Both the rolapitant and placebo groups also received oral granisetron (2 mg) plus oral dexamethasone (20 mg) about 30 minutes before chemotherapy and 2 mg oral granisetron once-daily after chemotherapy (days 2–3). At the end of cycle 1, a similar protocol was applied to eligible patients with regards to subsequent treatment. The choice of rescue therapy administered, once a patient was withdrawn from the study, was at the discretion of the treating physician[12].

A post-hoc analysis was performed on the subpopulation of patients in the MEC study who received carboplatin-based chemotherapy (n = 401)[13]. The rolapitant group had a significantly higher complete response rate in cycle 1 compared with placebo during both the delayed phase and the overall phase (Table 2). The proportion of patients who reported no impact on daily life in the FLIE questionnaire did not significantly differ between the rolapitant and placebo groups[13].

Table 2. Primary and secondary endpoints for carboplatin-based moderately emetogenic chemotherapy[12]

	Complete response*		p-value†
	Rolapitant (n = 192)	Placebo (n = 209)	
Primary endpoint			
Delayed phase (> 24–120 hours after chemotherapy)	158 (82.3%)	137 (65.6%)	< 0.001
Secondary endpoint			
Overall phase (0–120 hours after chemotherapy)	154 (80.2%)	135 (64.6%)	< 0.001
*Complete response is defined as no emesis and no rescue medication. †Unadjusted p-values			

3.3 Network meta-analyses (NMA)

To address the lack of direct comparative evidence, the company submitted a systematic review and NMA to estimate the relative efficacy and safety of rolapitant compared to existing combination treatments for the prevention of CINV after receiving MEC or HEC[1].

The systematic review included randomised controlled trials of adult patients undergoing MEC or HEC that were published up to November 2016[1]. The intervention of interest for the review was rolapitant in combination with any double therapy. The comparators of interest used in the search strategy included any NK_1RA with double therapy and double therapy only[1].

Outcomes in the review included complete response, complete protection (defined as no emesis, no rescue medication and no clinically significant nausea [< 25 mm on the visual analogue scale]), mortality, adverse events and treatment discontinuation[1]. Outcomes were extracted for delayed, acute and overall phases. Results were presented as odds ratios and 95% credible intervals; results were considered to show a difference if the credible intervals did not include 1[1].

3.3.1 HEC

An NMA was conducted for patients receiving cisplatin-based HEC[1]. Of the 13 studies included in the network analysis for complete response, two included rolapitant: the phase II dose-finding study (rolapitant with ondansetron plus dexamethasone)[14] and the phase III pooled HEC-1/HEC-2 studies (rolapitant with granisetron plus dexamethasone)[11]. The comparator NK_1RAs included aprepitant, fosaprepitant and netupitant (as NEPA). The 5-HT_3 receptor antagonists included were ondansetron, granisetron and palonosetron. No differences were observed between rolapitant and the comparator treatments for overall complete response (Table 3). Complete protection was also assessed; where comparison was possible no differences were observed between rolapitant versus aprepitant or placebo[1].

Table 3. Network meta-analysis results for cisplatin-based highly emetogenic chemotherapy[1]

[Commercial in confidence table removed.]

3.3.2 MEC

An NMA was performed for patients receiving carboplatin-based MEC[1]. Two studies were included in the analysis: one was the rolapitant MEC study (NCT01500226). No differences were observed between rolapitant compared to two other comparator treatments (aprepitant and placebo) for overall complete response. No network could be formed to assess complete protection[1].

3.4 Comparative safety

No direct comparative safety data are available for rolapitant and the relevant comparators. Studies assessing rolapitant were pooled to assess safety in 1,294 patients who received rolapitant at the licensed dose and 1,301 patients who received placebo[3]. Committee for the Medicinal Products for Human Use reported that adverse events associated with rolapitant were manageable and in line with those usually observed with antiemetic therapy. Treatment-related adverse events were comparable between rolapitant and placebo groups in cycle 1, with fatigue (1.9% versus 1.4%), constipation (1.5% versus 1.5%) and headache (1.5% versus 1.4%) being the most common events listed[3].

The company submitted an NMA for safety outcomes to address the lack of comparative safety evidence[1]. No differences in adverse events and discontinuations were observed between rolapitant and the comparators (aprepitant, fosaprepitant, netupitant and placebo) for cisplatin-based HEC. There was also no difference observed for serious adverse events, but rolapitant could only be compared with aprepitant or placebo for this outcome. Comparisons of adverse events and discontinuations were not possible for MEC (carboplatin-based or non-anthracycline/cyclophosphamide) as a network could not be formed for these outcomes. However, no differences were seen in MEC for serious adverse events with rolapitant compared to aprepitant or placebo[1].

3.5 AWTTC critique

- In their submission, the company has highlighted two specific subpopulations within the licensed indication of rolapitant: people who are given cisplatin-based HEC as a first-line treatment and people who are given carboplatin-based MEC.
- The rolapitant studies for cisplatin-based HEC used placebo (plus granisetron and dexamethasone) as the comparator, rather than an active NK_1RA. Therefore, only indirect comparisons with other NK_1RAs is possible. Indirect methods such as NMAs increase the uncertainty of relative treatment effects.
- Although the methodology used to inform the NMA was robust, evidence to inform the analyses was limited, particularly for the carboplatin-based MEC population. Systematic differences in baseline patient or study characteristics that might impact on results were not reported and their influence on the results does not appear to have been explored. Assessment of the quality of the included studies identified risks of bias; incomplete outcome data and unclear allocation concealment were the main areas of concern across all the studies. The NMA

found no significant differences between rolapitant and aprepitant (for HEC) or between rolapitant and placebo (for MEC), but many estimates of effectiveness have wide credible intervals, indicating considerable uncertainty around the effectiveness of rolapitant compared to the comparators.

- Based on international guidelines, the company propose the use of rolapitant (an NK_1RA) as an add on to double therapy for carboplatin-based MEC[4]. AWTTC-sought clinical opinion suggests that the majority of patients receiving carboplatin do not need add-on NK_1RAs, but a small amount of patients may receive NK_1RAs as secondary prophylaxis.
- The company suggests the NK_1RA aprepitant (with ondansetron plus dexamethasone) as the appropriate comparator for cisplatin-based HEC. AWMSG recommended NEPA (Akynzeo®) for HEC in 2016[9], which is a fixed-dose combination of $NK_1RA/5HT_3$ receptor antagonist. The company states that since NEPA is new to the market they did not propose it as a comparator. Netupitant is included in more recently published, international guidelines[4]. Clinical expert opinion sought by AWTTC confirmed that NEPA is available for HEC or for secondary prophylaxis.
- At present, the MASSC/ESMO guidelines state there are no comparative studies available to identify differences in efficacy and toxicity between the NK_1RAs[4]; therefore, the choice of medicine may be dependent on the respective convenience and cost.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes two cost–utility analyses (CUAs). The first CUA compares rolapitant with aprepitant as part of a first-line regimen for preventing CINV in patients receiving cisplatin-based HEC. The second compares rolapitant in combination with double therapy versus double therapy alone for patients receiving carboplatin-based MEC. A cost-minimisation analysis was also submitted for HEC but this will not be discussed in any detail; its plausibility is considered in the scenario analyses section (see Table 6).

The CUAs take the form of a simple decision tree with four possible outcomes: complete protection (no vomiting, nausea < 25 mm as measured by patients on a visual analogue scale and no rescue medication), complete response with nausea (no vomiting, no rescue medication, but significant nausea [> 25 mm on a visual analogue scale]), incomplete response without rescue (vomiting, no use of rescue medication), and incomplete response with rescue (vomiting and use of rescue medication). Complete response (the primary endpoint) in the clinical studies, comprises complete response with nausea and complete protection. The models adopt an NHS Wales and Personal Social Services perspective, and a five-day time horizon to correspond with the five-day CINV at-risk period that occurs on the first five days of a chemotherapy cycle.

Cost of treatment in the models includes medicine acquisition costs and CINV-related healthcare costs, including: telephone consultations (£27), A&E visits (£117.85) and hospitalisation (£1,345.85). Acquisition costs are calculated using dosing information detailed in Betsi Cadwaladr University Health Board guidelines[6]. Unit costs are sourced from the British National Formulary (BNF)[15] or the Drug Tariff[16]. The model uses list prices for all medicines except rolapitant, which is associated with a Welsh patient access scheme (WPAS). Patients who require rescue medication incur the cost of metoclopramide and domperidone. CINV-related healthcare costs are informed by a variety of sources. Resource use for patients with an incomplete response are derived from the analysis of hospital episode statistics for 2016 in chemotherapy patients admitted for nausea and vomiting within seven days of chemotherapy[17]. The model uses estimates of [commercial in confidence figure removed] of patients presenting to A&E within seven days of chemotherapy and [commercial in confidence figure removed] of patients who are admitted directly to hospital. A study exploring the healthcare costs of CINV across France, Germany and Italy informed the proportion of patients seeking telephone advice[18]. The study found 16.8% of patients required telephone consultation. The model assumes this applies to all patients with an incomplete response (regardless of whether rescue medication is taken). It is further assumed that patients with a complete response require 50% of the resource for telephone consultations as patients with an incomplete response and that patients with complete protection do not require this contact. Unit costs for CINV-related healthcare resource use are taken from the Personal Social Services Research Unit[19] and NHS reference costs[20].

The treatment effects of rolapitant and comparators for the HEC population are informed by an NMA using a Bayesian random effects model (see Section 3.3). In contrast, the treatment effects for the MEC population are informed by head-to-head trial data. Health state utilities are taken from published literature including an economic evaluation of NEPA[21] and two evaluations of aprepitant[22,23]. These evaluations are informed by prior research into utility values for patients experiencing CINV and these values are adapted where necessary to accommodate differences in research design and clinical expert opinion[24,25]. The base case uses health state utilities of 0.90, 0.70 and 0.24 for complete protection, complete response with nausea and incomplete response (with or without rescue), respectively. No utility decrements have been modelled for adverse events of treatment.

Sensitivity and scenario analyses test the influence of parameter and structural uncertainty on the robustness of the base case results. These explore the impact of varying the odds ratios, duration of the CINV at-risk period, utility values, treatment costs, treatment regimens and comparators. Exploration of alternative comparators (fosaprepitant and NEPA) also includes sensitivity analyses to explore the impact of a WPAS for NEPA.

4.1.2 Results

The CUA base case results (detailed in Table 4) reveal that the point estimate for the HEC population falls within the south west quadrant of the cost-effectiveness plane (i.e. rolapitant is shown to be less costly, but also less effective than aprepitant), producing an incremental cost effectiveness ratio (ICER) of [commercial in confidence figure removed]. In the south west quadrant, an ICER > £20,000 saved per quality-adjusted life-year (QALY) forgone is generally desirable. For the carboplatin-based MEC population, the ICER reported is [commercial in confidence figure removed] per QALY gained (north east quadrant, more costly but more effective than placebo). However, there is considerable uncertainty surrounding these results (see below and Section 4.1.3 for further details).

Table 4. Results of the base case analyses

	Rolapitant	Comparator	Difference
Cisplatin-based HEC population: comparator aprepitant (plus double therapy*)			
Total costs	¶¶	¶¶	¶¶
Total QALYs	0.0094	0.0096	−0.0002
ICER (£/QALY gained)	¶¶†		
Carboplatin-based MEC population: comparator double therapy* only			
Total costs	¶¶	¶¶	¶¶
Total QALYs	0.010	0.009	0.001
ICER (£/QALY gained)	¶¶		

¶¶: commercial in confidence figure removed.
*Double therapy made up of a $5HT_3$ receptor antagonist plus dexamethasone.
†The point estimate falls in the south west quadrant – therefore an ICER > £20,000 saved per QALY forgone is desirable
HEC: highly emetogenic chemotherapy; ICER: incremental cost effectiveness ratio; MEC: moderately emetogenic chemotherapy; QALY: quality-adjusted life-year.

The results of the sensitivity analyses show that the base case findings are generally most sensitive to the aprepitant odds ratio for the HEC population. For the carboplatin-based MEC population, the findings are most sensitive to the proportion of patients experiencing complete response for both treatments and the duration of the CINV at-risk period. The scenario analyses give ICERs ranging between [commercial in confidence figure removed] (in the south west quadrant) for the cisplatin-based HEC population, and [commercial in confidence figures removed] (in the north east quadrant) for the carboplatin-based MEC population (Table 5). Deterministic analysis of patient access scheme discounts for NEPA suggest that rolapitant remains a worthwhile treatment option when a discount of up to [commercial in confidence figure removed] is applied. However, at a [commercial in confidence figure removed] discount, the ICER falls below the desired £20,000 saving per QALY forgone threshold.

Probabilistic sensitivity analysis shows that at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, rolapitant has a [commercial in confidence figures removed] chance of being the most cost effective treatment option for the cisplatin-based HEC population, respectively. Applying the same willingness-to-pay thresholds for the carboplatin-based MEC population, rolapitant has a [commercial in confidence figures removed] chance of being the most cost effective treatment option, respectively. Notably, when probabilistic analyses are conducted, rolapitant is found to be the dominant treatment option for the cisplatin-based HEC (less costly and more effective), and an ICER of [commercial in confidence figure removed] for the carboplatin-based MEC population is estimated. The findings for the HEC population are notably different to the deterministic base case results. This can be attributed to the marked differences between the mean and median point estimates derived from the different methods of analysis.

To conclude, the simulation data reveals that [commercial in confidence figure removed] of the ICER estimates for the carboplatin-based MEC population fall within north east quadrant of the cost-effectiveness plane (i.e. additional costs for QALY gains). In contrast, the cisplatin-based HEC population ICER estimates are markedly dispersed: [commercial in confidence figure removed] fall in the south east quadrant (costs saved for QALYs gained; rolapitant dominates); [commercial in confidence figure removed] fall in the south west quadrant (costs saved for QALYs forgone); [commercial in confidence figure removed] fall in the north west quadrant (additional costs for QALYs forgone; rolapitant is dominated); and [commercial in confidence figure removed] fall in the north east quadrant (additional costs for QALYs gained). This variability is indicative of the uncertainty associated with the comparative results for this population. Treatment effects used in the model are relatively comparable which makes the ICER highly sensitive to exploration of treatment effects.

Table 5. Results of scenario analyses for the moderately and highly emetogenic chemotherapy populations

Scenarios	ICER/Cost difference	PSA WTP £20,000	PSA WTP £30,000	Plausibility
Scenario 1: Velindre cancer care guidelines a) Cisplatin-based HEC population b) Carboplatin-based MEC population	¶¶	¶¶	¶¶	This scenario offers a plausible alternative to the base case for patient being treated according to Velindre cancer care guidelines.
Scenario 2: alternative utility values and Betsi Cadwaladr cancer care guidelines a) Grunberg 1996 for cisplatin-based HEC population b) Grunberg 1996 for carboplatin-based MEC population c) Sun 2004 for cisplatin-based HEC population d) Sun 2004 for carboplatin-based MEC population	¶¶	¶¶	¶¶	There is notable uncertainty surrounding utility values; these scenarios offer possible alternatives to the base case, but remain uncertain.
Scenario 3: alternative utility values and Velindre cancer care guidelines a) Grunberg 1996 for cisplatin-based HEC population b) Grunberg 1996 for carboplatin-based MEC population c) Sun 2004 for cisplatin-based HEC population d) Sun 2004 for carboplatin-based MEC population	¶¶	¶¶	¶¶	There is notable uncertainty surrounding utility values; these scenarios offer possible alternatives to the base case, but remain uncertain.
Scenario 4: Cisplatin-based HEC population CMA - comparator aprepitant	¶¶			AWTTC considers a CUA to be a more suitable approach to CMA in this instance, given lack of equivalence evidence and the limitations of the NMA conducted. These CMA results are therefore not considered a plausible alternative for decision making to the CUA base case.

¶¶: commercial in confidence figures removed.
*The point estimate for these ICERs fall in the south west quadrant – therefore an ICER > £20,000 saved per QALY forgone is desirable
CMA: cost minimisation analysis; CUA: cost utility analysis; HEC: highly emetogenic chemotherapy; ICER: incremental cost-effectiveness ratio; MEC: moderately emetogenic chemotherapy; NMA: network meta-analysis; PSA: probabilistic sensitivity analysis; WTP: willingness-to-pay.

4.1.3 AWTTC critique

The strengths and limitations of the CUAs are listed below.

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the base case analysis.
- A variety of scenarios and sensitivity analyses have been considered to test the robustness of the base case results.
- The submission includes a probabilistic sensitivity analysis using 60,000 simulations from the NMA to complement the base case. Given the heterogeneity amongst the studies included in the NMA for the HEC population and the variability demonstrated by the credible intervals, this approach offers a valuable alternative for this population, which is able to account for the skew in the distribution of the estimated odds ratios from the NMA.

Limitations:

- The comparative efficacy of treatments for the HEC population is informed by the NMA. The company acknowledge the limitations of the NMA in this instance and suggest that the results should be treated with caution. There is notable heterogeneity between studies included in the NMA in terms of design and populations; this has resulted in wide credible intervals and uncertainty, which has implications for the dependability of the CUA results.
- The studies used in the NMA and the Summary of Product Characteristics guidance describe treatment regimens that are different to those used in the model, in terms of dexamethasone dose and type of 5-HT_3 receptor antagonist used. The use of these data effectively assumes equivalence of effect regardless of dexamethasone dose or type of 5-HT_3 receptor antagonist. This assumption creates uncertainty around the efficacy inputs and the relationship between cost and effects, which ultimately influences the ICERs generated.
- Despite the utility values being reflective of those used in other models in the literature[21-23], they are associated with uncertainty given that some of the health state values are based on opinion or assumptions. This has implications for the QALY calculations, which in turn influences the ICER. The company acknowledge this uncertainty and have consequently conducted sensitivity analyses to explore the impact of using alternative utility values.
- The model does not take into account any adverse events associated with the treatments being compared. This omission has the potential to bias the analyses.
- The resource use in the model takes into account the impact of CINV for up to seven days. This timeframe is at odds with the time horizon used. Whilst it is standard practice to use the same period for costs and effects, the sensitivity analyses conducted suggest that the model results are insensitive to resource use.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any CUAs focused on the treatment comparisons for the populations of interest included in this submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates that there are 11,123 people receiving HEC or MEC in Wales. These estimates are based on IMS-projected cancer prevalence and chemotherapy figures for the UK, which have been adjusted for the Welsh population. Again using IMS figures, the company estimates that 1,529 patients receiving cisplatin-based HEC are eligible for rolapitant. Assuming that 20% of MEC patients are eligible for treatment, the company estimates that 1,133 carboplatin-based MEC patients are eligible for rolapitant. The company forecasts that rolapitant will have a market share of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. To calculate medicine acquisition costs the company assumes an average of 4.3 chemotherapy cycles per patient and has averaged regimen costs across the Velindre Trust and Betsi Cadwaladr Health Board guidelines[5,6]. Sensitivity analyses explore the impact of varying market share, secondary care savings associated with MEC patients, the cost of ondansetron plus dexamethasone and displacement forecasts. In addition, the acquisition cost of NEPA is varied to explore the impact of the WPAS on this medicine.

5.1.2 Results

The estimated budget impact is presented in Table 6. The company estimates that the introduction of rolapitant would lead to net cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. While the medicine acquisition costs are effectively reduced for cisplatin-based HEC patients, overall there are increased costs (i.e. a positive budget impact) due to the introduction of a third component to the regimen for carboplatin-based MEC patients. The company sensitivity analyses predominantly support that the introduction of rolapitant would likely be associated with [commercial in confidence figure removed] to NHS Wales, ranging from [commercial in confidence figures removed] in Year 1 and [commercial in confidence figures removed] in Year 5. Exploration of a WPAS on the base case reveals that if a discount of up to [commercial in confidence figure removed] is applied to NEPA, this results in a budget impact ranging from [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5. The exceptions to these findings result from scenarios where rolapitant displaces either aprepitant only or NEPA only. In these scenarios, the introduction of rolapitant is associated with cost savings ranging from [commercial in confidence figures removed] per annum. In an AWTTC generated scenario in which rolapitant displaces NEPA only, exploration of the impact of a WPAS on NEPA suggests that the introduction of rolapitant is associated with cost savings, even if the list price of NEPA is reduced by up to [commercial in confidence figure removed].

Analysis of the impact on NHS resource use suggests savings of [commercial in confidence figure removed] in Year 1, increasing to savings of [commercial in confidence figure removed] in Year 5 for the carboplatin-based MEC population.

Table 6. Company-reported costs associated with use of rolapitant for the treatment of moderately and highly emetogenic chemotherapy

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (Indication covered in this submission)	2662	2662	2662	2662	2662
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Patients treated with rolapitant	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without rolapitant	£350,712	£358,061	£364,909	£372,258	£379,107
Medicine acquisition costs in a market with rolapitant	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Supportive medicine costs in a market without rolapitant	£40,984	£40,642	£40,252	£39,910	£39,519
Supportive medicine costs in a market with rolapitant	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicine costs	¶¶	¶¶	¶¶	¶¶	¶¶
Total net costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figures removed. Totals may not compute due to rounding.					

5.1.3 AWTTC critique

The budget impact analyses are characterised by both strengths and limitations, the most salient of which are detailed below:

- The submission gives a detailed, transparent account of the methods and data sources used in the budget impact analyses.
- A variety of sensitivity analyses explore the impact of varying parameter values and structural assumptions.
- It is unclear how market share has been forecast and uncertain whether or not these predictions are likely to be realised.
- The medicine acquisition costs included in the model are averaged regimen costs across the Velindre Trust and Betsi Cadwaladr Health Board guidelines. Using an averaged approach differs from the approach used in the CUA.

5.2 Comparative unit costs

Comparative unit costs are provided in Table 7.

Table 7. Examples of medicine acquisition costs for the prevention of chemotherapy-induced nausea and vomiting

Regimen	Example doses	Approximate cost per patient per cycle
Rolapitant (Varuby®)	Day 1: 180mg, orally	£47.42 (list price, WPAS available)
Aprepitant (Emend®)	Day 1: 125mg, orally Days 2-3: 80mg, orally	£47.42
Fosaprepitant (Ivemend®)	Day 1: 150mg, IV	£47.42
Netupitant/palonosetron (NEPA; Akynzeo®)	Day 1: 300mg/0.5mg, orally	£69.00 (list price, WPAS available)
Ondansetron	Day 1: 24mg orally Days 2-5: 8mg BD orally	£2.05
Granisetron	Day 1: 2mg orally Days 2-5: 2mg OD orally	£40.79
Palonosetron (Aloxi®)	Day 1: 500mcg, orally	£55.89
See relevant Summaries of Product Characteristics for full licensed indications and dosing details. Costs are based on MIMS list prices as of October 2017[26]. Costs of administration are not included. This table does not imply therapeutic equivalence of drugs or the stated doses. BD: twice daily; OD: once daily; WPAS: Welsh Patient Access Scheme.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, rolapitant (Varuby®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7–8 September 2017

Date range of evidence search: No date limits were applied to database searches.

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