Title: Proposal for the inclusion of Aprepitant as antiemetic drug for the supportive care of cancer patients receiving moderately to highly cytotoxic chemotherapy in the Essential List of Medicines of the World Health Organization (WHO EML).

List of Contributors: Jean Yves Douillard MD

1. Name of the focal point in WHO submitting or supporting the application
Andrè Ilbawi, WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention (NVI).

2. Name of the organization(s) consulted and/or supporting the application
European Society for Medical Oncology (ESMO)

3. International Nonproprietary Name (INN, generic name) of the medicine
Aprepitant.

4. Formulation proposed for inclusion; including adult and pediatric (if appropriate).
Aprepitant is an antiemetic drug, approved for the prevention of chemotherapy induced nausea and vomiting (CINV). Aprepitant is presented in the form of gelatin hard capsules filled with inert microcrystalline cellulose beads coated with aprepitant as active substance and sucrose, hydroxypropyl cellulose, microcrystalline cellulose, sodium lauryl sulfate, gelatin, shellac, black iron oxide and titanium dioxide. Capsules are opaque with a white body and mustard cap with as 40 mg, 80 mg, 125 mg and 165 mg. It is also available as oral suspension (125 mg)(1).

Aprepitant is approved for the use in pediatric and adult patients. Capsules are indicated for adult patients and children older than 12 years. For use in toddlers and infants from the age of 6 months to less than 12 years, oral suspension is indicated. A formulation in capsule of 40 mg is also available, approved for the prevention of post-operative nausea and vomiting (PONV) in adults after a surgical procedure. In case of chemotherapy, aprepitant is prescribed for patients receiving a single agent or regimen graded as “moderately” or “highly” emetogenic. For the prevention of CINV in adults and children over 12 years, aprepitant is administrated as 1 capsule 125 mg orally 1 hour before the chemotherapy (day 1). After the chemotherapy, on day 2 and day 3, 1 capsule of 80 mg is recommended. As an alternative regimen, aprepitant 165 mg day 1 can be considered. For 6 months – 12 years children, aprepitant as oral suspension is administered 1 hour before the treatment, on day 1, and followed by maintenance on day 2 and 3; for children, the dose is based on body weight. The
dose is calculated as 3 mg/kg orally day 1 (maximum dose 125 mg) and 2 mg/kg on day 2 and 3 (maximum dose 80 mg).

5. **International availability - sources, if possible, manufacturers and trade names.**
Aprepitant (brand name Emend) is included in multi-drug regimens for the prevention of CINV, including the combination with 5-HT3 inhibitors (e.g. ondansetron) and steroids e.g. dexamethasone. The schedule used per os is 125 mg – 80 mg – 80 mg (day 1- day 3) or 165 mg day 1 as capsule or 3 mg/kg – 2 mg/kg – 2 mg/kg as oral suspension (pediatric use).

6. **Whether listing is requested as an individual medicine or as an example of a therapeutic group?**
As an individual medicine.

7. **Information supporting the public health relevance’s**
Cancer is a public health problem, as the global second cause of mortality – accounting for 18,078,957 new cases in 2018 and 9,555,027 cancer-related deaths; 70% of the global burden of cancer is registered in low- and middle-income countries (2). Chemotherapy still represents the essential treatment for cancer, both in curative and non-curative care. 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), despite the considerable progress achieved in the last 30 years, vomiting and, especially, nausea, continue to be two of the most distressing side-effects of cancer chemotherapy (3). One of the most emetogenic antineoplastic product is cisplatin. When administered at high doses, namely over 50 mg/m², cisplatin can lead to emesis in 99% of the patients when no premedication for CINV is provided. Indeed, inadequately controlled CINV and radiation-induced nausea and vomiting (RINV) can precipitate a number of medical complications, resulting in life threatening conditions, including severe dehydration and electrolyte imbalance with ECG changes or myocardial dysfunctions and Mallory-Weiss tears of the esophagus; 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 (4). The distress resulting from these symptoms may potentially lead to the patient’s refusal to continue with the most effective antitumor therapy (5). According to a temporal criterion, the chemotherapy associated emetic symptoms are categorized in acute or delayed CINV. The acute phase is conventionally restricted to the first 24 hours after chemotherapy.
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 (6).

8. Methodology of research.

MASCC/ ESMO 2016 consensus on the prevention of chemotherapy and radiotherapy induced nausea and vomiting (3) was used as a reference source for relevant information, guiding the clinical indications. PubMed and Google Scholar were manually searched, retrieving the relevant papers for the discussion, with no time restriction. For the recommendation and level of evidence, where provided, ESMO levels of Evidence [I–V] and Grades of Recommendation [A–D] were used, according to the ESMO-adapted version of the grading of the Infectious Diseases Society (7, 8). Also, MASCC methodology was considered: the MASCC Levels of Scientific Confidence were classified as – high if repeated, randomized trials that were appropriately sized and well conducted; moderate if at least one randomized trial, supported by well conducted, phase II trials, or possibly several well-conducted phase II studies; low if formal clinical trials of a level less than that expressed above; very low if clinical impression only. The MASCC Levels of Consensus are given as high, moderate or low(3).


Mechanism of action. Aprepitant (also known as MK-0869 or L-754030) is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors. Aprepitant has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors. The NK1 receptor is the receptor of the substance P, a neuropeptide from the family of tachykinins. Substance P is an emetogenic endogenous mediator, active on NK1 receptor in the brainstem nuclei of the dorsal vagal complex, the regions of the brain involved in the regulation of emesis. Substance P is a neurotransmitter in the afferent pathway of the emetic reflex, functioning as the trigger of emetogenic signaling and causing nausea and vomiting (9). NK-1 is widely expressed in the gastro-intestinal vagal afferents and brain.
areas involved in the vomiting reflex: the nucleus solitary tract, the area postrema, the peripheral nervous system. The NK-1 receptor is involved in complex and different functions as pain transmission, endocrine and paracrine secretion, vasodilation and modulation of cell proliferation, having a role in brain homeostasis and the sensory neuronal transmission associated with depression, stress, anxiety and emesis (10-12). Aprepitant competes with substance P as ligand, with a highly selective central action. Cytotoxic chemotherapy can increase the release of 5-HT and substance P from the neuroendocrine cells of gastric mucosa and brainstem, as a reflex induced by cytotoxic agents when sensed by chemosensors of toxic substances in the modulation of the reflex of vomit, as a natural protective reflex. As experimental model of CINV, cisplatin-induced emesis is generally considered in study models. It is postulated that the highly emetogenic cisplatin is able to induce 5-HT release from the neuroendocrine cells in the gut mucosa, acting on the 5-HT3 receptor as trigger of the vagal afferent stimulus, which activates the central emetic circuitry in the medulla oblongata – including the substance P/NK1 receptor pathway, resulting in the activation of the efference through the dorsal motor nucleus of the vagus nerve, inducing an emetic reflex (13). Furthermore, substance P via NK1 receptors seems to enhance the release of 5-HT from neuroendocrine cells, suggesting a synergistic effect of 5-HT3 and NK1 receptors inhibitors to control the emetogenic reflex in patients receiving chemotherapy (14). Moreover, inflammatory cytokines (e.g. IL-1α and β) are also involved in the release of substance P from sensory nerve endings and neurons, supporting the synergistic action of corticosteroids (dexamethasone) and substance P antagonists (15).

Clinical use. MASCC/ESMO consensus guidelines recommended a three-drug regimen including single doses of a 5-HT3-receptor antagonist, dexamethasone and aprepitant given before chemotherapy to prevent acute nausea and vomiting following chemotherapy of high emetic risk and dexamethasone plus aprepitant or aprepitant alone to prevent delayed nausea and vomiting in cisplatin-or anthracycline and taxane-treated patients, respectively (3). There are two clinically relevant phases of CINV: acute CINV in the first 24 hours after chemotherapy, and delayed CINV at more than 24 hours after chemotherapy. Aprepitant is indicated for the prevention of both acute and delayed CINV. Oral administration of aprepitant in combination with ondansetron and dexamethasone prevents acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy including high-dose cisplatin. Aprepitant was tested in an Asian cohort of cancer patients receiving highly-emetogenic chemotherapy in a multicenter and double-blind placebo-controlled phase 3 clinical trial (16). The primary end point was complete response, defined as no emesis and no use of rescue therapy. Patients were randomized to receive granisetron (anti-5HT3) and dexamethasone both on day 1 with either aprepitant 125 mg day 1 and 80 mg day 2 and 3 or placebo (n=421). The addition of aprepitant increased the absolute rate of patients achieving a
complete response of +12.9% (p=0.007); however, the benefit was mainly attributable to a better control of the delayed CINV where +14.6% of patients reported a complete response (p=0.001) and no significant change in the acute phase (p=0.942). The safety profile was acceptable with 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%), anemia (2% and 0%), insomnia (2% and 5.7%), upper abdominal pain (0% and 2.9%), and noncardiac chest pain (0% and 1%). Overall, no severe drug-related serious AEs or laboratory anomalies were reported during cycle 1, and no discontinuations due to medication-related AEs. The efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen has been investigated in a trial in patients receiving carboplatin and paclitaxel. A multicenter, placebo-controlled, double-blind, study in Japanese patients with gynecologic cancer randomized 324 women to receive aprepitant or placebo together with both a 5-HT3 receptor antagonist and dexamethasone prior to chemotherapy (17). The percentage of patients with “no vomiting” was higher in the aprepitant group than in the placebo group in the overall (0–120 h) chemotherapy phase (78.2 vs. 54.8%, respectively; p<0.0001), in the delayed (24–120 h) phase (80.1 vs. 56.9%, respectively; p<0.0001), and even in the acute (0–24 h) 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 %, respectively; p=0.0143) and in the delayed phase (85.4 vs 76.0 %, respectively; p=0.0274), but there was no difference between groups in the acute phase. The data are consistent with the previous findings of a better control of the emetogenic reflex due to aprepitant, with a specific effect on the delayed phase for nausea and optimization of the vomit in both phases. Similar results were achieved 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 tumors trials in Asian and non-Asian populations (18-23). Interestingly, aprepitant resulted in better control of prevention of nausea and vomiting associated with stem cell transplant, as well (24). In a clinical trial in patients, candidate 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 3 days after the completion of the preparative high-dose cyclophosphamide regimens before the transplant (n=264). Patients who received aprepitant had higher complete response rates (81.9% versus 65.8%; p<0.001) compared to the standard ondansetron plus dexamethasone treatment; the
absolute benefit was +16.1%. Indeed, over the entire treatment period, 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. In the safety analysis of this trial, the incorporation of aprepitant had no effect on the engraftment and the survival, confirming the oncological safety also in term of the cancer outcome and excluding significant interference with the antineoplastic agents utilized. A further effort to assess the drug-to-drug pharmacokinetic interaction has been explored for cyclophosphamide, as it is an inactive prodrug that is converted to the cytotoxic metabolite 4-hydroxycyclophosphamide by the cytochrome P450 isoenzymes CYP2B6, CYP2C9, and CYP3A4/5 in the liver, with bioactivation potentially saturable at high doses and theoretically negatively affected by aprepitant, which is a moderate inhibitor of CYP3A4 plus a mild inducer of CYP2C9 when used for 3 days, and possibly an inducer of CYP3A4 when used longer. Pharmacokinetic studies showed that drug-drug interactions with aprepitant may exist but are not clinically meaningful (25). Aprepitant showed minimal effect on the area under the curve (AUC) of several chemotherapeutic agents tested, including cyclophosphamide, docetaxel, and vinorelbine and it does not alter prednisolone pharmacokinetics in patients with non-Hodgkin’s lymphoma receiving R-CHOP. No negative impact was seen in this and similar trials using aprepitant in the conditioning therapy for hematopoietic stem cell transplant (26, 27). The Italian Group for Antiemetic Research executed a trial studying aprepitant versus metoclopramide for the delayed cisplatin-induced CINV (28). Patients were randomly assigned to receive one of the following two oral antiemetic prophylaxes for delayed emesis: dexamethasone 8 mg once daily on days 2–4 plus aprepitant 80 mg daily on days 2 and 3 or dexamethasone 8 mg twice daily on days 2–4 plus metoclopramide 20 mg four times daily on days 2–4. Patients were surveyed with a diary for day 2-6, reporting the presence and grade of CINV. The primary endpoint of this study was the rate of complete response (no vomiting and no rescue treatment) from day 2–5 after chemotherapy (n=303 patients enrolled). Aprepitant was as effective as metoclopramide in controlling the delayed nausea for highly-emetogenic regimens, reaching a complete response in more than 80% of patients. The safety profile was consistent with previous findings and no difference in overall AEs reported. Though not resulting in superior CINV control, this trial provided the evidence to support the use of aprepitant as non-inferior to high dose metoclopramide (80 mg daily). High dose metoclopramide is no more recommended given safety concerns. In fact, a warning of the European Medicines Agency (EMA) recommended changes to the use of metoclopramide to reduce the risk of neurological side-effects like short-term extrapyramidal disorders and tardive dyskinesia: the revised indication restricts metoclopramide to be prescribed for short-term use (up to 5 days) and at a maximum dose of 30 mg a day (29); also, the use of aprepitant
may be considered where contraindications for metoclopramide exist, for the control of delayed nausea, like in Parkinson’s disease or previous intolerance to dopaminergic agents, where metoclopramide should be avoided (1).

**Aprepitant in Children** The safety and activity of aprepitant has been explored also in pediatric populations. In a randomized, double-blind, placebo-controlled trial, chemotherapy naïve children (5-18 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) 1 hour before chemotherapy or placebo (n=96) (30). The chemotherapy regimen considered highly-emetogenic are: ABVD in standard doses (doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m²); VAC (vincristine 2 mg/m², doxorubicin 75 mg/m², and cyclophosphamide 1200 mg/m²); VAdC (vincristine 2 mg/m², actinomycin-D 1 × 35 mg/m², and cyclophosphamide 2200 mg/m²); cisplatin and doxorubicin (over 3 days with daily dose of 40 mg/m² cisplatin and 25 mg/m² doxorubicin). The patients enrolled presented with both hematological and solid tumors: 25% received the treatment for Hodgkin lymphoma and around three-quart for sarcoma (osteosarcoma, Ewing sarcoma, rhabdomyosarcoma).

Overall, 84% of patients in the placebo arm had moderate to severe vomiting as compared to 56% in the aprepitant arm (p=0.004), resulting in +28% of CINV control. In particular, the acute phase seemed to be better impacted by the addition of aprepitant, resulting in less moderate and severe vomiting in the group receiving aprepitant as compared to the placebo group (38 vs. 72%, p=0.001) in the acute phase and non-significant difference between the two groups in moderate to severe vomiting 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 placebo arm (p<0.001).

The use of aprepitant resulted in better food intake (normal in 48% and 28% of the children receiving aprepitant vs placebo, p=0.04) and fluid intake (normal in 62% and 40%, p=0.03). No severe AEs were registered in both arms. The safety profile was consistent with the reports in adult populations and no differences registered in the experimental and placebo-controlled arm. In another phase 3 trial the role of aprepitant for CINV prevention was assessed in patients aged 6 months to 17 years scheduled to receive either moderately or highly emetogenic chemotherapy (31). Patients were randomized (n=307) to receive aprepitant (125 mg for ages 12–17 years; 3.0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12–17 years; 2.0 mg/kg up to 80 mg for ages 6 months to <12 years) 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 hematological and solid tumors. Seventy seven (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase (p<0.0001), reporting an increase of +25% in the delayed CINV; the same 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 analyzed systematically, addressing the role and benefit in cancer treatments(32): in one analysis performed in China, ten studies involving 4 376 oncology patients were included. 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% (p=0.004). The safety analysis showed in the aprepitant regimen a higher incidence of fatigue/asthenia in the (p=0.001), while the incidence of constipation was lower (p=0.002). The safety profile was consistent with other NK1 receptor antagonists, when surveyed all together in a metaanalysis of 17 studies and 8740 patients: patients receiving aprepitant had statistically significant but clinically not meaningful differences in fatigue and hiccups and lower constipation than control (33, 34). The addition of a NK1 receptor antagonists in patients receiving cisplatin chemotherapy increased the complete response on day 1 by 4%–14%, on days 2–5 by 8%–21% and on days 1–5 by 8%–20%, a difference considered not only statistically significant but also clinically relevant.

Level of Evidence and Grade of Recommendation: For the prevention of highly emetogenic chemotherapy CINV, a three-drug regimen including single doses of an anti-5HT3, 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 ESMO/MASCC Guidelines (3). Aprepitant augments the antiemetic activity of the 5-HT3 receptor antagonist ondansetron and the corticosteroid dexamethasone and optimizes the control both the acute and delayed phases of CINV.

10. Treatment details
Aprepitant is a NK1 receptor antagonist approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the prevention of CINV. Aprepitant is prescribed as 1 capsule 125 mg orally 1 hour before the treatment (day 1) and 80 mg after the treatment, on day 2 and 3. For 6 months – 12 years children, aprepitant oral suspension 3 mg/kg orally is recommended 1 hour before the treatment, on day 1, and followed by maintenance on day 2 and 3 at the dose of 2
mg/kg. The use is intended in combination with 5-HT3 antagonists (e.g. ondansetron) and dexamethasone.

11. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group.

The use of aprepitant has been associated with a better control of CINV, especially the delayed CINV, resulting in better fluid and food intake. As a medicine able to optimize the supportive care of patients, cost-effectiveness analysis have been provided – including the evaluation of less hospitalizations for AEs and the management of patients receiving highly-emetogenic regimens as outpatients (35). In a decision–analytic model study, an aprepitant regimen (aprepitant/ondansetron/dexamethasone) was compared with a control (ondansetron/dexamethasone) regimen, addressing clinical results and resource utilization, using the costs for Germany (36). 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 achieved by a CEA performed in UK, considering patients receiving chemotherapy for breast cancer (37). An average of £37.11 (78%) of the cost of aprepitant is 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 CINV-free day gained. The ICER with aprepitant, was £10,847/QALY. Interestingly, a CEA in Japanese patients receiving high-dose cisplatin showed a cost-effectiveness in the outpatient but not inpatient setting (38).

Benefit of aprepitant in cancer care: The magnitude of benefit in the overall control of nausea and vomit is around +12%, with particular relevance for delayed nausea (+15%). Indeed, as showed more precisely in children, the inclusion of aprepitant in the antiemetic strategy of supportive care in patients receiving high emetogenic regimen results in +20% of fluid and food intake, reducing the dehydration and hypo-nutrition complications. Moreover, the optimization of CINV control impacts directly on the improvement of quality of life, as showed in different studies with aprepitant. The use of aprepitant is safe, with no major adverse events described nor interactions with antineoplastic agents. The use is intended in adult and pediatric patients, for solid and hematological malignancies.

Reference
21. Olver IN, Grimison P, Chatfield M, et al. Results of a 7-day aprepitant schedule for the


