Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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rolapitant (as hydrochloride monohydrate) 90mg film-coated tablets (Varuby®)

SMC No 1266/17

Tesaro UK Limited

4 August 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rolapitant (Varuby®) is accepted for restricted use within NHS Scotland.

Indication under review: Prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Rolapitant is given as part of combination therapy.

SMC restriction: as a first-line option in adults undergoing highly emetogenic chemotherapy (HEC).

In phase III studies of patients scheduled to receive highly or moderately emetogenic chemotherapy, a greater proportion of patients treated with rolapitant-based combination therapy achieved a complete response (defined as no emesis or use of rescue medication) in the delayed phase (>24 to 120 hours after initiation of chemotherapy) of cycle one compared with combination therapy alone.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of rolapitant. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Rolapitant is given as part of combination therapy.[1]

Dosing Information

Rolapitant is given as part of a regimen that includes dexamethasone and a 5-HT_3 receptor antagonist. Two tablets (180mg) should be administered within two hours prior to initiation of each chemotherapy cycle but at no less than two-week intervals. The tablets should be swallowed whole with some water and can be taken with or without food.[1]

Please refer to the summary of product characteristics for dosage advice for dexamethasone and 5-HT_3 receptor antagonists.[1]

Product availability date

24 May 2017

Summary of evidence on comparative efficacy

Rolapitant is a selective antagonist of the substance P / neurokinin-1 (NK_1) receptor.[1] Central pathways involving action of substance P on the NK_1 receptor are associated with delayed nausea and vomiting, occurring 24 to 120 hours, following chemotherapy administration.[2]

The submitting company requested that SMC considers rolapitant when positioned for use in two patient populations:

- As a first-line option alongside current SMC recommendations for other NK_1 receptor antagonists in adults undergoing cisplatin-based highly emetogenic chemotherapy (HEC).
- As a second-line treatment option in patients who have experienced anti-emetic failure (grade 2 or above chemotherapy-induced nausea and vomiting [CINV]) with a dexamethasone / serotonin type-3 (5-HT_3) receptor antagonist combination. Typically this will be patients who have received non-cisplatin based HEC (eg anthracycline / cyclophosphamide combination regimens) or moderately emetogenic chemotherapy (MEC).

The key evidence for rolapitant in the prophylaxis of CINV comprises three similarly designed multi-national, randomised, double-blind, phase III studies in which the rolapitant containing anti-emetic regimen was compared with anti-emetic regimens comprising dexamethasone / 5-HT_3 antagonists (control). Two studies investigated use in patients scheduled for cisplatin-based HEC (HEC-1 and HEC-2), and a pooled analysis was pre-specified.[3] One phase III study investigated use in patients scheduled for an anthracycline / cyclophosphamide regimen or MEC.[4]

The HEC-1 and -2 studies recruited adults who were scheduled to receive cisplatin-based chemotherapy (dose ≥60mg/m^2) for the first time. Patients had a Karnofsky performance score ≥60, predicted life expectancy ≥4 months, and had adequate kidney, liver and bone marrow function. Patients with anticipatory nausea and vomiting or who had previously received cisplatin or were planned to receive cisplatin on multiple days in one cycle were excluded from the studies.[3]

All patients in the studies received granisetron 10 micrograms/kg IV plus dexamethasone 20mg orally approximately 30 minutes prior to commencement of HEC. Dexamethasone was continued at a dose of

8mg orally twice daily on day two to four; rescue anti-emetics were prescribed at the investigator's discretion. Patients were randomised in a 1:1 ratio (stratified by sex) to either rolapitant 180mg or placebo, given orally one to two hours prior to administration of HEC on day one of the cycle.

Patients could remain in the study for up to six cycles and each cycle was required to be a minimum of 14 days. The studies' protocols prohibited the use of 5-HT_3 receptor antagonists, NK_1 receptor antagonists, cannabinoids, domperidone, phenothiazines and benzamides in the 48 hours prior to day one of cycle one. Systemic corticosteroids and sedative antihistamines were prohibited within 72 hours of day one unless they were used as chemotherapy premedication (eg for docetaxel). Palonosetron was not permitted in the week prior to day one.[3]

The primary outcome was the proportion of patients achieving a complete response in the delayed phase of cycle one (>24 to 120 hours after initiation of chemotherapy). Complete response was defined as no emesis or use of rescue medication. Events were recorded in patient diaries and the primary analysis was conducted in a modified intention-to-treat (ITT) population which was defined as all randomised patients who received at least one dose of study drug at a good-clinical-practice compliant site.[3] The proportions of patients meeting the primary outcome in both studies and in the pooled analysis are presented in Table 3 below.

Table 1: Primary outcome results from the HEC-1 and -2 studies and pooled analysis (modified ITT populations)

	Proportion of patients achieving complete response in delayed phase (>24 to 120 hours after initiation of chemotherapy) in cycle one		**Odds ratio (95% CI), p-value**
	Rolapitant	**Control**	
HEC-1	73% (192/264)	58% (153/262)	1.9 (1.3 to 2.7) p=0.0006
HEC-2	70% (190/271)	62% (169/273)	1.4 (1.0 to 2.1) p=0.0426
Pooled analysis	71%	60%	1.6 (1.3 to 2.1) p=0.0001

HEC = highly emetogenic chemotherapy, CI = confidence interval

Key secondary outcomes were complete response in the acute phase (between 0 to 24 hours after initiation of chemotherapy) and the overall phase (0 to 120 hours after initiation of chemotherapy). There were inconsistent results between the two HEC studies; complete response rates with rolapitant versus control were statistically significant in the acute phase (84% versus 74%) and in the overall phase (70% versus 56%) in the HEC-1 study. However there was no statistically significant difference between the acute phase complete response rates in HEC-2 (83% versus 79%); the stepwise testing procedure precluded formal testing of complete response in the overall phase (68% versus 60%, respectively). In pooled analysis, both secondary outcomes significantly favoured rolapitant. Kaplan-Meier analysis of the time to first emesis or use of rescue medication suggests that rolapitant delayed these events when compared with control ($p<0.05$ in log-rank test in both HEC studies and in the pooled analysis).[3]

The third phase III study (NCT01500226) recruited adults who were scheduled to receive a first course of MEC or anthracycline / cyclophosphamide combination-based chemotherapy for the first time. Patients had a Karnofsky performance score ≥60, predicted life expectancy ≥4 months, and had adequate kidney, liver and bone marrow function. Those with anticipatory nausea and vomiting, or

previous use of MEC or HEC were excluded.[4] Just over half (53%) of patients were scheduled to receive anthracycline / cyclophosphamide combination-based chemotherapy.

All patients in the study received granisetron 2mg orally plus dexamethasone 20mg orally approximately 30 minutes prior to commencement of planned chemotherapy. Granisetron 2mg orally daily was continued on days two and three; rescue anti-emetics were prescribed at the investigator's discretion. Patients were randomised in a 1:1 ratio (stratified by sex) to either rolapitant 180mg or placebo, given orally one to two hours prior to administration of planned chemotherapy on day one of the cycle. Restrictions related to cycle duration and prior use of anti-emetics stipulated in the HEC studies were also applicable in NCT01500226.[4]

The primary outcome was complete response rate in the delayed phase of cycle one which was analysed as per the methodology employed by the HEC studies. Rolapitant was associated with a statistically significant greater proportion of patients achieving complete response during the period 24 to 120 hours after initiation of chemotherapy; 71% [475/666] versus 62% [410/666]), odds ratio 1.6 (95% confidence interval [CI]: 1.2 to 2.0), p=0.0002.[4]

There was no statistically significant difference in the complete response rates during the acute phase (83% versus 80%); formal testing of complete response rates in the overall phase (69% versus 58%) was not permitted with the stepwise testing procedure.[4]

Pre-specified subgroup analyses of the primary and key secondary outcomes were conducted in subgroups defined by the type of chemotherapy administered (anthracycline / cyclophosphamide combination-based regimen, or other chemotherapy classified as MEC). Clinical benefit of rolapitant for complete response in the delayed phase was observed regardless of planned chemotherapy subgroup.[4]

In all three phase III studies the Functional Living Index-Emesis (FLIE) questionnaire was used to obtain quality of life data as exploratory outcomes. The FLIE questionnaire comprised 18 questions covering two domains (nausea and vomiting), and their impact on daily living. Each question was marked on a seven-point scale and scores were summed for nausea, vomiting and a total score calculated. Average response scores >6 out of seven were considered to have no impact on daily life. The FLIE questionnaire was completed on day six of the first chemotherapy cycle. In the pooled analysis of the HEC studies, the proportions of patients reporting no impact on daily life were 76% versus 71%, for the rolapitant and control groups respectively.[3] A numerically greater proportion of patients in the rolapitant group in study NCT01500226 reported no effect on daily life due to CINV compared with patients in the control group, 73% versus 67%.[4]

Post-hoc pooled analysis of outcomes beyond cycle one in all three studies has been reported (n=2,015). Exploratory efficacy measures in cycles two to six were: a composite measure (no emesis or nausea interfering with daily life), no emesis, no interfering nausea, and time-to-first emesis. Rolapitant treatment led to numerically greater proportions of patients achieving each of these outcomes at all cycles when compared with control.[5]

Summary of evidence on comparative safety

Safety data from all three studies were presented for patients during the first cycle of chemotherapy only.

In the pooled dataset of the HEC-1 and -2 studies, similar proportions of patients in each treatment group experienced an adverse event (AE), 61% and 62% in the rolapitant and control groups respectively. AEs led to study discontinuation in 3.7% (20/535) of rolapitant patients and in 5.4%

(29/537) of control patients. Only a small proportion of patients experienced a treatment-related AE; 3.2% (17/535) of rolapitant patients and 4.1% (22/537) of control patients. The most common events were dyspepsia, headache, constipation and hiccups and they occurred in <1% of patients in each group.[3]

In the NCT01500226 study, approximately two-thirds of patients in each treatment group reported an AE, 64% and 66% of patients in the rolapitant and control groups respectively. Treatment-emergent AEs led to discontinuation in 2.1% and 2.4% of patients respectively. The most commonly reported treatment-related AEs were constipation, fatigue, dizziness and headache which were reported in similar proportions of patients in each group and in <5% of patients.[4]

Summary of clinical effectiveness issues

Vomiting and particularly nausea remain two of the most distressing side-effects of cancer chemotherapy.[6] Improved control of CINV enhances quality of life of patients with cancer and can help avoid discontinuation or dose reduction of chemotherapy.[2] Strategies for the management of these adverse events are built upon the knowledge of the emetogenicity of chemotherapy agents. Emetogenicity of agents are often stratified into four classifications: high emetic risk (>90%), moderate risk (30% to 90%), low risk (10% to 30%) and minimal risk (<10%). The risk is estimated from the proportion of patients with acute emesis in the absence of anti-emetic prophylaxis. In addition to the agent used, treatment-related factors include the dose, route and rate of administration. Patient-related factors also increase the risk, eg female gender, age <55 years, anxiety, fatigue, history of motion sickness, and no history of alcohol use.[2, 6]

Anti-emetics used in the management of CINV tend to target neurotransmitter receptors for dopamine, serotonin (5-HT_3) and substance P (NK_1) or are glucocorticoids (eg dexamethasone). Clinical guidelines recommend combinations of dexamethasone, 5-HT_3 receptor antagonists with or without NK_1 receptor antagonists, depending upon the patient's risk of emesis with the chemotherapy regimen.[6, 7] There are several NK_1 receptor antagonists licensed for the management of CINV in adults in the UK eg aprepitant, fosaprepitant and netupitant (co-formulated with palonsetron); in NHS Scotland all have been restricted for use to manage CINV associated with cisplatin-based HEC. The licence for aprepitant was extended to manage CINV associated with non-cisplatin-based HEC in January 2016. SMC will not be assessing this minor licence change; therefore use in this setting is a local formulary decision.

The company has proposed that rolapitant be considered first-line in the anti-emetic prophylaxis of cisplatin-based HEC. Relevant comparators for this population are the other NK_1 receptor antagonists; direct comparative data are not available between rolapitant and the NK_1 receptor antagonists. Clinical experts have advised a range of options are recommended in Scottish cancer network guidelines for the second-line prophylaxis of CINV in patients who have experienced anti-emetic failure with a dexamethasone / 5-HT_3 receptor antagonist combination such as: intensifying the regimen up one level (eg moderate to high-risk regimen), addition / substitution of agents (metoclopramide, cyclizine, prochlorperazine, levomepromazine) or use of NK_1 receptor antagonists (as per cancer network protocols).

In all phase III studies, addition of rolapitant to anti-emetic regimens was associated with significantly greater proportions of patients with no emesis or use of rescue medication during the period of risk for delayed CINV (between 24 and 120 hours following administration of emetogenic chemotherapy). The phase III studies included patients taking cisplatin-based HEC, anthracycline / cyclophosphamide regimens (now considered to be highly emetogenic), and MEC.

The primary outcome measure used in the phase III studies was a direct health outcome. While it focused on the period associated with risk of delayed CINV (24 to 120 hours after initiation of chemotherapy) which may be the period which NK_1 receptor antagonists may influence the most; the overall risk period (0 to 120 hours after chemotherapy) is also likely to be important to patients and was a key secondary outcome of the phase III studies. Response rates were numerically greater with rolapitant compared with control regimens for this outcome. However, as a result of the stepwise testing procedure, failure to demonstrate a significant improvement in complete response during the acute phase precluded formal statistical inferential analysis of the overall study phase in two studies.

Quality of life impairment from CINV was an exploratory endpoint in the phase III studies. Impairment in quality of life was reported by 25% to 33% of patients in the studies. Rolapitant compared with control was associated with numerically smaller proportions of patients with impairment (difference approximately 5% to 6%).[3, 4]

Post-hoc pooled analysis suggests efficacy and safety is maintained over multiple cycles of chemotherapy administration.[5]

While the background regimen used in the NCT01500226 study does not reflect current practice (guidelines recommend use of a 5-HT_3 receptor antagonist on day one and dexamethasone on days one to three), results demonstrate the benefit of adding rolapitant to an anti-emetic regimen in patients undergoing anthracycline / cyclophosphamide chemotherapy or MEC. Patient-related characteristics which are recognised risk factors for CINV such as history of anxiety, motion or pregnancy-related sickness were not collected during the studies. It is not known if these risk factors were balanced across treatment groups.

The company has not provided any clinical evidence for use of rolapitant as a second-line treatment option in patients who have experienced anti-emetic failure with a dexamethasone / 5-HT_3 receptor antagonist combination. The phase III studies recruited patients in the first-line setting.[3, 4]

To support the cost minimisation analysis use in the economic analysis, the submitting company conducted a Bayesian network meta-analysis (NMA) of the licensed NK_1 receptor antagonist anti emetic regimens (rolapitant, aprepitant, netupitant / palonsetron and fosaprepitant) when used in patients undergoing cisplatin-based HEC. Outcomes compared were complete response rate in the delayed phase and in the overall phase. The networks included 13 studies in the delayed phase and 14 studies in the overall phase. Odds ratios for complete response in the delayed and overall phases tended to favour the comparators; however there was insufficient evidence of a difference in treatment effect with wide credible intervals reported. Limitations of the analysis include a lack of identified sources of heterogeneity which may confound comparisons such as the proportions of females in the studies. The committee were able to cautiously accept that the NK_1 receptor antagonists had broadly similar outcomes in this patient population.

The company was unable to form a network of evidence for patients undergoing anthracycline / cyclophosphamide combination regimens. Bayesian NMA of two studies were presented to compare rolapitant and aprepitant in patients scheduled for MEC, however, the exceptionally large credible intervals mean no conclusions can be drawn from the results. In addition, the studies were conducted in two very different patient populations that do not match the proposed positioning of second-line use.

The currently available NK_1 receptor antagonists are inhibitors of the cytochrome P450 isoenzyme 3A4 (CYP 3A4), and as a result use of these agents requires careful consideration of potential drug-drug interactions.[8-10] Rolapitant has a different pharmacokinetic drug interaction profile; it has no clinically significant effect on CYP 3A4, but inhibits other metabolic proteins, specifically CYP2D6, the breast-cancer-resistance protein and P-glycoprotein.[1]

The duration of action of rolapitant permits single-dosing per chemotherapy cycle; aprepitant is recommended to be taken for three days. However in comparison with the other NK_1 receptor antagonist regimens, the patient's pill burden may be increased with use of rolapitant since a dose reduction of dexamethasone is not recommended.[1, 8-10]

Summary of comparative health economic evidence

The company submitted a cost- minimisation analysis comparing rolapitant with other NK_1 receptor antagonists (including aprepitant, fosaprepitant and netupitant / palonosetron) both in addition to ondansetron and dexamethasone, for the prevention of delayed nausea and vomiting associated with HEC and MEC in adults. Rolapitant has been positioned for use in two patient populations ie first-line in adult patients treated with cisplatin based HEC and second-line use in adult patients who have experienced anti-emetic failure on non- cisplatin based HEC (including anthracycline / cyclophosphamide) and MEC. The time horizon used in the analysis was five days. SMC clinical experts have noted that aprepitant and netupitant / palonosetron are the comparators most likely to be displaced in Scotland for patients receiving cisplatin based HEC population. It has been noted that some patients who have experienced anti-emetic failure on non- cisplatin based HEC and MEC may currently be receiving NK_1 receptor antagonists via local cancer network arrangements.

The clinical data used to support the assumption of comparable efficacy between treatments in patients undergoing cisplatin- based HEC were taken from a Bayesian NMA as described in the clinical effectiveness section above. Based on this analysis, no difference in complete response in the delayed or overall phase was identified between rolapitant anti-emetic regimen (rolapitant combined with granisetron or ondansetron and dexamethasone) and comparator anti-emetic regimen (aprepitant or fosaprepitant combined with ondansetron or granisetron and dexamethasone or netupitant / palonosetron and dexamethasone). It is worth noting that the company did not provide a network of evidence for patients undergoing anthracycline / cyclophosphamide combination regimens. A Bayesian NMA was provided to support the assumption of comparable efficacy between rolapitant and aprepitant in patients receiving MEC. However, as these analyses did not include patients who failed on first-line treatment (as per the company's positioning), the economic results presented for this patient group may lack validity and should be interpreted with caution.

Medicine acquisition costs were included in the analysis. In the base case analysis the company assumed that 50% of patients receiving rolapitant would receive dexamethasone 20mg on day 1, then 8mg twice daily on days 2 to 4, while the remaining 50% were assumed to receive dexamethasone 12mg on day 1, then dexamethasone 4mg twice daily on days 2 to 4. No administration or monitoring costs were included in the analysis as these were assumed to be the same for all treatments. Patients were assumed to be 100% adherent with anti-emetic treatment. AE costs were not considered.

A Patient Access Scheme (PAS) was submitted by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS is in place for the comparator netupitant / palonosetron and this was included in the analysis by using an estimate of the PAS price of netupitant / palonosetron.

The base case results and key sensitivity analyses are presented in Table 2 below. It should be noted that the company presented the economic results for HEC and MEC patient populations. HEC results therefore relate to (cisplatin and non-cisplatin) treated patients.

Table 2: Rolapitant base case results and sensitivity analysis (Cost per patient per cycle, without PAS)

Analysis	Total cost of rolapitant regimen	Incremental cost versus aprepitant regimen	Incremental cost versus fosaprepitant regimen	Incremental cost versus netupitant/ palonosetron regimen (using estimate of list price for netupitant/ palonosetron)
Base case				
HEC	£63.70	£4.89	£4.89	-£16.31
MEC	£55.14	£0.00	£0.00	£21.20
Dexamethasone dose as per summary of product characteristics				
HEC	£68.60	£9.79	£4.89	-£11.41
MEC	£53.92	£2.45	£2.45	-£18.75

Table 3: Weighted average comparison results (cost per patient per cycle, without PAS)

Analysis	Total cost of rolapitant regimen	Incremental cost (weighted comparator regimen)- using estimate of list price for netupitant/palonosetron
Base case		
HEC	£63.70	£3.83
MEC	£55.14	-£1.06
Dexamethasone dose as per summary of product characteristics		
HEC	£68.60	£8.48
MEC	£53.92	£1.39

The results presented do not take account of the PAS for netupitant/palonosetron or the PAS for rolapitant but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for netupitant/palonosetron due to commercial confidentiality and competition law issues.

There were a number of weaknesses with the analysis.

- There is some uncertainty surrounding the company's base case approach to estimating the dexamethasone dose in the rolapitant treatment arm (for cisplatin- based HEC patients). The approach does not accurately reflect the dose stated in the summary of product characteristics (SPC) for rolapitant and appears to underestimate costs for the rolapitant treatment regimen. The company provided a scenario analysis whereby dexamethasone use is estimated as per the SPC, as shown above. This analysis appears to represent a more appropriate base case.
- No clinical data were provided by the company to support the assumption of comparable treatment efficacy in HEC patients who experienced anti-emetic failure on non- cisplatin based anthracycline / cyclophosphamide combination regimens. As such, there is considerable uncertainty surrounding the assumption of comparable efficacy within this patient population.
- Due to prescribing/treatment variability within Scottish cancer networks, there is considerable uncertainty surrounding the comparator used for patients who have failed on first- line treatment in both the HEC (non- cisplatin) and MEC populations.
- The Bayesian NMAs used to support the assumption of comparable efficacy of rolapitant and comparator anti-emetic regimens have limitations which may undermine this assumption. In particular, there is considerable uncertainty surrounding the NMA in the MEC population which limits the validity of the economic results for this patient group. The primary concerns relate to the relevance of the patient population given the company's positioning ie the studies did not include patients who failed on first- line anti-emetic therapy, and the appropriateness of comparing against aprepitant (an NK_1 receptor antagonist).

Given these issues, the economic case has been demonstrated as a first line option in adults undergoing highly emetogenic chemotherapy.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The Multinational Association of Supportive Care in Cancer (MASCC) in collaboration with the European Society for Medical Oncology (ESMO) updated anti-emetic guidelines in 2016.[6] Emetogenicity risk for systemic anti-cancer therapies are defined, including the classification that anthracycline / cyclophosphamide in patients with breast cancer be considered highly emetogenic. First-line anti-emetic regimen recommendations are noted in the table below. The guideline notes that addition of an anti-emetic with a different mechanism of action than that used in the previous cycle of chemotherapy is a reasonable approach to managing patients with refractory emesis.

Table 4: Recommended anti-emetic prophylaxis for MEC and HEC.[6]

	Prophylaxis of acute CINV (administered prior to chemotherapy)	Prophylaxis of delayed CINV
Non-AC HEC (incl. cisplatin)	• 5-HT_3 RA • Dexamethasone • NK_1 RA	• Dexamethasone on days 2 to 4 • Aprepitant on days 2 to 3 (if aprepitant used on day 1)
AC HEC	• 5-HT_3 RA • Dexamethasone • NK_1 RA	• If aprepitant used on day 1: Aprepitant on days 2 and 3 or Dexamethasone on days 2 and 3 • If other NK_1 RAs used on day 1: nil
MEC	• 5-HT_3 RA • Dexamethasone	• MEC with potential for delayed CINV: Dexamethasone on days 2 and 3 • MEC without risk for delayed CINV: nil
Carboplatin-based MEC	• 5-HT_3 RA • Dexamethasone • NK_1 RA	• If aprepitant used on day 1: Aprepitant on days 2 and 3 • If other NK_1 RAs used on day 1: nil

CINV = chemotherapy induced nausea and vomiting, AC = anthracycline / cyclophosphamide, HEC = highly emetogenic chemotherapy, 5-HT_3 RA = serotonin type-3 receptor antagonist, NK_1 RA = neurokinin-1 receptor antagonist, MEC = moderately emetogenic chemotherapy.

Additional information: comparators

Regimens based on NK_1 receptor antagonists: aprepitant, fosaprepitant, netupitant (co-formulated with palonosetron). Various strategies employed for second-line prophylaxis of CINV after failure of dexamethasone / 5-HT_3 receptor antagonists (see clinical effectiveness section for detail) are not presented in the table below.

Cost of relevant comparators

Anti-emetic regimen	Dose regimen on day of chemotherapy	Dose regimen on days following chemotherapy	Cost per cycle (£)
rolapitant dexamethasone ondansetron	**rolapitant: 180mg orally dexamethasone: 20mg orally ondansetron: 8mg orally twice daily**	**dexamethasone: 8mg orally twice daily for three days**	**64**
netupitant / palonosetron (Akynzeo®) dexamethasone	Akynzeo®: one capsule (300mg / 500 micrograms) orally dexamethasone: 12mg orally	dexamethasone: 8mg orally for three days	77

fosaprepitant dexamethasone ondansetron	fosaprepitant: 150mg IV dexamethasone: 12mg IV ondansetron: 8mg IV	dexamethasone: 8mg orally once daily for one day, then 8mg twice daily for two days	63
aprepitant dexamethasone ondansetron	aprepitant: 125mg orally dexamethasone: 12mg orally ondansetron: 8mg orally twice daily	aprepitant: 80mg orally for two days dexamethasone: 8mg orally for three days	56

Doses are for general comparison and do not imply therapeutic equivalence. Regimens licensed for prophylaxis of cisplatin-based HEC presented in the table. Costs from MIMS on 31 July 2017; except for rolapitant (from company's submission), and IV ondansetron (from BNF online on 05 June 2017). Costs do not take any patient access schemes into consideration. IV=intravenous

Additional information: budget impact

The submitting company estimated there would be 6,000 patients eligible for treatment with rolapitant in all years. The estimated uptake rate was 5% in year 1 (300 patients) and 25% in year 5 (1,500 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 14 July 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice

Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.