Aprepitant

Essential medicine status

Section: 17. Gastrointestinal medicines > 17.2. Antiemetic medicines

EMLc | ATC codes: A04AD12

Indication	Nausea or vomiting ICD11 code: MG10
INN	Aprepitant
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Formulations	Oral > Liquid: 125 mg powder for oral suspension (in sachet) Oral > Solid: 80 mg ; 125 mg ; 165 mg
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Aprepitant
DrugBank	Aprepitant

Expert Committee recommendation

The Committee recognized the importance of adequate control of nausea and vomiting in patients undergoing cancer chemotherapy, in terms quality of life and clinical outcomes of treatment. The Expert Committee recommended the addition of aprepitant to the complementary list of the EML and EMLc as an antiemetic medicine for the supportive care of cancer patients receiving moderately to highly emetogenic chemotherapy on the basis of a favourable benefit to risk profile. The Committee noted that aprepitant, in combination with dexamethasone and a 5-HT3 receptor antagonist (e.g. ondansetron), is more effective than standard antiemetic therapy at reducing both acute and delayed onset nausea and vomiting associated with chemotherapy.

Background

The application requested the inclusion of aprepitant on the EML and EMLc as an antiemetic medicine for the supportive care of cancer patients receiving moderately to highly emetogenic chemotherapy. Aprepitant has not previously been considered for inclusion on the Model Lists.

Public health relevance

Chemotherapy-induced nausea and vomiting (CINV) is one of the most represented and significant side-effects related to chemotherapy. According to European Society of Medical Oncology (ESMO) and to the Multinational Association of Supportive Care in Cancer (MASCC), vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy (1). Inadequately controlled CINV and radiotherapy-induced nausea and vomiting (RINV) can precipitate a number of medical complications, resulting in life-threatening conditions, including severe dehydration and electrolyte imbalance with electrocardiogram (ECG) changes or myocardial dysfunctions and Mallory-Weiss tears of the oesophagus. These complications can

impact on the burden of care, increasing the efforts and costs of hospitalization and reducing the overall quality of life for patients, including a poorer outcome (2). The distress resulting from these symptoms may potentially lead to the patient's refusal to continue with the most effective antitumour therapy (3). According to a temporal criterion, the chemotherapy-associated emetic symptoms are categorized as acute or delayed: acute CINV occurs in the first 24 hours after chemotherapy, and delayed CINV at more than 24 hours. Aprepitant is indicated for prevention of both acute and delayed CINV. A four-level classification of chemotherapy agents has been accepted by registration authorities and groups producing recommendations on antiemetics, according to the emetogenic potential: high (emetic risk >90%); moderate (30%–90%); low (10%–30%); and minimal (<10%). To provide an example, anthracycline-taxane containing regimens and cisplatin > 50 mg/m2 are considered highly emetogenic; carboplatin, bendamustine and doxorubicin monotherapy are classified as moderately emetogenic; docetaxel monotherapy, gemcitabine, 5-FU and bortezomib are considered low emetogenic medicines (4).

Benefits

The application presented the findings of multiple clinical trials of aprepitant, using the MASCC/ESMO 2016 consensus guidelines for the prevention of chemotherapy and radiotherapy-induced nausea and vomiting (1) as a reference source. For the prevention of highly emetogenic chemotherapy CINV, a three-drug regimen including single doses of an anti-5-HT3, dexamethasone and anti-NK1 given before chemotherapy is recommended (MASCC level of confidence: high; MASCC level of consensus: high; ESMO level of evidence I; ESMO grade of recommendation: A) in the MASCC/ESMO guidelines. Adults: In a multicentre, double-blind, placebo-controlled trial in 421 Chinese cancer patients (5), addition of aprepitant to standard therapy with granisetron and dexamethasone resulted in an increased absolute rate of patients achieving a complete response (no emesis and no use of rescue therapy) during the overall phase (+12.9%, p=0.007). The benefit was mainly attributable to better control of delayed CINV with an increase of 14.6% of patients in absolute terms. Complete response rates for treatment groups were almost identical for acute CINV. In a multicentre, double-blind, placebo-controlled trial in 324 Japanese cancer patients (6), addition of aprepitant to therapy with a 5-HT3 receptor antagonist and dexamethasone prior to chemotherapy resulted in a higher percentage of patients with "no vomiting" in the overall phase (78.2 vs 54.8; p<0.0001), delayed phase (80.1 vs 56.9; p<0.0001), and acute phase 96.0 vs 91.1, respectively; p=0.0495). The percentage of patients with "no significant nausea" was higher in the aprepitant group than in the placebo group in the overall phase (85.4 vs 74.7; p=0.0143) and in the delayed phase (85.4 vs 76.0; p=0.0274), but there was no difference between groups in the acute phase. Similar results have been observed in patients receiving moderately to highly emetogenic chemotherapy in other disease-oriented clinical trials using moderately to highly emetogenic regimens, including treatments for lung cancer and germ-cell tumours trials in Asian and non-Asian populations (7–12). In a clinical trial of 264 patients preparing to undergo a stem cell transplant, patients were randomized to receive oral aprepitant or placebo in combination with oral ondansetron and dexamethasone during and for three days after the completion of the preparative high-dose cyclophosphamide regimens before the transplant (13). Patients who received aprepitant had higher complete response rates (81.9% vs 65.8%; p<0.001) compared to the standard treatment. 48.9% of patients in the aprepitant arm were able to maintain an intake of food >50% of normal versus only 14.6% of patients in the placebo arm, supporting the value of aprepitant in the overall supportive care of cancer patients. Children: In a randomized, double-blind, placebo-controlled trial, chemotherapy naive children aged 5 to 18 years receiving highly emetogenic chemotherapy were randomized to intravenous ondansetron (0.15 mg/kg) and dexamethasone (0.15 mg/kg) prior to chemotherapy followed by oral ondansetron and dexamethasone and either oral aprepitant (15-40 kg = days 1–3, 80 mg; 41-65 kg = day 1, 125 mg and days 2–3, 80 mg) one hour before chemotherapy or placebo (n=96) (14). The patients enrolled presented with both haematological and solid tumours: 25% received the treatment for Hodgkin lymphoma and the remaining 75% for sarcoma (osteosarcoma, Ewing sarcoma, rhabdomyosarcoma) or adenoid cystic carcinoma. Overall, 84% of patients in the placebo arm had moderate to severe vomiting compared to 56% in the aprepitant arm (p=0.004). There was less moderate and severe vomiting reported in the group receiving aprepitant compared to the placebo group (38% vs 72, p = 0.001) in the acute phase and a non-significant difference between the two groups in the delayed phase (42% vs 56%, p= 0.18). Complete response was higher in aprepitant arm, registered in the acute phase for 48% of patients compared to 12% in the placebo arm (p<0.001). The use of aprepitant resulted in better food intake (normal in 48% and 28% of the children receiving aprepitant versus placebo, p=0.04) and fluid intake (normal in 62% and 40%, p=0.03). In another Phase III trial, aprepitant for CINV prevention was assessed in patients aged six months to 17 years scheduled to receive either moderately or highly emetogenic chemotherapy (15). 307 patients were randomized to receive aprepitant plus ondansetron on day 1, followed by aprepitant on days 2 and 3, or placebo plus ondansetron on day 1 followed by placebo on days 2 and 3; dexamethasone was incorporated in nearly one third of the patients, with no difference between the study and control group. Patients presented with haematological and solid tumours. 77/152 (51%) patients

in the aprepitant group and 39/150 (26%) in the control group achieved a complete response in the delayed phase (p<0.0001), reporting an increase of 25% in absolute terms; similar results were found in the acute phase (complete response in the acute phase for aprepitant: 66% vs 52%, p=0.0135) and overall control (40% vs 20%, p=0.0002). Meta-analyses: Clinical data of aprepitant as antiemetic agent for moderately to highly emetogenic chemotherapy have been analysed systematically, addressing the role and benefit in cancer treatments. A meta-analysis performed in China, of ten studies of aprepitant for prevention of CINV, involving 4376 patients (16) found that for acute CINV, aprepitant improved the complete response by 14.21% in the acute phase, when combined with ondansetron and dexamethasone (83.33% vs 72.96%; p<0.001); patients receiving cisplatin seemed to derive a greater benefit than those who received an anthracycline plus cyclophosphamide regimen. For delayed CINV, aprepitant could improve vomiting by 14.98% compared with ondansetron (p=0.004).

Harms

The safety of aprepitant has been evaluated in the clinical trials. Hu et al (5) reported similar occurrences of drug-related adverse events (AEs) in 11.7% (24/205) of patients in the aprepitant group and 13.3% (28/210) of patients in the placebo-controlled therapy group. One or more AEs were reported in 40.0% (8/205) of patients in the aprepitant group and in 44.3% (93/210) of patients in the standard therapy group, representing similar occurrences. AEs included fatigue (5.9% and 1.9% in the aprepitant and placebo-controlled group, respectively), dizziness (2.4% and 0%), anaemia (2% and 0%), insomnia (2% and 5.7%), upper abdominal pain (0% and 2.9%), and non-cardiac chest pain (0% and 1%). Overall, no severe drug-related serious AEs or laboratory anomalies were reported during cycle 1, and there were no discontinuations due to medication-related AEs. In the trial of patients preparing for stem-cell transplantation (13), incorporation of aprepitant had no effect on the engraftment and the survival, supporting the oncological safety in terms of the cancer outcome and excluding significant interference with the antineoplastic agents used. Pharmacokinetic studies have shown that drug–drug interactions with aprepitant may exist, but are not considered clinically meaningful (17). In children, the safety profile of aprepitant appears consistent with the reports in adult populations (15).

Cost / cost effectiveness

The application presented two studies that evaluated the cost-effectiveness of aprepitant regimens for CINV. In a decision–analytic model study in Germany, an aprepitant regimen (aprepitant/ondansetron/dexamethasone) was compared with a control (ondansetron/dexamethasone) regimen, addressing clinical results and resource utilization (18). Incremental drug cost per patient and cycle for antiemetic prophylaxis was € 73.38. Expected health care utilization cost was € 154.99 in the aprepitant group and € 178.77 in the control group. Hence, it was estimated that 42% of the aprepitant drug cost was offset by lower resource use in the aprepitant group. Cost offsets arose mainly from lower doses of dexamethasone (€ 12.54), reduced use of rescue medication (€ 7.38), and avoided hospitalizations (€ 15.86). For the cost-effectiveness analysis (CEA), the range was € 26,135–31,646 per QALY gained with aprepitant and was judged cost-effective. The same conclusion was reached in a CEA performed in UK, considering patients receiving chemotherapy for breast cancer (19). An average of £ 37.11 (78%) of the cost of aprepitant was offset by the reduction in health care resource utilization costs; use of the aprepitant was associated with an additional cost of £ 28 for each emesis-free day gained and £ 22 for each CINVfree day gained. The ICER with aprepitant, was £ 10 847/QALY.

WHO guidelines

None available.

Availability

Aprepitant is available globally. Generic brands are available.

Other considerations

Aprepitant should be used in combination with dexamethasone and a 5-HT3 receptor antagonist.

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