I.16	Vinorelbine - Rhabdomyosarcoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The submission notes: Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents with an incidence of 0.5/100.000 in patients under 15 years of age. Treatment has been broadly standardized around the world and most patients are treated according to international treatments protocols largely based on clinical trials. As a cancer considered responsive to chemotherapy most patients receive neoadjuvant chemotherapy followed by surgery and often radiotherapy. The survival of patients, especially in the high- and very high-risk groups has improved significantly since the introduction of maintenance treatment to the backbone of induction chemotherapy. This maintenance treatment comprises oral, daily cyclophosphamide and vinorelbine administered either intravenously or orally once weekly. This treatment has proved to be highly effective with an overall good tolerance and low toxicity profile. Vinorelbine is a vinca alkaloid, that achieved USFDA approval for non-small cell lung cancer (NSCLC) in 1994 and EMA approval for rhabdomyosarcoma in children in 2019. Vinorelbine is not yet included in the WHO EMLc and hence the request for the inclusion of vinorelbine to the WHO EMLc 2021.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Oral or intravenous vinorelbine will be used along with oral cyclophosphamide as maintenance therapy, in children with high-risk and very high-risk rhabdomyosarcoma.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: The principal support is provided by study RMS 2005 The European Pediatric Soft Tissue Sarcoma Study Group and published by Bisogno et al in the Lancet in 2019 as “Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial”.
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable The primary support for the submission is provided by RMS 2005, a multicenter, open-label, randomized, controlled, phase 3 trial that was conducted at 102 hospitals in 14 countries. The study enrolled patients aged 6 months to 21 years with rhabdomyosarcoma who were at high risk of relapse. High-risk included: (1) Patients with non-metastatic but incompletely resected embryonal rhabdomyosarcoma occurring at unfavorable sites age ≥10 years or tumor size >5 cm, or both; those with any non-metastatic rhabdomyosarcoma with nodal involvement. (2) Patients with non-metastatic alveolar rhabdomyosarcoma but without nodal involvement. (3) Patients in remission after nine cycles of ifosfamide, vincristine, dactinomycin with or without doxorubicin, and surgery or radiotherapy, or both High risk patients were randomly assigned (1:1) to stop treatment or continue maintenance chemotherapy consisting of intravenous vinorelbine 25 mg/m^2 on days 1, 8, and 15, and daily oral cyclophosphamide 25 mg/m^2, on days 1–28 for

	six cycles. The primary outcome was disease-free survival in the intention-to-treat population. Secondary outcomes were overall survival and toxicity. The authors concluded that adding maintenance chemotherapy seems to improve survival for patients with high-risk rhabdomyosarcoma. They further added this approach would be the new standard of care for patients with high-risk rhabdomyosarcoma in future EpSSG trials.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Although toxicity was described as manageable in patients who received maintenance chemotherapy, the term manageable should not be confused with not-impactful given that: 136 (75%) of 181 patients had grade 3–4 leucopenia, 148 (82%) had grade 3–4 neutropenia, 19 (10%) had anemia, two (1%) had thrombocytopenia, and 56 (31%) had an infection. One (1%) patient had a grade 4 non-hematological toxicity (neurotoxicity). Two treatment-related serious adverse events occurred: one case of inappropriate antidiuretic hormone secretion and one of a severe steppage gait with limb pain, both of which resolved.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	RMS 2005 was conducted between April 20, 2006, and Dec 21, 2016, and enrolled 371 patients who were randomly assigned to one of two groups: 186 to stop treatment and 185 to receive maintenance chemotherapy. Median follow-up was 60.3 months (IQR 32.4–89.4). In the intention-to-treat population, 5-year disease-free survival did not achieve statistical significance with 77·6% (95% CI 70.6–83.2) of those receiving maintenance chemotherapy versus 69·8% (62.2–76.2) of those without maintenance chemotherapy (hazard ratio [HR] 0·68 [95% CI 0.45–1.02]; p=0.061) disease-free at five years. However, in 5-year overall survival maintenance chemotherapy achieved statistically significant improvement with 86.5% (95% CI 80.2–90.9) of patients with maintenance chemotherapy versus 73.7% (65.8–80.1) of those without (HR 0.52 [95% CI 0.32–0.86]; p=0.0097) alive at 5-years. A 12.8% improvement in overall survival at 5-years in this patient population is valuable. And as summarized above, although toxicity was described as manageable in patients who received maintenance chemotherapy, the term manageable should not be confused with not-impactful. However, this does not tip the balance of the benefit to risk ratio in favor of risk.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	As noted, the principal support is provided by study RMS 2005 The European Pediatric Soft Tissue Sarcoma Study Group and published by Bisogno et al in the Lancet in 2019 as “Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial”. Thew overall quality if very good.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: There are no special requirements that are not part of standard of care nor that would not be available where the proposed therapies would be administered.

Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost, and affordability of the medicine in different settings.	Vinorelbine has been available in generic formulations for many years and cost should not be an issue in any setting.
Any additional comments	As noted above toxicity was manageable but definitely impactful. The consequences of this maintenance therapy administered over six month included grade 3–4 leucopenia in 136/181 patients (75%) and neutropenia in 148 /181 patients (82%). At each site the burden this may represent has to be considered.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	For more than three decades, standard treatment for rhabdomyosarcoma in Europe has included 6 months of chemotherapy. The European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) conducted a clinical trial to assess whether 6 months of maintenance chemotherapy would improve survival in patients with high-risk rhabdomyosarcoma. The primary support for the submission is provided by RMS 2005, a multicenter, open-label, randomized, controlled, phase 3 trial that was conducted at 102 hospitals in 14 countries. The study enrolled patients aged 6 months to 21 years with rhabdomyosarcoma who were at high risk of relapse. The study demonstrated that adding maintenance chemotherapy improved survival for patients with high-risk rhabdomyosarcoma. This approach will be the new standard of care for patients with high-risk rhabdomyosarcoma in current European and American treatment protocols and is considered the standard of care. Vinorelbine may be administered either intravenously or orally, in combination with oral cyclophosphamide. The duration of treatment for high-risk and very high-risk patients is planned as 6 cycles (6 months) and 12 cycles (12 months), respectively. Its proven efficacy, and its low cost support its approval with emphasis that toxicity should be carefully evaluated and managed.
References (if required)	