The European Society for Paediatric Oncology (SIOP Europe)

Clos Chapelle-aux-Champs 30, Bte 1.30.30, B-1200
Brussels, Belgium

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Application for the Inclusion of Vinorelbine for the Treatment of Rhabdomyosarcoma as first line treatment on the WHO Essential Medicines List for Children 2021

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1. Summary statement of the proposal for inclusion

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. 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. Despite this, Vinorelbine is not yet included in the WHO EMLc. For this reason, we apply for the inclusion of Vinorelbine to the WHO EMLc 2021.

2. Relevant WHO technical department and focal point

This application has been pre-discussed with Bernadette Cappello, Lorenzo Moja, Albert Figueras, Elizabeth de Vries and Andrea Bondi. Further, the first draft was reviewed by Bernadette Cappello.

3. Name of the organisation(s) consulted and/or supporting the project

The European Society for Paediatric Oncology (SIOPE)

The European paediatric Soft tissue sarcoma Study Group (EpSSG)

Cooperative Weichteilsarkom Studiengruppe (CWS)

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

Vinorelbine, ATC L01CA04

5. Formulation proposed for inclusion

Vinorelbine (Navelbine™) and approved high-quality generics are supplied in vials containing 10 mg/1ml or 50 mg/5ml and as 20/30/80mg capsules. In the current FaR-RMS trial, Vinorelbine (either i.v. or oral) is given during maintenance therapy to newly diagnosed patients with high risk and very

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high risk disease as part of the first line treatment regime. In the FaR-RMS protocol, vinorelbine is administered at doses of 25 mg/m^2 i.v. or 60 mg/m^2 orally on day 1, 8, and 15 of each 28-days-cycle together with daily oral cyclophosphamide Treatment duration is either 6 (high risk patients) or 12 (very high risk patients)) cycles, as standard of care.

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

Listing is requested as an individual medicine.

7. Malignancy for which Vinorelbine is indicated for: Rhabdomyosarcoma in children

Sarcomas form a heterogeneous group of malignancies with more than 250 different entities. Very broadly, in children we can distinguish the bone sarcomas from the soft tissue sarcomas (STS). STS comprise approximately 7.4% of all paediatric malignancies, with rhabdomyosarcoma (RMS) being the most common soft tissue sarcoma in children [1]. RMS are malignant tumours of mesenchymal origin, committed to the skeletal muscle lineage, and belong to the broad group of small round blue cell tumours. The characteristic feature of RMS is the skeletal myogenic differentiation characteristics with the identification of muscle-specific proteins like myosin, desmin, myoglobin, Z-Band protein and Myo-D [2, 3]. In 1958, Horn and Enterline first classified RMS into four histopathological groups (embryonal, botryoid, alveolar, and pleomorphic) [4]. Since then, multiple modifications to this classification have been made. Nowadays, histopathologically RMS are divided into four major subtypes, embryonal, alveolar, pleomorphic, and sclerosing/spindle cell RMS [5-7]. The embryonal (eRMS) and alveolar (aRMS) are the two most common subtypes with frequencies of 60%-70% and 20%, respectively [7]. The term embryonal refers to the fact that eRMS histopathologically contain features of embryonic rhabdomyogenesis, whereas the term alveolar refers to the morphological resemblance of aRMS histology to foetal lung alveoli. The outcome of children with eRMS is much more favourable than the outcome of children with aRMS (5-year EFS 73% versus 29%) [8]. The majority of aRMS harbour a characteristic PAX3 or PAX7-FOXO1 fusion. The less favourable outcome in children diagnosed with aRMS is most probably related to this fusion, as aRMS without this fusion have similar prognosis as eRMS [8, 9].

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8. Treatment details for rhabdomyosarcomas in children

Within Europe, two European Clinical Trial Groups exist, who provide treatment protocols/treatment guidance for children and adolescents diagnosed with STS: The European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) and the Cooperative Weichteilsarkom Studiengruppe (CWS). Both clinical trial groups are long-standing, international organisations for and of professionals devoted to the care and treatment of children and adolescents with STS.

In the following section, we present the current open protocols and treatment recommendations of these two European groups, according to which most of the children/adolescents with rhabdomyosarcoma in Europe are treated with.

Most of the frontline drugs used to treat primary RMS in these protocols are already listed on the WHO-EML for children. However, vinorelbine being part of the standard frontline maintenance treatment in high and very high risk patients is not listed yet and so topic of this application.

CWS-guidance for risk adapted treatment of soft tissue sarcoma and soft tissue tumours in children, adolescents, and young adults: Guidance recommendations for the treatment of patients with rhabdomyosarcoma below 21 years of age categorised in different risk groups according to the European risk stratification schema [10].

CWS-2007-HR A randomised phase-III trial of the Cooperative Weichteilsarkom Studiengruppe for localised high-risk Rhabdomyosarcoma and localised Rhabdomyosarcoma-like Soft Tissue Sarcoma in children, adolescents, and young adults: Recommendations for the treatment of patients with localised Rhabdomyosarcoma (RMS), and localised extraosseous RMS-like soft tissue sarcoma (NCT00876031) [11].

EpSSG MTS 2008 and BERNIE study: Treatment for patients with metastatic rhabdomyosarcoma or other soft tissue sarcoma (non-rhabdomyosarcoma). EpSSG MTS 2008 prospectively included metastatic patients using a backbone of 27 weeks of intense chemotherapy followed by a year of maintenance therapy with iv vinorelbine and oral cyclophosphamide. The EpSSG-ITCC-Roche study,

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called the BERNIE study, used the same backbone randomising the addition of Bevacizumab to this backbone [12].

EpSSG RMS 2005 a protocol for non-metastatic rhabdomyosarcoma: First EpSSG study protocol for children and young people with non-metastatic rhabdomyosarcoma. The protocol contains two randomised questions for "high risk patients" and observational studies for patients categorised in other risk groups (NCT00339118) [13, 14].

EpSSG FaR-RMS Study: An overarching study for children and adults with Frontline and Relapsed Rhabdomyosarcoma: Study for patients with newly diagnosed and relapsed RMS including multi-arm, multi-stage questions. EudraCT number 2018-000515-24.

9. Information on public health relevance of soft tissue sarcomas

Soft tissue sarcomas form the fourth biggest group of malignancies in children after leukaemias/lymphomas, brain tumours and bone sarcomas.

As STS form a very heterogeneous group, the prognosis depends on multiple factors, including the exact type of soft tissue sarcoma (histopathology including molecular biology markers), grading, size, site, stage, and patient-related factors as sex, age, genetic predispositions and treatment-related factors as IRS postsurgical state, sensitivity to treatment but also availability of target treatment approaches. Due to these multiple varying factors and the heterogeneity of rhabdomyosarcomas, it is hardly possible to present a general statement of curability and survival of children and adolescents diagnosed with RMS. Newly diagnosed patients are assigned to a risk group, which subsumes the fusion status, IRS group, site, nodal stage, tumor size and age of the patients. Treatment is subsequently adapted to the assigned risk group.

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Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	**A**	Negative	I	Any	N0	Both Favourable
Standard Risk	***B***	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	***D***	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	***G***	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Table 1: Risk group assignment according to EpSSG FaR-RMS protocol

Children categorised into the low risk group, which were treated with a vincristine plus dactinomycin (VA) regime showed survival rates of up to 89%, children in the standard risk group additionally received cyclophosphamide and showed survival rates of 85% [15]. Patients treated in the EpSSG 2005 trial in the high-risk group were randomized to either be treated with IVA (ifosfamide, vincristine and dactinomycin) or with IVA plus doxorubicin. The 3-year event-free survival was 63,3%, respectively 67,5% in the IVA/IVA plus doxorubicin group [16]. Nonetheless, patients with metastatic RMS (very high risk group) still have a poor prognosis. In a pooled analysis by Oberlin et al., including 788 patients treated in Europe and the US, with metastatic RMS, treated with multiagent chemotherapy regimens built on a backbone of alkylating agents (cyclophosphamide or ifosfamide), vincristine, and dactinomycin, 3-year EFS and 3 year OS were 34 and 27% respectively. Some patients also received

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other drugs, depending on the specific protocol. Further all patients received local therapy (surgical resection and/or radiotherapy) [17, 18].

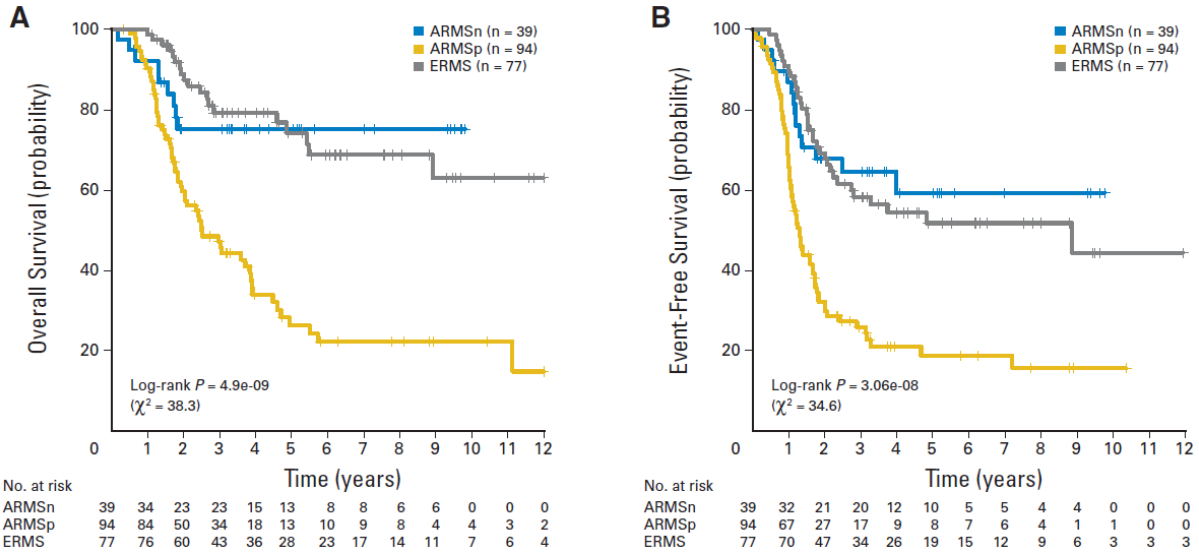

Figure 1: Kaplan-Meier curves showing significant poorer prognosis in (A) overall survival and (B) event-free survival for patients with fusion gene–positive alveolar rhabdomyosarcoma (ARMSp). Survival of patients with fusion gene–negative ARMS (ARMSn) and embryonal RMS (ERMS) is not significantly different [19].

10. Review of benefits, harms and toxicity for vinorelbine

Vinorelbine is a semi-synthetic third-generation vinca alkaloid that works as mitotic inhibitor by blocking microtubule polymerisation. It may also inhibit nucleic acid and protein synthesis and contribute to apoptosis in malignant cells.

It was initially approved in the USA in 1990's for adults in the treatment of advanced non-small cell lung cancer and breast cancer. For the patients diagnosed with soft tissue sarcomas it was first used in adults. In the last two decades several studies have confirmed its efficacy and safety for paediatric patients with refractory/relapsed solid tumors [20-22]

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 [21] ,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. 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. 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 [13].

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 [14, 16]. 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/m^2 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. Overall toxicity was well manageable in patients who received maintenance chemotherapy: mostly haematological toxicity, followed by infections. Only two treatment-related

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serious adverse events occurred which both resolved: one patient with inapportionate antidiuretic hormone secretion and one case of severe steppage gait with limb pain. [14].

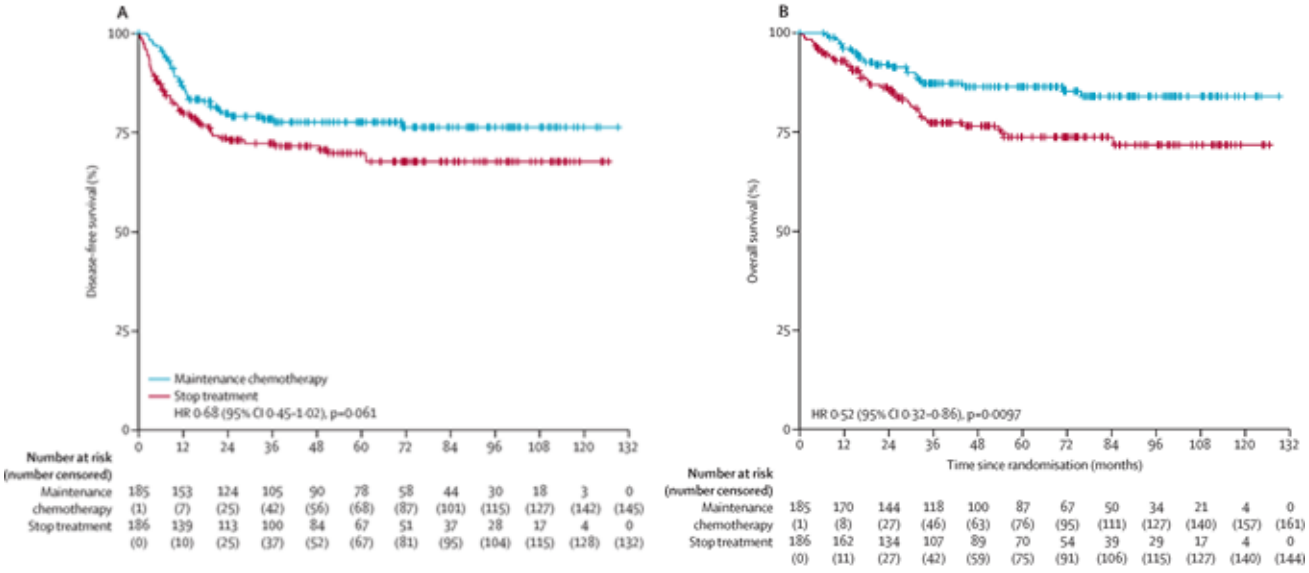

Figure 2: Kaplan-Meier estimates of disease-free survival (A) and overall survival (B) in patients receiving maintenance chemotherapy or not. HR=hazard ratio [14].

Based on these promising results and the poor overall survival of patients with metastasised rhabdomyosarcoma, Ferrari et al. have explored a new chemotherapy regimen (single center, compensate ground as new adopted institutional practice) that added vinorelbine to the standard treatment for patients with high-risk metastasised rhabdomyosarcoma (ifosfamide-vincristine-actinomycin-D (IVA) chemotherapy combination) in a small number of patients. In the VIVA regimen Vinorelbine was added on an outpatient basis to the classic IVA chemotherapy, and given intra-venous at a dose of 25 mg/m^2 on days 8 and 15 of each cycle. The first preliminary results are promising: on radiological assessment after three VIVA cycles, a major partial response was detected in four of four cases. At the time of the report, all patients were alive, two in radiological complete remission and two in partial remission. As side effects, grade 3 anaemia occurred in two patients and grade 4 neutropenia in all four. Infection/febrile neutropenia requiring IV antibiotics was seen in two patients. No grade 3/4 non-hematological toxicity was reported. Due to these side effects around 80% of patients had a reduction of at least one cycle. [23].

Vinorelbine has a good tolerance profile (myelosuppression was the main treatment-related toxicity with grade 3/4 neutropenia in 38% of patients) and with defined maximum tolerated dose of 30 mg/m^2 [20]. Recommended dose for intravenous vinorelbine in EpSSG RMS 2005 protocol is 25 mg/m2, given in 6 courses for 6 months [13]. It is less neurotoxic than vinblastine [20, 24]. Weekly schedule and ambulatory administration contribute to better compliance.

The only recently started Frontline and Relapsed-Rhabdomyosarcoma (FaR-RMS) study will investigate in high risk patients whether longer duration of maintenance therapy (12 months) with intravenous vinorelbine in combination with oral cyclophosphamide in high-risk rhabdomyosarcoma will further improve their outcome. For the very high risk category (metastatic patients, and patients with fusion positive tumors and lymph node involvement) one year of maintenance (historical standard) will be compared to 2 years of maintenance, allowing for both intravenous and oral vinorelbine formulations to be used according to FaR-RMS study guidelines. To make two years of maintenance feasible oral vinorelbine is the preferred formulation for the very high-risk category.

In summary, survival of the children and adolescents diagnosed with high-risk RMS improved significantly with maintenance therapy containing vinorelbine. Vinorelbine is standard of care in maintenance therapy in the current EpSSG protocols. Therefore, **vinorelbine, both intravenous and oral formulations, are considered an essential chemotherapeutic agents.**

Table 2: Summarizing the most important studies on vinorelbine in children with RMS

Author, year	Journal	Patients	Study	Compound	Outcome
Kuttesch 2009	Pediatr Blood Cancer	n=50 patients with recurrent soft tissue sarcoma (STS), neuroblastoma (NB), or primary brain tumor (CNS) Age 2-21 years	Prospective phase II clinical trial 1998-2002	Vinorelbine (intravenous)	Vinorelbine at a dose of 30 mg/m2 can be given safety in patients who have had prior chemotherapy and radiotherapy. Vinorelbine is demonstrably efficacious in the STS stratum, and particularly in RMS with a response rate of 36%. Vinorelbine has been associated with less neurotoxicity than other vinca alkaloids

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Casanova 2002	Cancer	n=33 patients with progressive sarcoma Age 2-29 years	Prospective study 1998-2001 Follow-up 24 months	Vinorelbine (intravenous)	Objective responses were observed in 6 of 12 patients with rhabdomyosarcomas
Minard-Colin 2012	European Journal of Cancer	n=117 (50 with RMS) patients with refractory/relapsed solid tumors (soft tissue sarcoma, neuroblastoma, osteosarcoma, Ewing`s sarcoma and medulloblastoma) Age 1-25 years	Multicentre prospective phase II study 2003-2008 Follow-up 3.6 year	Vinorelbine (intravenous)	ORR in the RMS group (n=50) was 34% after 2 cycles of therapy and the best ORR was 36%
Bisogno 2019	Lancet Oncol	n=371 patients with RMS at high risk of relapse Age 6 months to 21 years	Multicentre, open-label, randomised, controlled, phase 3 trial 2006-2016 Follow-up (median) 63.3 months	Vinorelbine (intravenous)	5-year overall survival was 86,5% with maintenance chemotherapy versus 73,7% without. This approach will be the new standard of care for patients with high-risk rhabdomyosarcoma in future EpSSG trials. Toxicity was manageable (mostly hematological toxicity and infections)
Casanova 2004	Cancer	n=18 high-risk patients with rhabdomyosarcoma after induction therapy Age 2-23 years	Prospective pilot study 4/2003-12/2003	Vinorelbine (intravenous)	Overall, there were 7 objective responses to treatment (one complete remission and 6 partial remissions) and 4 cases of disease stabilisation. vinorelbine was administered at a dose of 25 mg/m2, Grade > or = 3 neutropenia was observed in 37%
Ferrari 2020	Pediatr Blood Cancer	n=4 high-risk patients with rhabdomyosarcoma Age 6-17 years	Prospective study 2019 Follow-up 11 months	Vinorelbine (intravenous)	On radiological assessment after 3 VIVA cycles, a major PR was detected in four of four cases. At the time of the report, all patients were alive, two in radiological complete remission and two in partial remission; significant haematological toxicity was observed, but no other major complications

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11. Costs/Cost-effectiveness

Providing costs on the treatment with vinorelbine is difficult as prizes vary from country to country and patient to patient. However as an example, one vial of 5 ml vinorelbine (50mg/5ml) as a generic costs between 120 and 150 Euros. To treat a child with a body surface of 1 m^2 with a dosing of 25 mg/m^2 would cost 75 Euros each time. For 6 cycles (3 applications per cycle) this would cost 1,350 Euros in total.

According to the WHO book on "Introduction to Drug Utilization Research (2003; 49 pages)" about cost-effectiveness: *"Cost-benefit analysis is used to value both incremental costs and outcomes in monetary terms and therefore allows a direct calculation of the net monetary cost of achieving a health outcome. A gain in life-years (survival) may be regarded as the cost of the productive value to society of that life-year using, for example, the average wage. The methods for valuing gains in quality of life include techniques such as willingness-to-pay, where the amount that individuals would be willing to pay for a quality-of-life benefit is assessed"*. Having this statement in mind and considering the significant survival benefit with the introduction of maintenance therapy containing vinorelbine (see studies above) we as pediatric oncologist believe that 1350 Euros extra per patient are insignificant values 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.

12. Summary of regulatory status and market availability of the medicine

Vinorelbine is approved by the FDA for NSCLC and by EMA for children with soft tissue sarcoma

- US Food and Drug Administration (FDA):
    - Approved on 23.12.1994 for locally advanced or metastatic non-small cell lung cancer
- European Medicines Agency (EMA):
    - Approved as orphan designation on 11.01.2019 (EU/3/18/2133) for the treatment of soft tissue sarcoma
- Australian Government, Department of Health, Therapeutic Goals Administration

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13. Availability of pharmacopoeial standards

- The British Pharmacopoeia: no access
- The International Pharmacopoeia: no
- The United States Pharmacopoeia: yes
- The European Pharmacopoeia: no access

14. Summary and conclusion on essential compounds to treat rhabdomyosarcoma in children

i. Conclusion: According to the literature, the SIOPE Essential Medicine working group strongly recommends, that, vinorelbine is an essential medicine in the treatment of newly diagnosed paediatric soft tissue sarcomas in addition to the already included medicines on the WHO EMLc 2019 list.

ii. Rationale: Vinorelbine is an established compound in the current international European treatment protocols for patients with rhabdomyosarcomas. Further, multiple studies and trials have proofed efficacy of this compound. Unavailability of vinorelbine leads to impracticality of these well-established treatment regimens and might lead to a significant decrease of the treatment quality and prognosis of the affected children.

iii. Reality: Vinorelbine is longstanding and experiences with this compound is wide. Side-effects and toxicities are well manageable and the overall tolerance is good.

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