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Market access to new anticancer medicines for children and adolescents with cancer in Europe

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Abstract ***Background and aims:*** There is an alarming delay in Europe for anticancer medicines becoming accessible for children. Following a paediatric European Union marketing authorisation, national Health Technology Assessment (HTA) agencies evaluate effectiveness, and safety of medicines to support decision on their cost and reimbursement. This study (a SIOPE Access to Medicines project) aimed to evaluate how these HTA evaluations take place for anticancer medicines indicated for paediatric use in Europe and to explore where the delays for market access originate.

Methods: We obtained HTA reports from the public domain for nine European countries for blinatumomab, dinutuximab beta and tisagenlecleucel. We evaluated the time elapsed between marketing authorisation for a paediatric indication and a national HTA decision and the nature of the decision.

Results: Out of 23 HTA decisions (four countries without blinatumomab report), 18 were positive, two with restrictions, three negative. For blinatumomab, tisagenlecleucel and dinutuximab beta, the median time to an HTA decision after regulatory approval for paediatric use was 353 days (range 193–751), 141 days (range 77–517) and 515 days (range 0–780), respectively, with variability between countries. Dinutuximab beta and tisagenlecleucel were first introduced in children, but did not result in shorter time to HTA decision. For blinatumomab, marketing authorisation followed 1008 days after the indication in adults, with HTA

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applications submitted a median of 167 days later, and a recommendation after 145 days.
Conclusions: This study reveals ample variability in HTA decision making in nine European Union countries. Collaboration and alignment of required evidence is needed to facilitate robust scientific HTA assessments, also considering methodological challenges in paediatric oncology.

1. Introduction

Much awareness has been raised on the delayed patient access to new anticancer medicines within Europe compared to the US [1], but little attention has been paid to the accessibility of new medicines for children and adolescents with cancer. The introduction of the EU Paediatric Regulation in 2007 has been a game changer, but still therapeutic gaps remain in paediatric oncology and neonatology [2]. In the past 10 years, only 12/150 new anticancer medicines approved in the European Union were for use in children.

In the European Union, access to newly approved medicines is conditioned by pricing and reimbursement schemes, which are performed by health technology assessment (HTA) agencies. HTAs evaluate (comparative) effectiveness, safety, and the costs of the medicines, either through a budget calculation or by more advanced economic models, analysing cost-effectiveness over longer time periods. HTA agencies then recommend on reimbursement under an insurance or reimbursement scheme, reject or accept the application, or demand additional interventions such as price negotiations or the collection of additional data. In some countries, no benefit assessment is needed if an orphan drug is approved by the European Commission and the costs of the drug is below a certain threshold. In the European Union, most HTA assessments are performed at the country level (sometimes based on reports from other countries), but some countries have independent, regional assessments. Pharmaceutical companies often apply first in large and high-income countries, because of market size and price expectations [3].

Within paediatric oncology, all of the above mentioned challenges seem to be amplified. Paediatric cancers are by definition (ultra) rare diseases and consequently often do not meet the conventional criteria used by HTAs [4,5]. Due to the rarity of the disease (subgroups), randomised controlled trials may be impossible and single arm studies are often used to study new medicines. Consequently, the use of ICER (incremental cost-effectiveness ratio) thresholds and the comparison to QALYs (quality adjusted life years) may be challenging if not impossible. Moreover, within the paediatric oncology community, many stakeholders are unaware of the process of HTAs, resulting in misalignment between clinical trials and the information needed for HTAs and making medicines accessible to patients [6].

This study aims to evaluate how HTA evaluations took place for three selected anticancer medicines recently indicated for paediatric use in the European Union and to explore where the delays for market access originate. We additionally used a survey to compare our findings with the experience of the end-users (paediatric oncologists).

2. Methods

We evaluated time (in days) between the moment of European Union (EU) marketing authorisation for a paediatric indication and the subsequent national HTA decisions in nine European countries (France, Germany, Ireland, Italy, the Netherlands, Norway, Poland, Scotland and England/Wales), on access to three new anticancer medicines (dinutuximab beta, blinatumomab and tisagenlecleucel; Supplemental Document S1).

Only anticancer medicines, as new molecular entities, with a paediatric indication granted after 2007, the year of implementation of the EU paediatric regulation, and before 2019 were considered to allow at least 3 years for HTA evaluation. Selection was based on: [1] relevance for treatment of children with cancer (i.e. number of patients expected to benefit from the treatment), [2] first introduction in children (i.e. tisagenlecleucel, dinutuximab beta), [3] paediatric indication following first introduction in adults (i.e. blinatumomab) and [4] (high) price and expected budget impact.

Blinatumomab was chosen over dasatinib and nilotinib for chronic myeloid leukaemia, ipilimumab for melanoma, vandetanib for thyroid cancer and pembrolizumab for Hodgkin's disease since it concerns the largest population of patients, i.e. with acute lymphoblastic leukaemia, and thus has the largest potential budget impact, among anticancer medicines with a delayed approved paediatric variation after a first marketing authorisation in adults. Among anticancer medicines first approved to treat a paediatric haematological malignancy, tisagenlecleucel for CD19 acute lymphoblastic leukaemia was chosen over gemtuzumab

ozogamicin for acute myeloid leukaemia since this effective treatment has a major budget impact. Among anticancer medicines first approved for the treatment of a paediatric solid tumour, dinutuximab for neuroblastoma was chosen over everolimus for sub-ependymal giant cell astrocytoma and mifamurtide in osteosarcoma since it is a changing-practice treatment fully supported by the international paediatric oncology community. Of note, several targeted anticancer medicines have been approved since 2019 in the EU for a tissue-agnostic indication at once in children and adults (larotrectinib, entrectinib, selpercatinib). They were considered as too recently approved and raising specific issues related to their tissue-agnostic indication for HTA evaluation that would have made the specific paediatric related issues more difficult to identify at this moment.

2.1. Data and analyses

Data on national HTA decisions were searched in the public domains of the national HTA agencies (Table S1) and the EUnetHTA Network (eunethta.eu/about-eunethta/eunethta network/) between April 1, 2020 and November 12, 2020. Two authors (MO, RS) searched independently for the reports, translated the reports into English by an online machine (deepl.com) if none of the authors was fluent in the respective language and then extracted data. If both authors could not find the respective information, a third author (GF) performed an additional search. The selection of nine countries from the European Union was based on the availability of at least one HTA report with a clear recommendation for one of the three case medicines for an individual country. This criterion was chosen to test the efficiency of our search strategy for HTA reports in the public domain and to test whether the respective country has a functioning and transparent HTA system in place.

The date of the European Union marketing authorisation for a paediatric indication for the three case medicines were retrieved from the Union Register of Medicinal products from the European Commission (https://ec.europa.eu/health/documents/community-register/html/index_en.htm). To understand where the delay in market access originated, we reported the total duration between market authorisation and HTA recommendation and calculated the time duration of the actual HTA evaluation process. We searched in the HTA reports and on the HTA websites for the dates that the requests were submitted by the pharmaceutical companies and the date the recommendations were published. For Italy, we collected (if available) both the date a recommendation was published in the Gazzetta Ufficiale, an official daily publication by the Italian government, and the date from the AIFA (Italian Medicines Agency) report. In Germany, no efficacy and cost-effectiveness analyses are required for following market authorisation for orphan medicines, if the expected costs are below a certain threshold. In this situation, the HTA recommendation comes available the day market authorisation, was published in the community register.

In addition, we also evaluated the nature of the HTA decision, i.e. positive recommendation, positive with restrictions, negative. We flagged when no HTA report was available, which could be interpreted in various ways, e.g. no application for a paediatric HTA evaluation in the individual country, HTA decision still pending or decision has been made but not reported yet.

Finally, we explored the accessibility from the end users' perspective, i.e. paediatric oncologists. We contacted the representative of each of the nine National Paediatric Haematology-Oncology Societies. Questions were: i) Is there a HTA in your country? And for each of the three medicines, ii) are you able to prescribe this medicine in your country? iii) How are the costs covered?

3. Results

3.1. Recommendations

We found HTA reports for the paediatric indication in 5/9 countries for blinatumomab and for all countries for tisagenlecleucel and dinutuximab beta (Table 1). In Ireland, full HTA recommendation followed a rapid review for blinatumomab in early 2019. No HTA report was found online, but it was stated that the HSE (health service executive) approved reimbursement following confidential price negotiations in May 2019. Similarly, only an abbreviated report was available for blinatumomab in Scotland. In the Netherlands, no HTA assessment was performed for blinatumomab in children, but reimbursement was made possible via an alternative approval process (add-on list). In Norway, Poland and England/Wales, only reports for adult indications were available for blinatumomab.

Out of 23 HTA decisions, 18 were positive, 2 with restrictions, and 3 were negative (Table 1). For blinatumomab, all available HTA reports (N = 5) were positive; for tisagenlecleucel, 7/9 recommended positively, 2/9 negatively; for dinutuximab beta, 6/9 were fully positive, 2/9 with restrictions and 1/9 was negative.

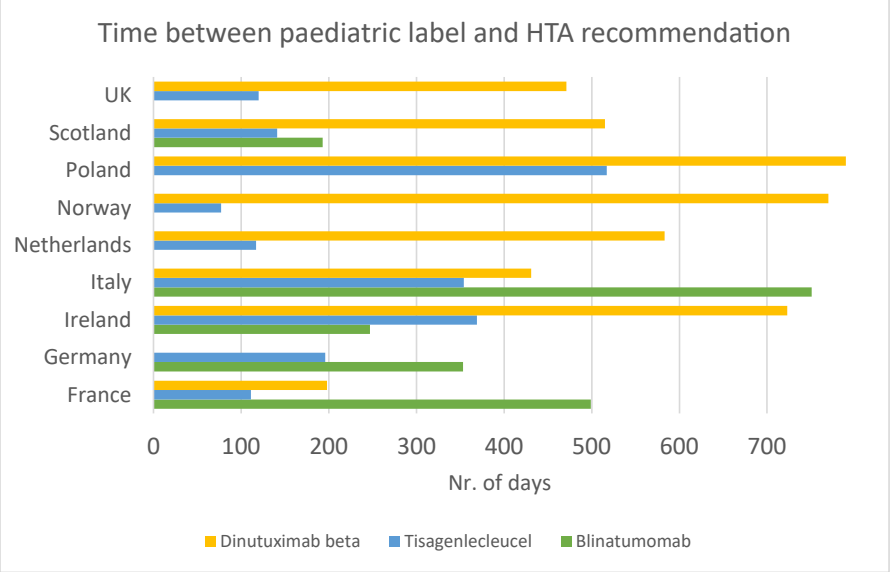
The outcome of the HTA reports is summarised in Table 1. Interestingly, the French HTA (Haute Autorité de Santé) approved the reimbursement of blinatumomab despite doubting the additional benefit on morbidity and mortality compared to historical treatment results, because blinatumomab can be administered at home. For one of the case medicines, tisagenlecleucel, there were contradicting recommendations by the respective countries. Although five out of nine countries doubted the efficacy data supporting

Table 1
Health technology assessments of the three case medicines per country

	UK	Scotland	Poland	Norway	NL	Italy	Ireland	Germany	France
Blinatumomab									
Recommendation	Adult	+	Adult	Adult	NA[b]	+	+	+	+
Restrictions	–	–	–	–	–	–	–	–	–
Evaluation		?[a]				€	?[c]	[d]	
Tisagenlecleucel									
Recommendation	+	+	–	+	+	+	–	+	+
Restrictions	–	–	–	–	–	–	–	–	–
Evaluation							€		
Dinutuximab beta									
Recommendation	+ R	+	+	+	+ R	+	–	+	+
Restrictions	No previous dinutuximab, no relapsed or refractory disease	–	–	–	Not for relapsed or refractory disease	–	–	–	–
Evaluation		€	€			€	€		

R; restrictions, NF; not found, NA; not available
Concerns about data, price acceptable € Data convincing, price too high, + Positive decision, + R Positive decision with restriction, - Negative decision, Data convincing and price acceptable, ? No clear recommendation could be extracted from the reports found.
[a] Only an abbreviated report was available for the approval in paediatrics, so no details were available on the evaluation.
[b] No report available, blinatumomab approved for add on list.
[c] Only (positive) decision available on website, no report supporting this decision.
[d] Because of the orphan designation, no efficacy assessment was required and because of acceptable costs, no economic evaluation was performed.

tisagenlecleucel, this resulted in a negative recommendation in two countries (Poland and Ireland) and positive recommendations in the other three (though with additional requirements). In England/Wales it was decided that the size of the clinical benefit compared with blinatumomab or salvage chemotherapy was uncertain and decided not to recommend tisagenlecleucel for routine use, but to recommend alternative reimbursement via the Cancer Drugs Fund with a request for additional data collection.



	Date of paediatric label	HTA approval (median nr of days, range)
Blinatumomab	27 Aug 2018	353 (193-751)
Tisagenlecleucel	23 Aug 2018	141 (77-369)
Dinutuximab beta	08 May 2017	515 (0-780)

UK: refers to England and Wales

Fig. 1. Time between regulatory approval for pediatric use by the European Commission (baseline) and HTA recommendation by country.

3.2. Time to HTA decision

Blinatumomab was the only medicine first authorised in adults; market authorisation for the paediatric indication was granted 1008 days after the initial indication in adults.

For blinatumomab, tisagenlecleucel and dinutuximab beta, the median time to an HTA decision after regulatory approval of paediatric use was 353 days (range 193–751), 141 days (range 77–517) and 515 days (range 0–780), respectively. Individual countries showed large variability on time to decision (Fig. 1). For blinatumomab in Italy, the date of recommendation was published in the Gazzetta Ufficiale, an earlier report by AIFA may have been available but was not found. In Germany, HTA evaluation for dinutuximab beta was not required and the HTA recommendation became available at the same day as the market authorisation. For tisagenlecleucel and blinatumomab a cost analysis was required in Germany, and thus an HTA evaluation performed.

For blinatumomab, date of submission was found for all 5 HTA reports: HTA applications were submitted with a median of 167 days (range 141–450) after regulatory approval, with a decision following a median of 145 days (range 49–587). For Ireland, a rapid review was published, recommending a full HTA assessment for the paediatric indication. However, no report was found, only a statement that 'The HSE has approved reimbursement following confidential price negotiations; May 2019'.

For tisagenlecleucel, date of submission was retrieved for 5/9 reports and for dinutuximab beta for 4/9 reports. Once submitted, the HTAs needed a median of 111 days (range 37–209) and 50 days (range 0–363), respectively, to generate a decision. In Ireland a rapid review was commissioned for tisagenlecleucel and completed 30 days later. The request for full HTA assessment was submitted after 103 days with a decision 209 days later.

The survey of national paediatric oncology representatives confirmed the overall findings from the HTA report analyses (Table 2). For England/Wales, Scotland and Ireland a combined response was received from the Children's Cancer and Leukaemia Group representative, describing the situation in England only. All representatives were aware of an HTA in their country. The experience of the representatives prescribing the medicines aligned with the HTA reports, except for blinatumomab in England/Wales. The representative answered that the prescription of blinatumomab is feasible within the National Health Services (NHS), where no HTA report on blinatumomab in children was found. Lastly, costs are mostly covered by NHS or insurance, except for Norway, where costs for all three medicines are covered by the hospital, and Poland, where tisagenlecleucel is covered by charities (in line with the negative HTA decision).

4. Discussion

This study shows ample variability in HTA decisions of nine EU member states for three anticancer medicines with an EU marketing authorisation in children. This variability significantly affects the use of these medicines in clinical practice. We evaluated 23 HTA decisions, i.e. 18 positive, 2 positive with restrictions and 3 with a negative recommendation for use. For blinatumomab, initially approved for adults, HTA reports for the paediatric indication were retrieved in 5/9 countries. The largest variability in HTA decisions

Table 2
Results from survey of national paediatric haematology–oncology representatives, of countries included in this manuscript.

Country	Is there an HTA?	Blinatumomab		Tisagenlecleucel		Dinutuximab beta	
		℞	€	℞	€	℞	€
France	+	+	NHS	+	NHS	+	NHS
Germany	+	+	Insurance	+	Insurance	+	Insurance
Italy	+	+	NHS	+	NHS	+	NHS
Netherlands	+	+	Other[a]	+	Insurance	+	Insurance
Norway	+	+	Hospital[b]	+	Hospital	+	Hospital
Poland	+	+	NHS	−	Charities	+	NHS
UK[c]	+	+	NHS	+	NHS[d]	+	NHS

HTA: health technology assessment
℞ Are you able to prescribe in your country?
€ How are the costs covered?

[a] Add on list
[b] Reimbursement not yet approved for paediatric indication (only adults).
[c] Response on behalf of Ireland and UK by CCLG (Children's Cancer and Leukaemia Group), response based on situation in England.
[d] Reimbursed within NHS but via the 'Cancer Drugs Fund', which means that it is not routinely funded, but has to be applied for on a case-by-case basis.

was found in comparing the time to decision, ranging between 0 and 780 days. We additionally found that quite some time elapsed between the EMA recommendation, the European Commission decision and the subsequent HTA applications, with variability across countries and products. In some countries there seemed to be no HTA decisions at all, i.e. in the case of blinatumomab.

The variability in time between EMA recommendations and the different HTA decisions may be affected by the strategy from the pharmaceutical company or by differences in methodology between HTAs and the subsequent time needed for the application. Differences in methodology could concern a request to provide an overview of all trials that were conducted with the medicine in question, a review of public guidance or the request for economic evaluations of the expected costs [8].

From this study, we could not conclude where the delay in market access originated, other than several aspects which may have contributed to the delay. It took 1008 days before marketing authorisation was granted for blinatumomab in children. Until then, physicians prescribed blinatumomab off label, as it was commercially available for adults. Requesting marketing authorisation for a paediatric label requires additional efficacy and safety data, which is costly for pharmaceutical companies. Due to the rarity of paediatric cancer, requesting a paediatric label may be less attractive and sometimes not cost effective, even with extension of the Supplementary Protection Certificate. In Norway, Poland and England/Wales we could not find HTA reports for blinatumomab in children, while adult reports were available. From the public websites, it was not clear whether separate assessments in children were not needed because the costs were within a given range. We advocate considering co-development in both populations if the malignancy is biologically similar in children and adults leading to first EMA licensing in both populations at the same time and facilitate subsequent timely evaluations by HTAs.

Even though the number of medicines in this study was small, the data illustrate that the delay in market access for children was not only driven by HTA variability, although the duration of the assessment took often longer than the 2–3 months reported by EUnetHTA (European network for health technology assessment) [9]. An additional factor was the timing of the pharmaceutical company to apply for HTA evaluation with each competent authority of the different countries.

Although the time between marketing authorisation and market access was indeed shorter for tisagenlecleucel (first authorised in paediatrics) compared to blinatumomab (first authorised adults), this was not the case for dinutuximab beta (first authorised in paediatrics). We found no clear explanation for this difference and hypothesised that the complicated assessment of antiGD2 monoclonal antibody predecessor, i.e. dinutuximab (Unituxin™), in England/Wales may have contributed to the delay in evaluating dinutuximab beta (Qarziba™) by HTA [10,11]. After Unituxin™ was granted an EU marketing authorisation in August 2015 for the treatment of high-risk neuroblastoma, based on the results of the Yu trial [7], NICE (HTA agency for England/Wales) decided not to recommend Unituxin™ for reimbursement. Although the committee found that 1.97 incremental life years were gained with the addition of dinutuximab, they decided that the cost of the quality adjusted life years did not meet the criteria set for reimbursement within the NHS. An exception could be made for treatments extending life expectancy, provided that life expectancy is short (i.e. $<$ 24 months). However, this was considered not applicable to the high risk neuroblastoma cohort under investigation; median life expectancy was four years (on the control arm). Parents appealed the decision by NICE [10], but before a final decision was made, the pharmaceutical company withdrew the marketing authorisation from Europe in March 2017. Later, Qarziba™ was approved for reimbursement, with strong involvement of the patients and parents community, but in the interim antiGD2 therapy was not available for neuroblastoma patients in Europe.

There were several limitations to this study. First, the choice of the three case medicines; our findings may not necessarily reflect the full picture of HTA assessments of other medicines. Further, the collection of HTA reports from the public domain, the translation in an online machine and the interpretation of the data from the heterogenic reports, with great variability in structure and outcome parameters, may have affected our findings. Nevertheless, we feel confident of the search method as we found at least two of the three medicines for all included countries and double-checked data collection by at least two authors. Moreover, the survey confirmed our findings.

The large variability between HTA decision making across Europe is not new [12,13]. Our study provides insight on how this variability influences access to newly approved anticancer medicines for children and adolescents across the EU. The paediatric oncology community acknowledges that trials often have a single arm design in paediatric oncology research, since patient numbers are smaller, and outcomes may differ from adults. Therefore, the assessment of efficacy, safety and cost-effectiveness needs to be adapted to the paediatric needs with innovative development designs. Early discussion with HTA should be set up in the design of paediatric development plans to warrant that data generated will be relevant for HTA evaluation. This is particularly true when randomised trials are not feasible, but single arm trials with robust data from real life can generate the requested

information. HTA evaluation could benefit more from real world data and innovation in trial design in paediatrics, as well as joint scientific parallel advice [14].

The specificities of the paediatric population need to be taken into account during the health technology assessment. As mentioned by Jeffrey Bernstein, a father of a child who has been treated for a neuroblastoma and a parent advocate for the approval of dinutuximab by NICE, we should avoid that "a toddler who might survive four years after diagnosis is less deserving of special consideration for access to effective new treatments than a senior citizen who has been told that he/she will live only for another 18 months" [11]. Harmonisation of evaluation by HTA bodies across member states would facilitate timely access to new anticancer medicines for all children in the EU.

To conclude, this study reveals ample variability in HTA decision making on paediatric oncology products in nine European Union countries. A scattered HTA landscape does not help patients and does not help strengthening paediatric oncology in Europe. Lack of harmonisation has at least two reasons: [1] sovereignty of EU member states to govern their own health systems, [2] bureaucratic/procedural differences between member states leading to lack of harmonised access. In terms of prioritising, tackling the issues under 2 by fuelling awareness, making visible the impact of non-harmonised access and on facilitating coalitions of the willing, are key to address. Our study adds to that. Collaboration between academia, pharmaceutical companies, parent and patient advocates, EMA and HTA organisations is needed to facilitate robust, transparent and timely scientific HTA evaluations. We like to coin the initiative of ACCELERATE [15], a platform that has demonstrated the value of such a truly multi-stakeholder collaboration in the field of paediatric oncology drug development. ACCELERATE is ready and keen to engage with HTA representatives and all other stakeholders in significantly improving and accelerating access to newly approved anticancer therapies for children and adolescents. Accelerated introduction of new medicines in standard treatments along with equal access to therapies is urgently needed to treat more children and adolescents with cancer.

Author contributions

Reineke Schoot: conceptualization, methodology, investigation, data curation, writing – original draft, writing – review & editing, visualization **Maria Otth:** methodology, investigation, data curation, writing – review & editing, visualization **Geert Frederix:** conceptualization, methodology, investigation, writing – review & editing **Bert Leufkens:** conceptualization, methodology, writing – review & editing, supervision **Gilles Vassal:** conceptualization, methodology, writing – review & editing, supervision.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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