Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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netupitant/palonosetron 300mg/0.5mg, hard capsule (Akynzeo®)

SMC No. (1109/15)

Chugai Pharma UK Limited

04 December 2015

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

netupitant/palonosetron (Akynzeo®) is accepted for restricted use within NHS Scotland.

Indication under review: in adults for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy.

SMC restriction: prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

In patients receiving a first course of highly emetogenic cisplatin-based chemotherapy, treatment with netupitant/palonosetron plus dexamethasone resulted in a significantly higher proportion of patients achieving no emesis and no breakthrough medication compared with palonosetron plus dexamethasone.

This advice takes account of the benefits of Patient Access Scheme (PAS) that improves the cost-effectiveness of netupitant/palonosetron. This advice is contingent upon the continuing availability of the patient access scheme 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

in adults for the:

- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Dosing Information

Netupitant/palonosetron one capsule (300mg/0.5mg) should be administered approximately one hour prior to the start of each chemotherapy cycle. The recommended oral dexamethasone dose should be reduced by approximately 50% when co-administered with netupitant/palonosetron.

Product availability date

01 September 2015.

Summary of evidence on comparative efficacy

Akynzeo® capsules contain two antiemetics: netupitant, a selective neurokinin 1 (NK_1) receptor antagonist, and palonosetron, a selective 5-hydroxytryptamine (serotonin) type 3 ($5\text{-}HT_3$) receptor antagonist, in a fixed dose oral formulation licensed for prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.[1] This is the first licensed preparation containing netupitant. Nausea and vomiting is a common side effect of chemotherapy and is defined as acute (0 to 24 hours) or delayed (occurring after the first 24 hours). Acute vomiting mainly relates to 5-HT and the use of $5\text{-}HT_3$ receptor antagonists in the acute phase is well established. Multiple mechanisms including substance P, which belongs to the NK family, are likely to be involved in delayed vomiting.[2]

The submitting company has requested that SMC considers netupitant/palonosetron when positioned for use in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy (HEC).

The pivotal study for the proposed positioning is NETU-07-07, a phase II, randomised double-blind dose-ranging study in adult patients receiving a first course of cisplatin chemotherapy (≥50mg/m^2, alone or with other chemotherapy treatments) for a histologically or cytologically confirmed solid tumour.[2,3] Patients were chemotherapy naive, and had a Karnofsky performance scale score of ≥70%, and were not due to receive moderately emetogenic chemotherapy (MEC) or HEC from day 2 to 5, moderately or highly emetogenic radiotherapy either within one week before day 1 or from day 2 to 5 or a bone marrow or stem cell transplant. Patients were randomised equally (stratified by gender) to one of five arms:

- netupitant oral 100mg + palonosetron oral 0.5mg + dexamethasone oral 12mg (day 1); and then dexamethasone oral 4mg twice daily (days 2 to 4) (referred to as netupitant 100mg + palonosetron)
- netupitant oral 200mg + palonosetron + dexamethasone (doses as before) (referred to as netupitant 200mg + palonosetron)
- netupitant oral 300mg + palonosetron (doses as before) (licensed dose, referred to as netupitant 300mg + palonosetron)
- palonosetron oral 0.5mg + dexamethasone oral 20mg (day 1); and then dexamethasone oral 8mg twice daily (days 2 to 4) (referred to as palonosetron)

- and an exploratory arm; aprepitant oral 125mg + ondansetron intravenously (IV) 32mg + dexamethasone oral 12mg (day 1); then aprepitant oral 80mg (days 2 to 3) + dexamethasone oral 4mg twice daily (days 2 to 4) (referred to as aprepitant + ondansetron)

Rescue medication (excluding 5-HT_3 receptor antagonists and NK_1 receptor antagonists) was permitted for refractory or persistent nausea and vomiting but use was considered as a treatment failure.[3]

The primary outcome was complete response (CR), defined as no emesis and no rescue medication during the overall post-chemotherapy phase (0 to 120 hours), analysed in the intention-to-treat (ITT) population which included all randomised patients who received the protocol defined dose of cisplatin, and at least one dose of study treatment. A patient diary was used to collect information on the timing and duration of each emetic episode, severity of nausea, concomitant medications (including rescue medication) and patients' overall satisfaction. A 100mm visual analogue scale (VAS) was used to score patients' nausea: 0mm was 'no nausea' and 100mm was 'nausea as bad as it could be'.[3]

The proportion of patients with a CR was significantly higher for all netupitant + palonosetron arms versus the palonosetron arm. An exploratory statistical comparison between the netupitant + palonosetron and aprepitant + ondansetron arms has been undertaken. Results for the primary and some secondary endpoints for netupitant 300mg + palonosetron (licensed dose) and the comparator arms are included in the table below.[3]

Table: proportion of patients achieving primary and secondary outcomes for netupitant 300mg + palonosetron (licensed dose), aprepitant + ondansetron and palonosetron [3]

	netupitant 300mg + palonosetron	**aprepitant + ondansetron**	**palonosetron**
	n=135	n=134	n=136
Primary endpoint			
Complete response (no emesis and no rescue medication), %			
Acute	98%*	95%	90%
Delayed	90%⌠	89%^	80%
Overall	90%*	87%^	76%
Secondary endpoints			
No emesis, %			
Acute	98%*	95%	90%
Delayed	92%*	90%^	80%
Overall	91%*	87%^	76%
No significant nausea (visual analogue scale score of <25mm), %			
Acute	98%⌠	94%	93%
Delayed	90%*	88%	81%
Overall	90%⌠	86%	79%
Complete protection (complete response and no significant nausea), %			
Acute	97%*	90%	88%
Delayed	84%⌠	82%	74%
Overall	83%*	78%	70%

*p≤0.01 vs. palonosetron; ⌠p≤0.05 vs. palonosetron; ^ p≤0.05 vs. palonosetron (post hoc analysis)

In the exploratory analysis there was no significant difference between the netupitant + palonosetron and aprepitant + ondansetron arms although the percentage of responders was numerically higher in the former group for all efficacy endpoints during each phase.[2]

Supportive efficacy data come from NETU-10-29, a double-blind, randomised, phase III, safety study in adult patients diagnosed with a malignant tumour, naïve to chemotherapy and scheduled to receive repeated consecutive courses of single dose MEC or HEC.[4] Patients were also required to have an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2. Patients were randomised in a ratio of 3:1, stratified by chemotherapy emetogenicity and gender, to receive:

- netupitant oral 300mg + palonosetron oral 0.5mg + dexamethasone oral 12mg (day 1); then dexamethasone oral 4mg twice daily (on days 2 to 4 for HEC only) (n=309) (referred to as netupitant + palonosetron)
- aprepitant oral 125mg + palonosetron oral 0.5mg + dexamethasone oral 12mg (day 1); then aprepitant oral 80mg (days 2 to 3) + dexamethasone oral 4mg twice daily (days 2 to 4 for HEC only) (n=104) (referred to as aprepitant + palonosetron).

Rescue medication was permitted for established, refractory or persistent nausea and vomiting, but use was considered a treatment failure.[4]

Efficacy was analysed as a secondary endpoint. In the netupitant + palonosetron and aprepitant + palonosetron arms respectively, CR was achieved in the following proportions of patients: cycle 1 (81% versus 76%); cycle 2 (86% versus 81%); cycle 3 (91% versus 87%); cycle 4 (90% versus 88%); cycle 5 (92% versus 86%); and cycle 6 (91% versus 86%). In the subgroup of patients receiving HEC (24% of study population), CR across the cycles was achieved in 79% to 91% of patients in the netupitant + palonosetron arm and 58% to 86% of patients in the aprepitant + palonosetron arm. The proportions of patients with no significant nausea across the cycles were 84% to 92% in the netupitant + palonosetron arm and 81% to 87% of patients in the aprepitant + palonosetron arm.[4]

Summary of evidence on comparative safety

In study NETU-07-07 the proportion of patients with any adverse event (AE) was 50% (68/136) in the netupitant 300mg + palonosetron group, 53% (71/134) in the aprepitant + ondansetron group and 49% (67/136) in the palonosetron group, and treatment-related AEs occurred in 15% (21/136), 19% (26/134) and 12% (17/136) of patients in respective groups. Common (≥2%) treatment-related AEs in the netupitant 300mg + palonosetron group, aprepitant + ondansetron and palonosetron groups respectively were: hiccups (5.1%, 0% and 3.7%), headache (0.7%, 2.2% and 1.5%), leukocytosis (1.5%, 0.7% and 2.2%), alanine aminotransferase increased (1.5%, 1.5% and 0.7%), aspartate aminotransferase increased (0.7%, 1.5% and 0.7%), dyspepsia (0.7%, 0% and 1.5%), bradycardia (0%, 2.2% and 0%), bundle branch block (2.2%, 0% and 0%) and anorexia (0.7%, 0% and 2.2%).[3]

In study NETU-10-29 the proportion of patients with treatment-related AEs in cycle 1 was 5.2% (16/308) in the netupitant + palonosetron group and 2.9% (3/104) in the aprepitant + palonosetron group, and in the entire multiple cycle study period was 10% (31/308) and 5.8% (6/104) in the respective groups. In cycle 1, the most common treatment-related AE in the netupitant + palonosetron and aprepitant + palonosetron groups respectively were: constipation (2.3% versus 0%), dyspepsia (0% versus 1.0%), eructation (0.3% versus 1.0%) and headache (1.0% versus 1.0%). Over the entire multiple cycle study period, the most common treatment-related AE in the netupitant + palonosetron and aprepitant + palonosetron groups, respectively were: constipation (3.6% versus 1.0%), dyspepsia (0.3% versus 1.0%), eructation (0.3% versus 1.0%) and headache (1.0% versus 1.0%).[4]

One AE was considered severe and possibly antiemetic (including dexamethasone) treatment-related and led to discontinuation: acute psychosis in the netupitant + palonosetron group in cycle 1.[4]

Summary of clinical effectiveness issues

Emetogenicity of IV chemotherapy is categorised as high >90%; moderate 30% to 90%; low 10% to 30%; and minimal <10%, and cisplatin is classed as HEC.[2,3] The submitting company has requested that SMC considers netupitant/palonosetron when positioned for use in the prevention of acute and delayed nausea and vomiting associated with cisplatin-based HEC.

Two studies provide efficacy data for the indication and positioning under review. There are no statistical analyses (other than exploratory) of netupitant/palonosetron + dexamethasone with valid comparator regimens (NK_1 receptor antagonist + 5-HT_3 receptor antagonist + dexamethasone) in patients receiving cisplatin-based HEC. Furthermore, no studies included granisetron in the comparator antiemetic regimen, which is used as part of an antiemetic regimen in one cancer network in NHS Scotland.

In the pivotal study (NETU-07-07) netupitant 300mg/palonosetron 0.5mg + dexamethasone was significantly superior to palonosetron + dexamethasone for CR. In the exploratory analysis of the NK_1 receptor antagonist + 5-HT_3 receptor antagonist containing regimens there was no significant difference between groups for key endpoints. The study has limitations including use of a dose of ondansetron which exceeds the maximum recommended dose given as a single infusion now included in the summary of product characteristics.[5] Although the study was of phase II, dose-ranging design, the European Medicines Agency (EMA) considered that it was adequate to demonstrate efficacy to support use in HEC.[2] Palonosetron capsules are licensed for the prevention of nausea and vomiting associated with MEC only.[6] Therefore, the key comparator in the study was used outwith its European marketing authorisation. However, non-inferiority of palonosetron 0.5mg oral with palonosetron 0.25mg IV was demonstrated in a double-blind study where patients received cisplatin HEC.[7]

Supportive data come from NETU-10-29, a phase III randomised, double-blind safety study where 24% of patients received HEC. CR was achieved in a high proportion of patients overall and the EMA considered the results to be supportive of the pivotal study.

The availability of netupitant/palonosetron 300mg/0.5mg (Akynzeo®) would allow the NK_1 receptor antagonist and 5-HT_3 receptor antagonist components of the antiemetic regimen to be given orally on day 1 (with dexamethasone on days 1 to 4).[1] This provides a simplified approach compared with current antiemetic regimens, where some components are given IV and over additional days.[8-10] It may be a preferred treatment option in some patients, although others may benefit from regimens that are given IV on day 1, particularly when anticipatory nausea and vomiting is present. The recommended oral dexamethasone dose should be reduced by approximately 50% when co-administered with netupitant/palonosetron.[1] Dexamethasone dose reduction is also recommended when co-administered with aprepitant or fosaprepitant.[11,12]

The marketing authorisation for netupitant/palonosetron does not include use in the prevention of nausea and vomiting with HEC other than that associated with cisplatin chemotherapy.[1]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing netupitant/palonosetron with aprepitant and ondansetron for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy. SMC clinical experts have highlighted these comparators are appropriate. The time horizon of the analysis is a single cycle of chemotherapy.

The efficacy data to support the cost-minimisation analysis came from the findings of the NETU-07-07 study described above. The company presented the results stating that netupitant/palonosetron (at the licensed dose of 300mg) was associated with a numerical advantage in terms of efficacy in all primary endpoints compared to aprepitant and ondansetron. No statistical analysis was undertaken to determine the statistical significance of this difference. On this basis, the company asserted that a cost-minimisation analysis (CMA) was appropriate. In the CMA, the cost of netupitant/palonosetron was the cost of one tablet. For aprepitant, the analysis assumed use on day one pre-chemotherapy and on days two and three. The ondansetron analysis was based upon a weighted average of the proportions of patients using treatment on day one only, or for five days and depending on whether these treatments were given orally or IV.

No adverse events were considered in the analysis and administration costs were not included in the model. There could be additional nurse time costs associated with setting up the IV infusion plus consumables for the administration of ondansetron; this part of the company's case for netupitant/palonosetron could therefore be considered conservative, given that it is an oral treatment.

The results indicated that netupitant/palonosetron costs £69 per patient per chemotherapy cycle compared to £51 for aprepitant and ondansetron. Thus netupitant/palonosetron costs £18 more per patient than aprepitant and ondansetron. On this basis, netupitant/palonosetron is not the preferred treatment option.

A patient access scheme (PAS) was submitted for netupitant/palonosetron and has been assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was proposed on the price of netupitant/palonosetron. With the PAS, netupitant/palonosetron became a cost-effective treatment option.

The following weaknesses were noted;

- There was no statistical comparison with the relevant comparators. However, it was felt that, in the context of a CMA, comparable efficacy had been demonstrated by the exploratory analysis.

- SMC clinical experts indicated that ondansetron could be used in different ways e.g. on day one only, and as an IV or oral treatment. The cost-effectiveness results varied but the medicine remained a cost-effective treatment option with the PAS except in a conservative analysis in which oral ondansetron was used only on day 1.

Despite these issues, the economic case was considered demonstrated.

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

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The Multinational Association of Supportive Care in Cancer (MASCC) in collaboration with the European Society for Medical Oncology (ESMO) published antiemetic guidelines in January 2013.[8] For the prevention of acute nausea and vomiting following HEC the guidelines recommend a 5-HT_3 receptor antagonist + dexamethasone + NK_1 receptor antagonist (oral aprepitant or intravenous fosaprepitant). For delayed nausea and vomiting following HEC, the guidelines recommend dexamethasone + aprepitant (unless fosaprepitant was given on day 1 of the cycle in which case only dexamethasone should be given on days 2 to 4).

The American Society of Clinical Oncology (ASCO) published 'Antiemetics: American Society of Clinical Oncology focussed guideline update' in November 2015.[9] For the prevention of nausea and vomiting with HEC an antiemetic regimen including a NK_1 receptor antagonist + 5-HT_3 receptor antagonist + dexamethasone is recommended. Netupitant/palonosetron 300mg/0.5mg + dexamethasone is included as a treatment option.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Antiemesis were published in April 2012.[10] For the prevention of nausea and vomiting with HEC an NK_1 receptor antagonist + 5-HT_3 receptor antagonist + dexamethasone is recommended.

Additional information: comparators

For the prevention of acute and delayed nausea and vomiting associated with HEC, a regimen including a NK_1 receptor antagonist + 5-HT_3 receptor antagonist + dexamethasone is used. The regimens included in the cost table below reflect clinical expert feedback as well as Scottish cancer networks antiemetic guidance.

Cost of relevant comparators

Regimen	Day 1	Days 2 to 4	Total cost per cycle
netupitant/ palonosetron + dexamethasone	**netupitant 300mg /palonosetron 0.5mg oral; dexamethasone 12mg oral.**	**dexamethasone 4mg oral twice daily, days 2 to 4.**	**£83**
granisetron + aprepitant + dexamethasone	granisetron 2mg oral; aprepitant 125mg oral (or fosaprepitant 150mg IV on day 1 only); dexamethasone 12mg oral.	granisetron 1mg oral once daily*, days 2 to 4; aprepitant 80mg oral once daily, days 2 to 3; dexamethasone 4mg orally twice daily, days 2 to 4.	£87
ondansetron + aprepitant + dexamethasone	ondansetron 8mg IV or 8mg oral twice daily aprepitant 125mg oral (or fosaprepitant 150mg IV on day 1 only); dexamethasone 8mg to 12mg oral.	aprepitant 80mg orally once daily, days 2 to 3; dexamethasone 2mg three times daily to 4mg twice daily oral, days 2 to 4.	£58 to £63

Doses are for general comparison and do not imply therapeutic equivalence. Costs do not take any patient access schemes into consideration. Costs from eVadis (September 2015), BNF and MIMS online on 22 September 2015. *Dose of granisetron on days 2 to 4 is out with its marketing authorisation[13]. The costs shown for dexamethasone are for oral administration. Some regimens use dexamethasone 8mg to 12mg IV, which costs £1.82 to £2.73, compared with dexamethasone 8mg to 12mg oral which costs £3.12 to £4.68.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 1,564 patients per year with an estimated uptake rate of 20% in year 1 and to 45% by year 5.

Without PAS: The gross impact on the medicines budget was estimated to be £109k in year 1 rising to £245k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £22k in year 1, rising to £50k in year 5; these estimates are based on 4 cycles per patient.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Netupitant/palonosetron hard capsule (Akynzeo®). Summary of product characteristics. Chugai Pharma UK Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 25 May 2015.

2. European Medicines Agency European Public Assessment Report. Netupitant/palonosetron (Akynzeo®). 26 March 2015, EMA/236963/2015. www.ema.europa.eu

3. Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomised dose-ranging pivotal study. Ann Oncol 2014 Jul;25(7):1340-6.

4. Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 2014 Jul;25(7):1333-9.

5. Ondansetron injection 2mg/mL (Zofran®). Summary of product characteristics. GlaxoSmithKline UK. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 18 June 2015.

6. Palonosetron soft capsule (Aloxi®). Summary of product characteristics. Chugai Pharma UK Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 23 March 2010.

7. Karthaus M, Tibor C, Lorusso V, et al. Efficacy and safety of oral palonosetron compared with IV palonosetron administered with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with solid tumors receiving cisplatin-based highly emetogenic chemotherapy (HEC). Support Care Cancer 2015 Feb 28.

8. Gralla, R J., Roila, F, Tonato, M., et al. MASCC/ESMO Antiemetic Guideline January 2013. 2013.

9. Hesketh P, Bohlke K, Lyman G et al. Antiemetics: American Society of Clinical Oncology focussed guideline update 2015. J Clin Oncol. 2 November 2015 [published ahead of print].

10. Ettinger DS, Armstrong DK, Barbour S, et al. Antiemesis. Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. J Natl Compr Canc Netw 2012 Apr;10(4):456-85

11. Aprepitant hard capsules (Emend). Summary of product characteristics. Merck Sharp & Dohme Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated December 2013.

12. Fosaprepitant powder for solution for infusion (Emend®). Summary of product characteristics. Merck Sharp & Dohme Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated December 2013.

13. Granisetron film-coated tablets (Kytril®). Summary of product characteristics. Roche Products Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 5 December 2014.

This assessment is based on data submitted by the applicant company up to and including 12 November 2015.

**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*

Drug 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.