I.16	Vinorelbine - rhabdomyosarcoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents ((0.5/100.000 in patients < 15 years). Treatment has been broadly standardized around the globe and a majority of patients are treated according to international treatments protocols and clinical trials. Due to its chemo-responsiveness, neoadjuvant chemotherapy is used in the majority of patients followed by surgery and often radiotherapy. Survival of patients, especially in the high and very high risk group has significantly improved since the introduction of maintenance treatment to the backbone of induction chemotherapy. This maintenance treatment comprises oral, daily cyclophosphamide and vinorelbine either intravenously or orally once weekly.
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.	Survival of Rhabdomyosarcoma patients, especially in the high and very high risk group has significantly improved since the introduction of maintenance treatment to the backbone of induction chemotherapy. This maintenance treatment comprises oral, daily cyclophosphamide and vinorelbine either intravenously or orally once weekly. This treatment has proved to be highly efficient with an overall good tolerance and low toxicity profile. Vinorelbine is a longstanding vinca alkaloid, which achieved FDA approval for non-small cell lung cancer (NSCLC) already in the 1994 and EMA approval for rhabdomyosarcoma in children in 2019.
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:

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Prognosis for paediatric patients with high-risk rhabdomyosarcoma is still unsatisfactory despite the intensification of therapy. Great effort was taken to identify new agents that would improve their outcome. Following the first Italian feasibility and toxicity study on Vinorelbine in patients with advanced sarcomas, which had shown a favourable toxicity profile and evidence of biological activity, the same group performed a second pilot study to define the optimal dose of vinorelbine when used in combination with oral low-dose cyclophosphamide in children with refractory or recurrent sarcoma. 18 already pre-treated patients were treated with the study regimen. Ninety cycles were administered in total. One complete remission and 6 partial remissions were noted among the 17 patients who had measurable disease. Three of the eight assessable patients with rhabdomyosarcoma had responses to treatment. Following these promising results, this combination therapy (oral cyclophosphamide with intravenous vinorelbine) was introduced as maintenance treatment in the next EpSSG trial (EpSSG RMS 2005 a protocol for non-metastatic rhabdomyosarcoma) as one of the study questions: The study was designed as a multicentre, open-label, randomised, controlled, phase 3 trial. In 102 hospitals in 14 countries 371 patients were enrolled with high risk rhabdomyosarcoma. After completion of standard treatment (nine cycles of ifosfamide, vincristine, dactinomycin with or without doxorubicin, and surgery/radiotherapy) which were in remission were randomly assigned to either stop treatment or continue maintenance chemotherapy (six cycles of intravenous vinorelbine 25 mg/m2 on days 1, 8, and 15, and daily oral cyclophosphamide 25 mg/m2, on days 1-28). 186 patients were assigned to stop treatment and 185 to receive maintenance chemotherapy. Median follow-up was 60, 3 months. The 5-year disease-free survival was 77,6% with maintenance chemotherapy versus 69,8% without maintenance chemotherapy and 5-year overall survival was 86,5% with maintenance chemotherapy versus 73,7% without. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Italian pilot study: Two cases of grade 4 neutropenia were observed among 5 patients who received vinorelbine at a dose of 30 mg/m2 and 15 cases (37%) of grade 3 neutropenia in patients who received vinorelbine at a dose of 25 mg/m2, no other major toxicity was documented. Toxicity considered globally manageable, with haematological toxicities (anaemia, leukopenia, neutropenia, thrombocytopenia) and infections the most commonly reported.

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.)	Vinorelbine is an established compound in the current international European and North America treatment protocols for patients with rhabdomyosarcomas. Multiple studies and trials have proofed efficacy of this compound (see references). Adopted as standard of care also in the Children Oncology group for RMS protocols. Side effects and toxicities are well manageable and the overall tolerance is good. Available IV or orally, per os formulation is more adapted in less favourable settings.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Considering the fact that randomized studies in paediatric oncology are not easy to perform considering the low numbers, and even more if we consider that Rhabdomyosarcoma is a rare disease; the results of the randomized study showed a high evidence for the use of vinorelbine as maintenance therapy.
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:
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 (Navelbine™) and approved high-quality generics are supplied: Vials containing 10 mg/1ml or 50 mg/5ml or 20/30/80mg capsules. For developing countries, it is interesting because vinorelbine in capsules is available, easier to administer. Regarding the cost: Introduction of maintenance therapy containing vinorelbine will have an additional cost of 1350 Euros extra per patient which is acceptable considering the increased survival and life-quality. Especially, considering costs that would come up in the case of a relapse situation, the extra costs for vinorelbine are negligible.
Any additional comments	

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.	The addition of oral and intravenous vinorelbine to the EMLc for the maintenance treatment of rhabdomyosarcoma. Vinorelbine, used in combination with oral cyclophosphamide, demonstrates relevant survival benefits in children with RMS, with a manageable toxicity profile and favourable cost benefit ratio.
References (if required)	Casanova, M., et al., Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. Cancer, 2004. 101(7): p. 1664-71. Bisogno, G., et al., 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. Lancet Oncol, 2019. 20(11): p. 1566-1575. Casanova, M., et al., Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. Cancer, 2002. 94(12): p. 3263-8. Minard-Colin, V., et al., Phase II study of vinorelbine and continuous low doses cyclophosphamide in children and young adults with a relapsed or refractory malignant solid tumour: good tolerance profile and efficacy in rhabdomyosarcoma--a report from the Société Française des Cancers et leucémies de l'Enfant et de l'adolescent (SFCE). Eur J Cancer, 2012. 48(15): p. 2409-16.