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Market access for medicines treating rare diseases: Association between specialised processes for orphan medicines and funding recommendations

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ABSTRACT

Access to medicines treating rare diseases ('orphan medicines') has proven challenging due to high prices and clinical uncertainty. To optimise market access to these medicines, some healthcare systems are implementing specialised pathways and/or processes during marketing authorisation (MA) and/or health technology assessment (HTA). Comparing one setting where these medicines are classed as "orphan" (Scotland) to another where they considered "non-orphan" (Canada), this study aims to explore whether the presence of specialised pathways and processes at MA and HTA levels is associated with more favourable funding recommendations and faster time to market access. A matched sample of 116 medicine-indication pairs with MA approval from 2001 to 2019 in Europe and Canada was identified, and publicly available sources were used for data extraction. Descriptive statistics were used for data analysis. All medicines were commercially marketed in both countries, except one instance in Scotland. In Scotland, more orphan medicines (68.1%) had a favourable HTA recommendation than in Canada (60.4%), while Canada issued more negative HTA recommendations (20.7%) than Scotland (15.5%). Low levels of agreement on HTA recommendations and the main reasons driving recommendations were found between settings. In both countries, medicines with specialised MA approval were less likely to receive negative HTA recommendations than medicines with standard MA. Time to market access was faster in Canada than Scotland, though medicines with specialised MA approval had slower timelines than medicines with standard MA approval in both countries. However, it is unclear whether the presence of orphan designation and HTA specialised processes alone could result in favourable funding recommendations without accounting for other healthcare system-related factors and differences in the decision-making processes across settings. Holistic approaches and better alignment of evidentiary requirements across regulators are needed to optimise access to orphan medicines.

1. Background

Safe and effective medicines contribute to longer, better lives. Promoting access to medicines is, therefore, essential for well-functioning and efficient healthcare systems. There are several steps before patients have access to a new therapy: a product must receive marketing authorization (MA), obtain coverage from the healthcare insurance (market access), and subsequently reach patients through appropriate prescribing and care provisions (patient access). MA is based on a risk-benefit assessment of clinical trial data, while health technology assessment (HTA) bodies consider clinical and economic evidence, often alongside other socioeconomic factors, to decide whether a new medicine offers good value for money (Angelis et al., 2018; Fontrier et al., 2021). Institutions responsible for making these decisions face particular challenges when dealing with medicines used to treat rare diseases ('orphan medicines'). Guaranteeing access to orphan medicines is usually more complex than for non-orphan medicines, as orphan drugs are more challenging to develop because of small populations sizes and frequently carry high price tags (Chambers et al., 2020; Simoens, 2011), in part due to the institutionalised market exclusivity granted to their manufacturers in some settings (Franco, 2013; Picavet et al., 2011; Sarpatwari et al., 2018; Simoens, 2011; Tafuri et al., 2022). Recent studies have highlighted delays in access and inequalities in several high-income countries, owing primarily to high prices and poor cost-effectiveness (Chambers et al., 2020; Gammie et al., 2015; Merlini et al., 2020; Zamora et al., 2019).

To ensure market access for treatments that address high unmet need, such as orphan medicines, some healthcare systems implement specialised pathways and/or processes for MA and/or HTA. These pathways exist, first, to mitigate high levels of uncertainty resulting

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from limited clinical data (due to reasons such as small sample sizes, lack of active comparators, reliance on short-term studies and often on surrogate outcomes) and typically high prices, and, second, to reflect societal values around equity (Clarke et al., 2021; Nicod et al., 2020; Simoens, 2011; Vreman et al., 2019). Additionally, an orphan designation may be given during MA in some settings to encourage manufacturers to invest in research and development (Franco, 2013; Sarpatwari et al., 2018; Simoens, 2011; Tafuri et al., 2022).

There is substantial controversy around whether orphan medicines should be treated differently than other medicines, as increasing MA approvals and funding for these medicines puts pressure on health care budgets and means that there is less money available to treat other patient populations suffering from more common diseases (Chambers et al., 2020; Franco, 2013; Gammie et al., 2015; Garau and Mestre-Ferrandiz, 2009; Herder, 2017; Kesselheim et al., 2017; Luzzatto et al., 2018; McCabe et al., 2005, 2010; Nicod et al., 2020; Nicod and Kanavos, 2016; Ward et al., 2022). There is conflicting evidence on whether the use of specialised pathways and/or orphan status at MA and designated HTA processes contribute to improving market access for orphan medicines. Some studies (Arnold et al., 2015; Attwood et al., 2018; Franco, 2013; Gammie et al., 2015; Ward et al., 2022) suggest that the presence of such policies during MA have been successful in ensuring more MA approvals for orphan medicines. However, a recent study (Lexchin and Moroz, 2020) showed no differences in MA approvals, time spent during the regulatory process, and marketing delays for orphan medicines between countries which differ in terms of whether they grant orphan designation. At HTA level, some studies have found a positive correlation between specialised HTA processes for orphan medicines and positive HTA recommendations for funding (Chambers et al., 2020; Clarke et al., 2021; Dupont and Van Wilder, 2011; Gammie et al., 2015; Gutierrez et al., 2015; McCormick et al., 2018).

No study has examined whether both specialised MA and HTA policies targeting medicines for high unmet need have a positive impact on funding recommendations and time to market access for orphan medicines. Even though the evidence submitted for MA through these specialised pathways might be sufficient for regulatory agencies to authorise these products, the same evidence could be insufficient for HTA where decision-makers have different trade-offs to make (Pinilla-Dominguez et al., 2020; Vreman et al., 2019; Zamora et al., 2019).

This paper compares two settings - one of which has clear and well-established evaluation processes for orphan medicines during MA and HTA (Scotland), and another which has no orphan designation at MA and no designated HTA process for orphan medicines (Canada) – to study differences in HTA recommendations for funding for medicines classed as “orphan” in one setting and “non-orphan” in another. The aim is to evaluate whether the presence of orphan designation at MA and specialised HTA processes might be associated with a larger percentage of favourable funding recommendations and faster time to market access. Additionally, in recognition of the fact that many orphan medicines are likely to be approved through specialised MA pathways in both settings (due to factors such as low quality clinical trial data and unmet need), regardless of presence of orphan medicines regulations (Lexchin and Moroz, 2020), this study also compares HTA recommendations and time to market access between orphan medicines with a MA through a specialised pathway and orphan medicines approved through the standard pathway.

1.1. Conceptual framework

This study focuses on market access, rather than patient access, to allow for systematic comparisons of market availability and HTA recommendations for funding. Patient access depends, in part, on other system and macro-related factors and could be challenging to quantify, especially in the case for orphans where access may be granted on a case-by-case basis or through dedicated funds (Gammie et al., 2015; Zamora et al., 2019). A conceptual framework showcases the different levels and metrics used to assess market access (Fig. 1).

1.2. Levels

Medicines undergo several steps to achieve market access. MA is a regulatory process which allows for the use of specialised pathways if the product is a therapeutic innovation or addresses high unmet need or serious and life-threatening conditions for which there is no therapeutic alternative. Some countries have also specialised processes for the value assessment of orphan medicines to capture the needs of small, vulnerable populations and account for the unique nature of these medicines (Dupont and Van Wilder, 2011; Garau and Mestre-Ferrandiz, 2009; Gutierrez et al., 2015; McCormick et al., 2018; Nicod et al., 2020; Zamora et al., 2019). Some settings further optimise market access through parallel review processes allowing HTA to commence prior to MA approval. Coverage is determined after HTA outcomes are issued. However whether HTA recommendations translate into funding depends on the HTA system, the role of the HTA body, and whether HTA recommendations are legally binding or not, amongst other factors (Fontrier et al., 2021). Generally, positive HTA outcomes result in positive funding decisions.

1.3. Metrics of market access

This study uses the following points to observe key trends in time: *market availability* defined as whether a medicine has been commercially launched in markets after MA and *market access* when a positive/restricted HTA recommendation for funding is issued. This definition of market access was chosen to partially account for patient access, which is more likely to be achieved if medicines are publicly funded. However, it recognises that negative HTA recommendations do not necessarily translate into no funding, particularly in the case of orphan medicines. *Time to market access* was determined by the time (in months) between MA approval to the issue of a positive/restricted HTA recommendation.

2. Methods

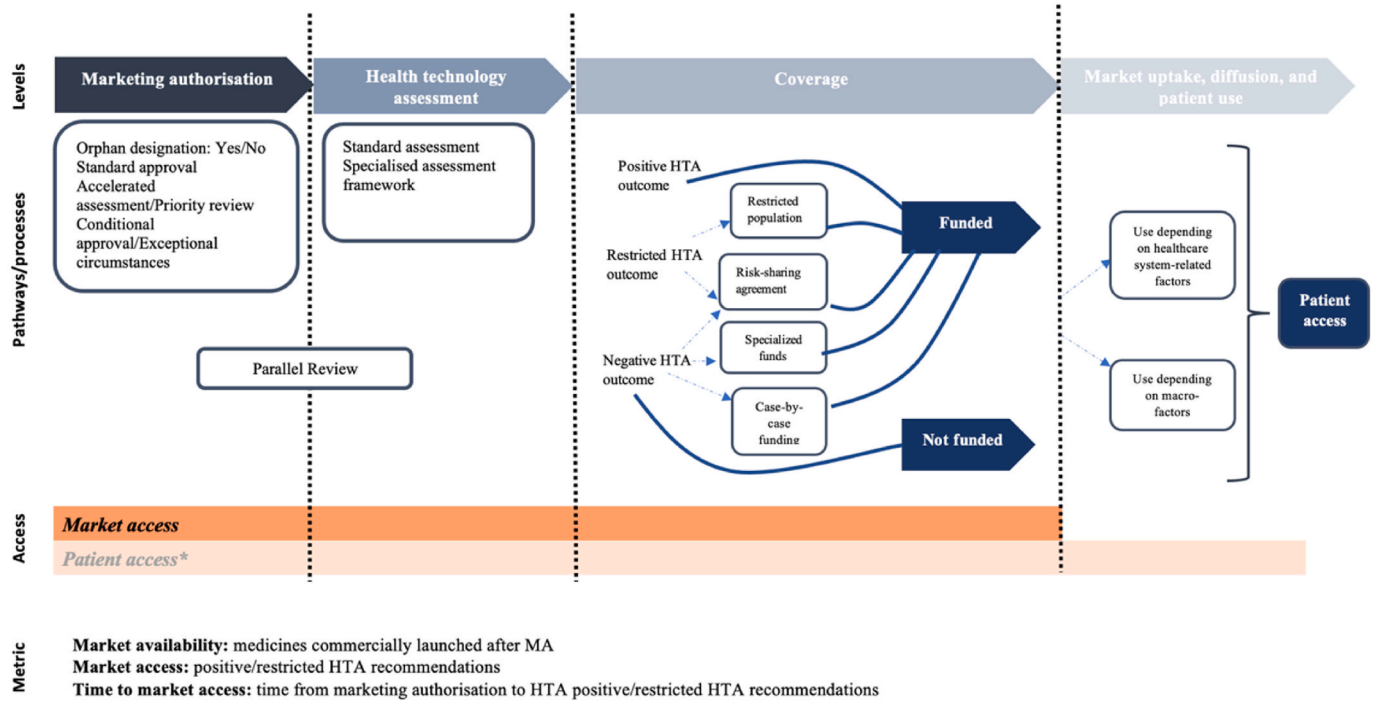
2.1. Country setting

Scotland and Canada were selected for their similarities in HTA set-up, the cost-effectiveness assessment model employed, and how HTA decisions may inform funding decisions. However, there are three fundamental differences: (i) the existence of orphan designation at MA level, (ii) the presence of dedicated processes for assessment of orphan medicines, and (iii) availability of parallel review processes at MA and HTA. Table 1 summarises the main features of the two settings.

2.2. Sample identification

A matched sample of orphan medicines that were available both in Scotland and Canada was identified through four steps.

First, orphan medicines were identified using both the US Food and Drug Agency (FDA) and the European Medicines Agency (EMA) websites; the FDA served as a proxy for Canada (where no orphan designation exists). The US FDA and EMA orphan designations were used to account for differences in the definition of rare diseases across settings (Chambers et al., 2020; Franco, 2013; Lexchin and Moroz, 2020; McCabe et al., 2010; Richter et al., 2015). The FDA Orphan Medicine Product designation database was used to identify orphan medicines approved for use from January 2000 to December 2018, a timeline set to include a comprehensive sample of orphan medicines and allow sufficient time for these medicines to undergo MA in both Europe and Canada. First indication(s) at MA approval and extension of indication(s) with orphan destination, if applicable, were included in the sample. The FDA was the starting point for sample selection as it tends to have more MA approvals than the EMA (Downing et al., 2017), and includes



Note: *Patient access is out of the remit of this study.

Fig. 1. Analytical framework of access to medicines for rare diseases.
Sources: The Author.

products which had orphan designation at the time of their MA, generally providing a broader sample.

Second, EMA-approved medicines with the same therapeutic indication (henceforth referred to as medicine-indication pairs) were identified through the European public assessment reports database and additional searches in the EMA website and were matched with the orphan medicine-indication pairs from the FDA. FDA medicine-indication pairs which never had an orphan designation from the EMA were excluded. Medicine-indication pairs with a withdrawn orphan designation by the EMA or which were later withdrawn from the EU market were included in the sample, in case they had undergone HTA assessment under the orphan/ultra-orphan equivalent process of the Scottish Medicines Consortium (SMC). Inclusion of these medicine-indication pairs did not have an impact on the study's analysis which looked at the funding recommendations at the time where the products had an orphan status and were available within markets.

Third, the matched medicine-indication pairs by the EMA and the FDA were reviewed for MA by Health Canada. Medicine-indication pairs which were not approved by Health Canada or orphan medicines with a different approved indication in Canada were excluded from the sample. Again, medicine-indication pairs where the product was later withdrawn from the Canadian market but had undergone HTA assessment by the Canadian Agency for Medicines and Technologies in Health [CADTH] (including the Common Drug Review [CDR] or the pan-Canadian Oncology Medicine Review [pCODR]) were included in the sample.

Finally, the medicine-indication pairs which were not assessed or for which there was no HTA dossier submission by the manufacturer in both Scotland and Canada were excluded. Medicine-indication pairs which were assessed at least by one of the two agencies were included in the final sample. All HTA assessments performed up until December 2019 were included.

2.3. Data sources and extraction

Relevant information was extracted from publicly available sources. For MA endpoints, data were extracted from the EMA website and Health Canada's notice of compliance database. For market availability, information for commercially marketed products was extracted through the Drug Product Database of Health Canada and the SMC website. An additional search was carried through the British National Formulary (BNF), under the assumption that the formulary contains medicines which have been commercially marketed in the United Kingdom (UK) since they have been funded through the National Health Service (NHS). For HTA endpoints, information was collected through HTA reports published on the websites of the HTA agencies in Scotland (SMC) and Canada (CADTH). Endpoints of interest were grouped and categorised as follows:

MA dates**:** The MA dates of the matched medicine-indication pairs were recorded for the first indication and the extension of indication, when applicable.

Specialised pathways at MA: The presence of specialised regulatory pathways was recorded at the time of MA of the relevant indication. Orphan medicines were categorised into those which received MA through standard approval pathways and those which received MA through specialised pathways including (i) conditional MA, and (ii) accelerated assessment/priority review. Appendix 1 outlines all the available MA specialised pathways in Europe and Canada.

HTA dates: The dates of the latest HTA recommendations were recorded, in case of re-submission. However, for medicines with a previous assessment which had resulted in a favourable recommendation, the date of the first positive/restricted recommendation was recorded, when available.

HTA recommendations: HTA outcomes were collected for the most recent assessment (including re-submissions). HTA outcomes were grouped into four main categories: positive; positive with restrictions;

Table 1
Key characteristics of MA and HTA in Canada and Scotland.

	Scotland	Canada
Marketing Authorisation		
MA agency	European Medicines Agency (EMA)[a]	Health Canada
Orphan designation	Yes	No
Specialised regulatory pathways for MA	Yes	Yes
Health Technology Assessment		
HTA body	Scottish Medicines Consortium (SMC)	Canadian Agency for Medicines and Technologies in Health (CADTH) (including the Common Drug Review (CDR) and the pan-Canadian Oncology Medicine Review (pCODR))[b]
Geographical coverage of the HTA body	National	National
Role of HTA on reimbursement decisions[c]	Advisory	Advisory
Type of HTA recommendation[d]	Non-binding	Non-binding
HTA model	Comparative clinical benefit and cost-effectiveness model	Comparative clinical benefit and cost-effectiveness model
Designated assessment frameworks for orphan medicines	- Orphan designation - Pricing agreements: Patient Access Scheme - Patient and Clinician Engagement (PACE) group process - SMC modifiers	No
Parallel review of MA and HTA evaluation	No	Yes

Notes.
[a] Until December 2020 following Brexit.
[b] CADTH makes federal reimbursement recommendations to provinces, having set up two different committees (and a subcommittee for plasma protein products) that are responsible for the evaluation of medicines depending on the disease area (oncology and non-oncology medicines). These two committees follow two different and independent review processes: The Canadian Drug Expert Committee (CDEC) is evaluating medicines that are non-oncology medicines and follow the Common Drug Review (CDR); whereas the pan-Canadian Oncology Drug Review Expert committee (pERC) evaluates oncology medicines though the pan-Canadian Oncology Drug Review (pCODR). HTA recommendations for both pCODR and CDR are published by CADTH (CADTH, 2022).
[c] HTA agencies that act as advisors make reimbursement or pricing recommendations to the national or regional government, a ministerial department or a self-governing body.
[d] HTA recommendations can either be binding or non-binding for the final funding decision. When the HTA recommendation is non-binding, a negative recommendation is not necessarily translated into a negative coverage decision (Fontrier et al., 2021).
Source: The Author.

negative; not assessed. In case of non-submission by the manufacturer, medicines in both settings have an unfavourable HTA recommendation.

HTA restrictions: Listed with restrictions outcomes were recorded for clinical and economic restrictions. Clinical restrictions included limited access to specific populations, restrict monitoring or prescription only to specialists, restrict medicine administration, or suggestions on when treatment should be initiated, continued and/or discontinued. Economic restrictions included funding mechanisms such as patient access schemes (PAS) (applicable only in Scotland), reductions in price of the medicine, and reimbursement in some jurisdictions only (applicable to a few cases in Canada).

Main reasons for recommendation: The main reasons for recommendation were recorded and categorised into four options: clinical achievement in terms of significant improvement in the clinical benefit; optimal cost-effectiveness; achievement of both (clinical and cost-effectiveness); failure to achieve both clinical and cost-effectiveness. Medicines with no dossier submission and those not assessed by the HTA agency were excluded from analysis on this endpoint.

Parallel review: Medicines where HTA started prior to MA in Canada were noted to examine whether time from MA to favourable HTA recommendation was faster.

2.4. Statistical analysis

Descriptive statistics were used to establish key trends across the two settings. Chi-square and Fisher's exact test were used to identify statistically significance (p-value $\leq$0.05 was considered statistically significant). Kappa scores were calculated to examine agreement for HTA recommendations and main reasons for recommendation issued in Scotland and Canada. Results were interpreted using the benchmark scale suggested by Landis and Koch (1977) (Landis and Koch, 1977). Level of concordance between the two settings was measured by looking at the proportion of HTA assessments with identical decisions and reasons for recommendation, as done in a previous study (McCormick et al., 2018).

Kaplan-Meier curves were used to estimate time to market access in both countries across the entire sample and for subsamples of orphan medicines which were granted MA through a specialised pathway and those who underwent standard MA. A subgroup analysis was performed for Canada for medicines with pre-MA submissions (parallel review) and medicines which underwent standard HTA. The Mann-Whitney *U* test was used to assess the equality of distributions for Scotland and Canada and Welch's *t*-test was used to test the statistical significance of mean times.

The data were analysed using Stata version 16.

3. Results

3.1. Sample of orphan medicines

Fig. 2 outlines the results of the sample selection process. 116 orphan medicines-indication pairs approved by FDA, EMA and Health Canada and assessed by SMC and/or CADTH before December 2019 were included in the final sample. A full list of the sample is provided in Appendix 2.

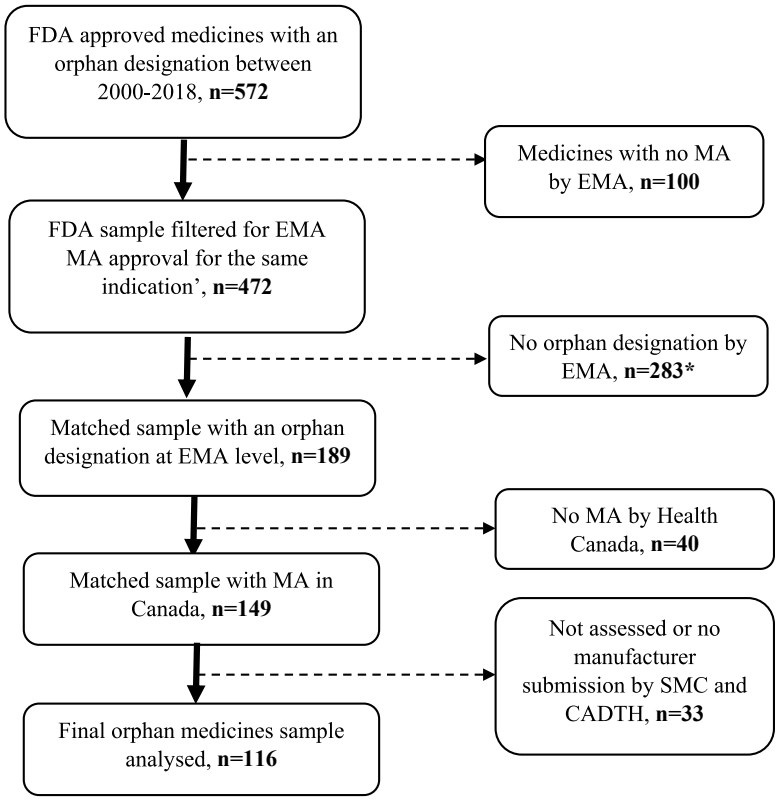
In Scotland, 38.8% of included medicines received MA through a specialised pathway. In Canada, 61.2% of the medicines had been granted MA through a specialised pathway, with 42.3% through accelerated assessment/priority review. 21.7% of the medicines in Scotland and 11.7% in Canada had a dossier re-submission. Table 2 provides statistics about the sample.

3.2. Market availability

All the included medicine-indications pairs (n = 116) were commercially marketed in Canada after MA. In Scotland, out of 97 medicine-indication pairs assessed by SMC, information on market availability was not available for eight. Searching through the BNF, four medicine indication pairs were not listed (out of the 116), including one that was also identified with no information on market availability through the SMC search. Therefore, combining the SMC and BNF searches, only one drug-indication pair was identified with no clear information on marketing status after MA.

3.3. HTA recommendations for funding

Differences in HTA recommendations, the main reasons for recommendation and, when applicable, the type of restrictions showed statistical significance according to chi-square and Fisher's exact test (see



Note: Differences in the definition of rare diseases in Europe and the USA, in disease prevalence, and in the time orphan designation incentives entered into force might reflect the large number of medicines with no orphan status at the EMA compared to the FDA.

Fig. 2. Flow chart of sample selection.

Appendix 3).

(i) HTA outcomes and level of agreement between Scotland and Canada

Positive HTA recommendations**:** Scotland had more positive HTA recommendations than Canada (10.4% vs. 2.6%, respectively). However, the proportion of positive recommendations was low in both settings. In Scotland, half of positive HTA recommendations were made when medicines were proven to be both clinically and cost-effective, similar to all positive recommendations in Canada. The other half of positive recommendations in Scotland were made based on proven clinical benefit only, without being cost-effective.

Positive with restrictions HTA recommendations: More than half of orphan medicines had restricted recommendations in both Canada and Scotland (57.8%). In Canada, the majority of medicines with a restricted HTA recommendation (80.6%) had both clinical and economic restrictions for reimbursement. In Scotland, economic restrictions (46.3%) were more prevalent than only clinical restrictions (22.4%) or both clinical and economic restrictions (31.4%). While in Canada, most of the clinical restrictions imposed multiple conditions, 77.8% of the restrictions in Scotland limited the use of these medicines in certain patient populations. All the economic restrictions in Scotland suggest funding these medicines through PAS, a type of pricing agreement between manufacturers and payers. In Canada, the most common type of economic restrictions were requests for price reductions to improve cost-effectiveness (86.7%). Most medicines with restricted recommendations (83.6%) in Canada only proved a significant clinical benefit, similar to Scotland (86.2%).

Negative HTA recommendations: CADTH issued more negative HTA recommendations (20.7%) than SMC (15.5%). In Canada, the main reasons for a negative recommendation were because CADTH was not able to conclude the medicine was both clinically and cost-effective (91.7%). In Scotland, the majority of negative HTA recommendations (72.2%) were made even when medicines were proven to be clinically effective. Only 27.8% of the medicines with negative recommendations in Scotland were neither clinically nor cost-effective.

Level of agreement on HTA recommendations and main reasons for recommendation: The Kappa score analysis suggested that there was only fair agreement on HTA recommendations (kappa = 0.33, $p < 0.001$), on whether the orphan medicines undergoing assessment had achieved a clinical benefit (kappa = 0.29, p = 0.003) and whether the medicines assessed were cost-effective (kappa = 0.29, p = 0.003). However, no agreement (kappa = −0.02, p = 0.581) was observed when looking at whether additional dimensions of value, such as other socioeconomic criteria, were considered for the recommendation.

The degree of concordance in Scotland and Canada was 66.2% for HTA recommendations, 70.8% on whether the clinical benefit was achieved, 87.7% on whether the medicine was cost-effective and 43.8% for consideration of other socioeconomic criteria when decisions are being made.

(ii) HTA recommendations and HTA restrictions for orphan medicines with MA through specialised pathways versus orphan medicines with standard MA

Differences in the HTA recommendations and types of restrictions for orphan medicines which were granted MA through specialised pathways across the two settings did not show statistical significance. In Scotland, more positive recommendations without restrictions were observed for

Table 2
Orphan indication-pair sample characteristics.

	Canada		Scotland	
	Entire sample (N = 116)			
	N	%	n	%
Conditional MA[a]	26	22.4%	32	27.6%
p = 0.363				
Accelerated MA [b]	49	42.3%	15	12.9%
p < 0.001				
MA through specialised pathways [c]	71	61.2%	45	38.8%
p < 0.001				
MA through standard pathway	45	38.8%	71	61.2%
p < 0.001				
Orphans with positive/restrictive HTA outcomes	70	60.4%	79	68.1%
p = 0.270				
Medicines assessed by HTA	**N = 94, 81.0%**		**N = 97, 83.6%**	
p = 0.606				
HTA re-submission	11	11.7%	21	21.7%
p = 0.095				
Parallel review submission	32	34.4%	N/A	
p < 0.001				

Notes.
[4] N/A: Not applicable.
[a] Includes both conditional MA and MA under exceptional circumstances from the EMA. In Canada, this relates to conditional notice of compliance (NOC/c) by Health Canada.
[b] Includes both MA with accelerated assessment and PRIME at the EMA and priority review in Health Canada. From the study sample, only one medicine in Europe underwent MA through PRIME.
[c] Includes both conditional and accelerated MAs. Seven medicines (three in Europe and four in Canada) have been both granted conditional MA and underwent an accelerated assessment review. Therefore, the sum of conditional and accelerated MA does not match to the total number of medicines with MA through specialised pathways.

medicines which underwent standard MA compared to those with MA through a specialised pathway (standard approval: 12.7% vs. specialised approval: 6.7%), whilst in Canada the opposite was observed (standard approval: 2.2% vs. specialised approval: 2.8%). Medicines approved through specialised MA pathway were more likely to have a favourable recommendation with restrictions than those undergoing standard MA in Canada (standard approval: 54.9% vs. specialised approval: 62.2%), whilst in Scotland the exact opposite was observed (standard approval: 62.2% vs. specialised approval: 54.9%). Both clinical and economic restrictions were more likely to be recommended in Canada for medicines with standard MA than medicines with specialised MA (standard: 82.2% vs. specialised approval: 79.5%). In Scotland the type of restrictions for medicines undergoing MA through specialised pathways were broadly similar to the types of restrictions applied to medicines with standard approval (clinical restrictions only: 25.0% vs. 20.5%; economic restrictions only: 42.9% vs. 48.7%; both clinical and economic restrictions: 32.2% vs. 30.8%, respectively). Negative recommendations for medicines approved through specialised pathways were less in both settings compared to medicines approved through standard MA. However, in Scotland negative HTA recommendations for medicines with standard approval (21.1%) were significantly higher than for medicines approved through specialised pathways (6.7%). In Canada, differences in negative HTA recommendations between medicines with standard vs. specialised approval were smaller (standard approval: 24.5% vs. specialised approval: 18.3%).

3.4. Time to access

68.1% of medicines in Scotland and 60.4% in Canada had a positive/restricted HTA recommendation (see Table 2). The results for the time to market access analysis are summarised in Table 3.

Table 3
Time to market access in months from MA to positive/restricted recommendations in Canada and Scotland.

	Minimum	Maximum	Median	Mean
All sample				
Canada	5	19	8	10.5
Scotland	7	28	13	19
		p = 0.024		*p = 0.002*
Medicines in Canada only undergoing parallel review vs. standard HTA				
Pre-MA HTA submission	3	6	4	5.1
Standard HTA submission	8	22	14	13.3
		p < 0.001		*p < 0.001*
Medicines with standard MA Vs. medicines with MA through specialised pathways				
Canada: Standard approval	4	21	8	10
Canada: Specialised MA pathway	6	17	9	10.9
		p = 0.632		*p = 0.675*
Scotland: Standard approval	6	25	12	16.9
Scotland: Specialised MA pathway	7	33	14	22.1
		p = 0.329		*p = 0.394*

(i) Time from MA to positive/restricted HTA recommendations

Fig. 3 (panel A) shows the months elapsed from a MA approval to a positive/restricted HTA recommendation. Canada (median: 8 months; mean: 10.5 months) showed considerably faster access compared to Scotland (median: 13 months; mean: 19 months).

Parallel review: In Canada, access to orphan medicines for which HTA assessment started prior to MA approval was much faster than those which were assessed after MA was granted (Fig. 3 [panel B]).

(ii) Time from MA to positive/restricted HTA recommendations depending on the presence of MA specialised pathways

Fig. 3 (panel C) shows that within both countries time to access was faster for medicines which underwent standard approval than those which granted MA through specialised pathways.

4. Discussion

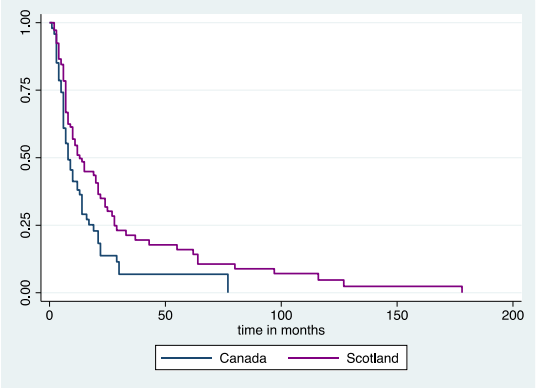
Scotland, where orphan designation and specialised HTA processes for orphan medicines exist, showed slightly more positive/restricted and fewer negative HTA recommendations than Canada, where these processes are not implemented. However, in both settings proportion of positive HTA recommendations with no restrictions was very low. In Canada, orphan medicines were more likely to be approved through a specialised MA pathway than Scotland despite lack of an orphan designation. In both settings, medicines which received MA through specialised pathways were less likely to receive an unfavourable funding recommendation than medicines with standard MA. Across all time to market access analyses, Scotland had slower time to access than Canada.

Nevertheless, conclusions on whether the presence of specialised pathways for orphan medicines results in better market access cannot be drawn based only on the data used in this study. Differences in the decision-making process and value assessment methods employed in the two settings (highlighted from the low levels of agreement seen in this study), as well as other system related factors might further impact patient use and market uptake of orphan medicines.

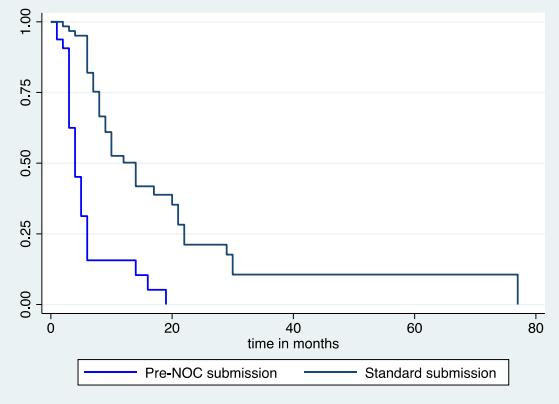
4.1. Market availability

All medicine-indication pairs were commercially marketed in both settings, except for one instance in Scotland. Thus, the presence of orphan designation at MA did not seem to have an impact on the commercial availability of orphan medicines.

Panel A: Time to market access for all the sample



Panel B: Time to market access in Canada for medicines undergoing parallel review vs. medicines with standard HTA submission



Panel C: Time to market access for medicines undergoing MA through standard vs. specialised pathways

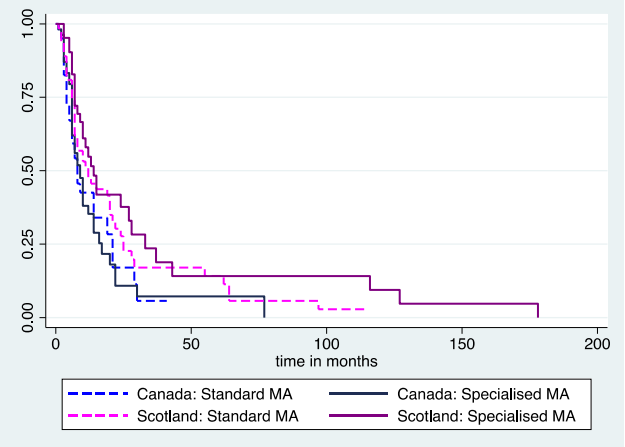


Fig. 3. Kaplan–Meier curves for time to market access.

4.2. HTA recommendations for funding

Percentages of positive recommendations without restrictions were low in both countries, which could have further implications for market, and ultimately patient access. In Scotland, orphan medicines had less negative recommendations for funding compared to Canada. Funding recommendations for orphan medicines in Scotland were more likely to be accompanied by economic restrictions only, whereas in Canada funding recommendations were often subject to both clinical and economic restrictions, potentially limiting patient access to a greater extent. Clinical and economic restrictions are predominately suggested by HTA agencies to mitigate affordability concerns regarding efficient allocation of finite healthcare recourses. In fact, positive recommendations with restrictions were most often issued in both countries due to failure in proving cost-effectiveness. Thus, the high presence of economic restrictions in the form of price reductions (Canada: 86.7%) or funding mechanisms (Scotland: 100%) was expected due to the associated high costs of orphan medicines.

Negative recommendations for funding in Scotland were made even when medicines were proven to be clinically effective (n = 13). Interestingly, of these 13 medicines, eight underwent assessment through the Patient and Clinician Engagement (PACE) process, which reflects on opinions of clinicians, patients, and patient organisations before a final HTA recommendation is issued (Scottish Medicines Consortium, 2021). For these eight medicines, manufacturers failed to justify their cost in relation to health benefits. In six of these cases, PAS were proposed by the companies which may imply that the suggested discounted prices were not low enough to justify the high cost per quality-adjusted life years (QALY).

Negative recommendations in Canada were most often made when CADTH was not able to conclude that the medicine was both clinically- and cost-effective. This is contradictory to recent studies, which concluded that the main reason for a negative HTA recommendation in Canada was lack of observed clinical benefit (Janoudi et al., 2016; McCormick et al., 2018).

The low levels of agreement between the two countries on HTA recommendations and the main reasons for final recommendations may suggest discrepancies in the way clinical benefit and cost-effectiveness are assessed, and whether other value dimensions, such as unmet need, and burden of disease among others, have an impact on the final recommendation. In fact, the level of concordance/identical outcomes between the two settings on whether other value dimensions had a positive impact on the final recommendation was low (43.8%) and might reflect the absence of a specialised assessment process for orphan medicines in Canada. The results of this study are in alignment with findings of a previous study which showed that the level of agreement in HTA recommendations between Canada and other settings, including Scotland, was low (McCormick et al., 2018).

4.3. Market access

Market access was measured through positive/restricted HTA recommendations. While evidence from Canada shows that there is not always alignment between CADTH recommendations and provincial reimbursement decisions (Allen et al., 2016) and medicines with negative HTA recommendations can still be found reimbursed in provinces (Liden et al., 2014; McCormick et al., 2018), recommendations can generally be considered “equally impactful as binding” in both settings as national/regional healthcare systems will provide funding to medicines with favourable HTA recommendations (Fontrier et al., 2021; Liden et al., 2014; Scottish Medicines Consortium, 2021).

Scotland (68.1%) showed slightly better market access to orphan medicines than Canada (60.4%). This could be in part, because certain processes in Scotland are implemented to account for high clinical uncertainty, such as SMC accepting more uncertainty in the economic case analysis or a higher cost per QALY for orphan medicines by applying modifiers which account for additional value dimensions such as whether the medicine treats a life-threatening disease or substantially improves patients’ quality of life (Scottish Medicines Consortium, 2012), a practice not seen in Canada. Another example is the explicit patient and clinician consultation through the PACE process (Scottish Medicines Consortium, 2021; Nicod et al., 2020). PACE was introduced in response to criticism from key stakeholders as a high proportion of medicines treating end-of-life and rare diseases were receiving unfavourable HTA recommendations based only on cost-effectiveness criteria. Since its introduction in 2014, favourable HTA recommendations for orphan medicines have increased (Montgomery, 2016). The current study provides further evidence in support of this finding: after introduction of the PACE process, positive HTA recommendations increased from 74.2% to 84.4%, while negative recommendations decreased from 25.8% to 15.6%. HTA recommendations of almost 91% orphan medicine-indications pairs assessed by SMC after 2014 considered the views expressed during the PACE meeting. Stakeholder consultation is part of assessments in Canada, but the type of participant may differ across health technologies or assessments, thus the potential impact to the final recommendation is hard to be established.

The larger number of dossier re-submissions in Scotland than in Canada could also contribute to slightly better market access in Scotland, as submission of new and/or additional information could be likely to change previously negative HTA outcomes (Vreman et al., 2020).

Finally, favourable HTA recommendations may be more prevalent in Scotland than Canada because of price negotiations through PAS during HTA process. Companies can suggest a discount from the NHS list price or submit new or revised PAS to SMC for previously negative HTA recommendations to improve the cost-effectiveness of medicines (National Services Scotland, 2020). On the contrary, negotiations or managed entry agreements take place at provincial level in Canada, after national HTA recommendations are issued (Allen et al., 2016). Thus, more negative recommendations in Canada could be expected based on potentially high prices and poor cost-effectiveness associated with orphan medicines which are not mitigated during the HTA process.

Similar to these findings, another study also concluded that a causal relationship between the presence of special HTA criteria for orphans and positive/restricted HTA recommendations cannot be established (Kawalec et al., 2016). However, other evidence showed no difference between positive/restricted HTA recommendations in Canada and Scotland (McCormick et al., 2018).

As a final note, access to medicines cannot only be determined by looking at commercial market availability and HTA recommendations: evidence showcased a high rate of reimbursement in Europe for ultra-orphan medicines which had not undergone an HTA assessment (Kawalec et al., 2016). Thus, the access metrics used in this study can only signal whether the medicine is available within markets and potentially publicly funded.

4.4. Time to market access

Canada has shorter time periods between receiving MA to a positive/restricted HTA recommendation than Scotland across both the entire sample and the subsection of medicines which underwent MA through specialised pathways. This might be explained by additional steps in the Scottish assessment process, such as the PACE and consideration of PAS and/or the implementation of parallel review in Canada aiming to tackle delays occurring when MA and HTA assessments take place consecutively.

Beyond the remit of this study, further delays to time to access are expected after issue of HTA recommendations such as time for pricing and reimbursement negotiations between national and/or provincial payers with manufacturers. A recent study (Ward et al., 2022) showed that, in Canada federal pricing negotiations have been shown to add a median of 9.9 months after CADTH recommendations, with another 1.2 months for provincial funding (Ward et al., 2022). Usually, commercial market availability occurs earlier than publication of HTA recommendations and delays in time to access are not often due to this (see Appendix 4 for additional results on time to market access).

4.5. Specialised pathways for MA beyond orphan designation

Since orphan medicines are likely to be approved through specialised pathways at MA, this study explored whether market access to orphan medicines is delayed at the HTA stage due to discrepancies in the remits of and the factors driving decision-making in MA and HTA stages. Until recently with the introduction of interim acceptance in Scotland (Scottish Medicines Consortium, 2018), there were no specific dedicated processes for the evaluation of medicines granted MA through specialised pathways in either setting which allowed comparisons of HTA recommendations with medicines granted standard MA. No interim acceptance was recorded in Scotland for this study’s sample.

More than half of the sample was granted MA through specialised pathways in Canada while less than half of the sample received MA

through specialised pathways in Europe. Interestingly, even in the absence of an orphan designation in Canada, orphan medicines were more likely to be approved through specialised pathways than Scotland. In both Scotland and Canada, medicines with MA through specialised pathways were less likely to receive a negative HTA recommendation. In Canada, those medicines were almost equally likely to receive a positive HTA recommendation (without restrictions) than those with standard approval. The oppositive was observed in Scotland, where more unrestricted favourable recommendations were recorded for medicines with standard MA. However, the difference between the percentage of negative recommendations for medicines with standard approval vs. those with specialised approval was considerably larger in Scotland than in Canada, potentially suggesting that access to medicines with MA through a specialised pathway is not halted at HTA level when specialised HTA processes are in place.

These findings are contradictory to previous studies considering access to non-orphan medicines undergoing MA through specialised pathways. One study found half of HTA recommendations for conditionally approved medicines were negative (Vreman et al., 2019). Another study reported that there was no difference in positive recommendations for medicines with conditional MA and medicines with standard MA (Lipska et al., 2015). A study focusing on the English HTA body showcased that the proportion of positive recommendations for medicines undergoing MA through specialised pathways was similar to overall recommendations of the technology appraisals program (Pinilla-Dominguez et al., 2020).

In the time to market access analysis, orphan medicines with MA through specialised pathways took more time to market access compared to medicines undergoing standard approval in both countries. Evidence on non-orphan medicines concluded similarly that expedited assessments for MA did not lead to earlier access because of later unfavourable funding recommendations (Vreman et al., 2019). A possible reason for this finding could be that HTA agencies might be unprepared to assess medicines which are approved through conditional MA. However, Scotland had slower time to market access than Canada despite the implementation of a specialised assessment framework for orphan medicines which may lead to the suggestion that SMC should actually be more prepared to assess medicines with high clinical uncertainty. However, in both countries, HTA processes might take more time regardless of the implementation of a specialised assessment framework to mitigate higher levels of uncertainty. In addition, as 42.3% of the sampled orphans undergoing accelerated assessment were in Canada, it is apparent that Health Canada is making considerable efforts to accelerate MA assessments to allow the HTA process to commence as quickly as possible. However, this was not reflected in the time analysis where medicines with standard MA showed faster timelines in comparison to medicines with MA through specialised pathways. In an additional time to market access analyses in Appendix 4, when the date of manufacturer's submission for MA to the regulatory body was used (instead of MA date), orphan medicines with a specialised MA showed faster timelines compared to those with standard MA in both settings.

4.6. Policy implications

Whether specialised assessment processes and orphan designation status can ensure better and faster access to orphan medicines is still unclear.

On one hand, the presence of processes and policies targeting orphan medicines might emphasize affordability issues. Even though these processes may be considered critical in motivating manufacturers to invest in research and development, they may contribute to why orphan medicines are now amongst the most expensive and profitable medicines worldwide (Herder, 2017; Hollis, 2019). The policy environment for rare diseases in some countries has given leeway to manufacturers of orphan medicines to make considerable profit, as they are able to exercise monopolistic power to request and retain high price tags while testing the flexibility of healthcare systems in accepting higher costs per QALY (Gammie et al., 2015; Godman et al., 2018; Herder, 2017; Hollis, 2019; Hughes-Wilson et al., 2012; Kesselheim et al., 2017; Luzzatto et al., 2018; Ollendorf et al., 2018; Simoens et al., 2013). For example, despite the positive impact of the Scottish PACE process, concerns remained as to whether it might reduce manufacturers' incentives to lower prices, and further weakened the negotiation position of the Scottisch NHS (Montgomery, 2016; Morrell et al., 2017; Nicod et al., 2020). Even though manufacturers take risks in investing in the development of orphan medicines, the prices charged may not be always based on the actual cost of their production or development but on a profit-maximizing price (Hollis, 2019). Affordability concerns are not limited to price: policies for rare diseases have also been criticized for taking up finite resources of healthcare systems that could have been redirected to other diseases (Gammie et al., 2015; Herder, 2017; Hughes-Wilson et al., 2012; Kesselheim et al., 2017; Simoens et al., 2013). For instance, the Dutch Healthcare Insurance Board made tough decisions regarding the reimbursement of enzyme replacement therapy for Fabry and Pompe diseases in 2012, as favourable funding decisions would have resulted in limited resources not being available for the funding of other, more cost-effective, medicines (Simoens et al., 2013).

On the other hand, dedicated assessment processes for orphan medicines ensure that the patient's voice is considered during the assessment process (Montgomery, 2016), or even during drug development such as in the case of ivacaftor where trials were conducted with the help of the Cystic Fibrosis Foundation (Luzzatto et al., 2018). This may be particularly important for rare diseases: as the number of patients with these diseases is smaller, the resources available to, and power of, patient organisations for rare diseases to influence a negative HTA recommendation may be limited in the absence of dedicated processes (Mikami and Sturdy, 2017). Additionally, specialised assessment processes increase the readiness of HTA agencies to handle submissions where high uncertainty due to limited clinical evidence exists (Nicod et al., 2020). This is illustrated by the Scottish HTA recommendations, as positive restrictions were mainly limited to funding mechanisms.

Different ways forward can be pursued to find the right balance between the aforesaid points, accounting for sustainability of healthcare systems and a public health desire to drive prices of orphan medicines down, and continuing to incentivise manufacturers to develop these medicines. Introduction of competitive pricing negotiations (i.e.: potentially through pricing schemes or specialised funds) as part of the value assessment process, could be considered to aid in the mitigation of cost-effectiveness concerns during the HTA process. For instance, since the implementation of the new Cancer Drugs Fund (CDF) in England, in 2016, all oncology medicines undergo HTA assessment. In cases where high clinical uncertainty is established, oncology medicines can be recommended for use within the CDF by the English HTA body to avoid long delays until more evidence is gathered (National Healthcare System, 2016; National Institute for Health and Care Excellence, 2021). Use of multiple criteria decision analysis (MCDA) tools could also be considered in HTA to account for the unique nature of orphan medicines, diverging views of key stakeholders, other value criteria along with clinical benefit and cost-effectiveness, and the quality of the submitted evidence, as seen in the Netherlands and the UK (Blonda et al., 2021; Godman et al., 2018, 2021). In addition, new value assessment systems could inform both pricing and funding of orphan medicines based on pre-defined evaluation criteria including, amongst others, the level of research undertaken by the developer including manufacturing complexity, and follow-up measures required by regulatory or other authorities (Hughes-Wilson et al., 2012). Alternatively, a value-based pricing policy based on HTA recommendations could be used for pricing of orphan medicines to link prices to added clinical benefit and cost-effectiveness (Godman et al., 2018). Another possibility could be for medicines with conditional MA to become available through compassionate use schemes, similar to the temporary authorisation

programme (ATU) in France, though this solution should apply to products with MA, and not just pre-MA medicines as is the case in the ATU (Haute Autorité de Santé (HAS), 2021; Jacquet et al., 2021). Furthermore, requirements for additional data collection should be aligned between MA and HTA bodies to reduce further complexity, such as seen in the new SMC interim acceptance decision option (Scottish Medicines Consortium, 2018). In addition, use of performance-based managed entry agreements which rely on real-world evidence can be explored to optimise access to medicines with uncertain clinical evidence (Facey et al., 2021; Godman et al., 2021).

Yet, these suggestions are not the panacea to access challenges observed in the case of orphan medicines. Introduction and use of programmes such as the ones mentioned above and other regulatory and value assessment policies targeting orphan medicines should be thoroughly assessed before their introduction and during their implementation. Specialised processes for orphan medicines should be accompanied by strict and transparent guidelines regarding the safety, clinical effectiveness, pricing of eligible medicines, and appropriate mechanisms to prevent potentially catastrophic costs should be in place. Implementation of processes should also reflect on lessons learned from existing programmes. For instance, the French ATU scheme was recently reformed after criticism for possible interference and delays of formal pricing and reimbursement decisions after MA, and allowing manufacturers to set high initial prices due to its free pricing period coupled with purchasers' low price sensitivity (Degrassat-Théas et al., 2013; Jacquet et al., 2021; Martinalbo et al., 2016). Similarly, the old English CDF was heavily criticised due to a lack of transparency on how the fund operates, miscalculations of true costs of funding unapproved cancer drugs, high levels of usage of cancer medicines undermining care for other diseases, and diversion from funding recommendations by the English HTA body (Lancet, 2010).

Important concluding messages are that (i) efforts focusing on access should take both patient and market access into account; (ii) increased transparency is needed on research and development costs and pricing of orphan medicines; (iii) better collaboration between key stakeholders can help in achieving better and timely access to orphan treatments, and; (iv) targeted efforts at different stages in the access pathway should be aligned to achieve their aims jointly. Where there are discrepancies, such as in varying clinical evidentiary requirements at MA and HTA levels, the presence of specialised pathways for MA cannot ensure better and faster access to medicines with poor clinical evidence within countries. Where the remits of MA processes and HTA agencies are different, intermediate processes or collaborative efforts could be established or strengthened.

4.7. Study limitations

First, Canada and Scotland differ in country size, population, and gross domestic product, as well as their willingness-to-pay thresholds per QALY and where funding decisions are made (i.e.: in Canada, funding of medicines is the competence of provincial jurisdictions), among other factors which can impact access to orphan medicines. However, these settings serve as good examples to explore whether differences in how medicines for rare diseases are treated at MA and HTA levels are highlighted in funding recommendations and time to market access, given their similarities in the role of, and assessment model followed by the HTA body. Second, positive/restricted HTA recommendations can only be used as an approximation of market access. Manufacturers can still decide not to market a product despite a favourable HTA recommendation and other system related factors might impact funding decisions. Third, the time to market access analyses measure the time from MA to favourable HTA recommendations. However, any further delays after HTA that might occur during subsequent pricing and reimbursement negotiations, or market launch are not captured. Fourth, the FDA was used as a surrogate for Canada for the sample selection as there is no orphan designation in Canada at MA level. However, there is an established collaboration and exchange of information between the FDA and Health Canada (Federal Register, 2003). Fifth, the methodology used for the sample identification was used to ensure a wider range of products were included from the outset, though all possible sampling strategies will have had an impact on the number and products included in the sample. Sixth, data on previous submissions for medicines with re-submission in Scotland were not always available, limiting our data on whether a positive/restricted HTA recommendation had been issued previously. Instead, the HTA dates of the latest submission for positive/restricted recommendations were used when this information was not available. The impact of this is considered minimal as re-submissions in Scotland usually take place to change previously negative HTA recommendations (Scottish Medicines Consortium, 2021). Seventh, Scotland has local formularies which are not publicly available, therefore, information on market availability for Scotland was extracted from the BNF, among other sources, assuming that medicines included in the BNF would have been marketed across the UK. Finally, due to lack of a comparative group of non-orphan medicine-indications pairs, it cannot be determined with certainty whether more favourable HTA recommendations in Scotland are seen due to the presence of specialised pathways only and not due to other system related factors or differences in the way medicines are assessed in these two settings.

5. Conclusion

Scotland, with specialised processes at MA and HTA levels for orphan medicines, showcased only slightly more favourable funding recommendations than Canada, where these medicines are assessed as any other medicine. Low levels of agreement between the two agencies suggest discrepancies in their clinical- and cost-effectiveness assessments and consideration of other societal value dimensions during HTA. In Canada, orphan medicines were more likely to be granted MA through specialised pathways than Scotland. In both settings, these medicines were less likely to receive an unfavourable funding recommendation in comparison to orphan medicines with standard MA. However, from the findings of this study, it is unclear whether the presence of orphan designation and HTA specialised processes for orphan medicines alone could result in more favourable funding recommendations, and it is not possible to suggest a single remedy for achieving better access to orphan medicines. Holistic approaches at all levels of the access pathway are necessary, together with better collaborations across respective agencies and relevant stakeholders while use of innovative pricing and assessment mechanisms for orphan medicines are needed to make these medicines more affordable while mitigate high levels of uncertainty.

Author statement

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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References

Allen, N., Walker, S.R., Liberti, L., Sehgal, C., Salek, M.S., 2016. Evaluating alignment between Canadian Common Drug Review reimbursement recommendations and provincial drug plan listing decisions: an exploratory study. CMAJ open 4, E674.

Angelis, A., Lange, A., Kanavos, P., 2018. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. Eur. J. Health Econ. 19, 123–152.

Arnold, R.J., Bighash, L., Nieto, A.B., de Araújo, G.T.B., Gay-Molina, J.G., Augustovski, F., 2015. The Role of Globalization in Drug Development and Access to Orphan Drugs: Orphan Drug Legislation in the US/EU and in Latin America. F1000Research 4.

Attwood, M.M., Rask-Andersen, M., Schiöth, H.B., 2018. Orphan drugs and their impact on pharmaceutical development. Trends Pharmacol. Sci. 39, 525–535.

Blonda, A., Denier, Y., Huys, I., Simoens, S., 2021. How to value orphan drugs? A review of European value assessment frameworks. Front. Pharmacol. 12, 695.

Canadian Agency for Drugs and Technologies in Health (CADTH), 2022. Procedures for CADTH Reimbursement Reviews. In: https://www.cadth.ca/sites/default/files/Drug_Review_Process/CADTH_Drug_Reimbursement_Review_Procedures.pdf. (Accessed 27 April 2022).

Chambers, J.D., Silver, M.C., Berklein, F.C., Cohen, J.T., Neumann, P.J., 2020. Orphan drugs offer larger health gains but less favorable cost-effectiveness than non-orphan drugs. J. Gen. Intern. Med. 35, 2629–2636.

Clarke, S., Ellis, M., Brownrigg, J., 2021. The impact of rarity in NICE's health technology appraisals. Orphanet J. Rare Dis. 16, 1–7.

Degrassat-Théas, A., Paubel, P., Parent de Curzon, O., Le Pen, C., Sinègre, M., 2013. Temporary authorization for use: does the French patient access programme for unlicensed medicines impact market access after formal licensing? Pharmacoeconomics 31 (4), 335–343.

Downing, N.S., Zhang, A.D., Ross, J.S., 2017. Regulatory review of new therapeutic agents—FDA versus EMA, 2011–2015. N. Engl. J. Med. 376, 1386–1387.

Dupont, A.G., Van Wilder, P.B., 2011. Access to orphan drugs despite poor quality of clinical evidence. Br. J. Clin. Pharmacol. 71, 488–496.

Facey, K.M., Espin, J., Kent, E., Link, A., Nicod, E., O'Leary, A., Xoxi, E., van de Vijver, I., Zaremba, A., Benisheva, T., 2021. Implementing outcomes-based managed entry agreements for rare disease treatments: nusinersen and tisagenlecleucel. Pharmacoeconomics 39, 1021–1044.

Federal Register: The daily journal of the United States Government, 2003. Memorandum of Understanding between the Food and Drug Administration and the Health Products and Food Branch, Health Canada of Canada Regarding Sharing and Exchange of Information about Therapeutic Products.

Fontrier, A.-M., Visintin, E., Kanavos, P., 2021. Similarities and differences in health technology assessment systems and implications for coverage decisions: evidence from 32 countries. PharmacoEconomics-Open 1–14.

Franco, P., 2013. Orphan drugs: the regulatory environment. Drug Discov. Today 18, 163–172.

Gammie, T., Lu, C.Y., Babar, Z.U.-D., 2015. Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. PLoS One 10, e0140002.

Garau, M., Mestre-Ferrandiz, J., 2009. Access Mechanisms for Orphan Drugs: a Comparative Study of Selected European Countries. OHE briefing.

Godman, B., Bucsics, A., Vella Bonanno, P., Oortwijn, W., Rothe, C.C., Ferrario, A., Bosselli, S., Hill, A., Martin, A.P., Simoens, S., 2018. Barriers for access to new medicines: searching for the balance between rising costs and limited budgets. Front. Public Health 328.

Godman, B., Hill, A., Simoens, S., Selke, G., Selke Krulichová, I., Zampirolli Dias, C., Martin, A.P., Oortwijn, W., Timoney, A., Gustafsson, L.L., 2021. Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications. Expert Rev. Pharmacoecon. Outcomes Res. 21, 527–540.

Gutierrez, L., Patris, J., Hutchings, A., Cowell, W., 2015. Principles for consistent value assessment and sustainable funding of orphan drugs in Europe. Orphanet J. Rare Dis. 10, 1–9.

Haute Autorité de Santé (HAS), 2021. Prescribe Early Access Medication [WWW Document] (accessed 12.1.21). https://www.has-sante.fr/jcms/p_3274103/fr/prescrire-un-medicament-en-acces-precoce.

Herder, M., 2017. What is the purpose of the orphan drug act? PLoS Med. 14, e1002191.

Hollis, A., 2019. Orphan drug pricing and costs: a case study of Kalydeco and Orkambi. Healthc. Policy 15, 70.

Hughes-Wilson, W., Palma, A., Schuurman, A., Simoens, S., 2012. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? Orphanet J. Rare Dis. 7, 1–8.

Jacquet, E., Kerouani-Lafaye, G., Grude, F., Goncalves, S., Lorence, A., Turcry, F., Brunel, L., Belgodere, L., Monard, A., Guyader, G., 2021. Comparative study on anticancer drug access times between FDA, EMA and the French temporary authorisation for use program over 13 years. Eur. J. Cancer 149, 82–90.

Janoudi, G., Amegatse, W., McIntosh, B., Sehgal, C., Richter, T., 2016. Health technology assessment of drugs for rare diseases: insights, trends, and reasons for negative recommendations from the CADTH common drug review. Orphanet J. Rare Dis. 11, 1–13.

Kawalec, P., Sagan, A., Pilc, A., 2016. The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe. Orphanet J. Rare Dis. 11, 1–11.

Kesselheim, A.S., Treasure, C.L., Joffe, S., 2017. Biomarker-defined subsets of common diseases: policy and economic implications of Orphan Drug Act coverage. PLoS Med. 14, e1002190.

Lancet, T., 2010. New£ 50 million cancer fund already intellectually bankrupt. Lancet 376, 389.

Landis, J.R., Koch, G.G., 1977. An Application of Hierarchical Kappa-type Statistics in the Assessment of Majority Agreement Among Multiple Observers. Biometrics, pp. 363–374.

Lexchin, J., Moroz, N., 2020. Does an orphan drug policy make a difference in access? A comparison of Canada and Australia. Int. J. Health Serv. 50, 166–172.

Liden, D., Jaksa, A., Daniel, K., Ho, Y., 2014. CADTH recommendations as predictors for drug availability in British Columbia and Ontario. Value Health 17, A6.

Lipska, I., Hoekman, J., McAuslane, N., Leufkens, H.G.M., Hövels, A.M., 2015. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? Clin. Pharmacol. Ther. 98, 489–491.

Luzzatto, L., Hyry, H.I., Schieppati, A., Costa, E., Simoens, S., Schaefer, F., Roos, J.C., Merlini, G., Kääriäinen, H., Garattini, S., 2018. Outrageous prices of orphan drugs: a call for collaboration. Lancet 392, 791–794.

Martinalbo, J., Bowen, D., Camarero, J., Chapelin, M., Démolis, P., Foggi, P., Jonsson, B., Llinares, J., Moreau, A., O'Connor, D., Oliveira, J., 2016. Early market access of cancer drugs in the EU. Ann. Oncol. 27 (1), 96–105.

McCabe, C., Claxton, K., Tsuchiya, A., 2005. Orphan drugs and the NHS: should we value rarity? Bmj 331, 1016–1019.

McCabe, C., Stafinski, T., Menon, D., 2010. Is it Time to Revisit Orphan Drug Policies?.

McCormick, J.I., Berescu, L.D., Tadros, N., 2018. Common drug review recommendations for orphan drugs in Canada: basis of recommendations and comparison with similar reviews in Quebec, Australia, Scotland and New Zealand. Orphanet J. Rare Dis. 13, 1–12.

Merlini, G., Gribben, J., Macintyre, E., Piggin, M., Doeswijk, R., 2020. Access to affordable orphan medicines in Europe: an EHA position paper. HemaSphere 4.

Mikami, K., Sturdy, S., 2017. Patient organization involvement and the challenge of securing access to treatments for rare diseases: report of a policy engagement workshop. Research involvement and engagement 3, 1–13.

Montgomery, B., 2016. Review of Access to New Medicines: Independent Review. Scottish Government.

Morrell, L., Wordsworth, S., Fu, H., Rees, S., Barker, R., 2017. Cancer drug funding decisions in Scotland: impact of new end-of-life, orphan and ultra-orphan processes. BMC Health Serv. Res. 17, 1–8.

National Healthcare System (NHS), 2016. Cancer Drug Fund [WWW Document] (accessed 12.6.21). https://www.england.nhs.uk/cancer/cdf/.

National Institute for Health and Care Excellence (NICE), 2021. Cancer Drugs Fund [WWW Document]. Available from: (accessed 12.6.21). https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund.

Nicod, E., Kanavos, P., 2016. Scientific and social value judgments for orphan drugs in health technology assessment. Int. J. Technol. Assess. Health Care 32, 218–232.

Nicod, E., Whittal, A., Drummond, M., Facey, K., 2020. Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. Orphanet J. Rare Dis. 15, 1–14.

Ollendorf, D.A., Chapman, R.H., Pearson, S.D., 2018. Evaluating and valuing drugs for rare conditions: no easy answers. Value Health 21, 547–552.

Picavet, E., Dooms, M., Cassiman, D., Simoens, S., 2011. Drugs for rare diseases: influence of orphan designation status on price. Appl. Health Econ. Health Pol. 9, 275–279.

Pinilla-Dominguez, P., Naci, H., Osipenko, L., Mossialos, E., 2020. NICE's evaluations of medicines authorized by EMA with conditional marketing authorization or under exceptional circumstances. Int. J. Technol. Assess. Health Care 36, 426–433.

Richter, T., Nestler-Parr, S., Babela, R., Khan, Z.M., Tesoro, T., Molsen, E., Hughes, D.A., 2015. Rare disease terminology and definitions—a systematic global review: report of the ISPOR rare disease special interest group. Value Health 18, 906–914.

Sarpatwari, A., Beall, R.F., Abdurrob, A., He, M., Kesselheim, A.S., 2018. Evaluating the impact of the Orphan Drug Act's seven-year market exclusivity period. Health Aff. 37, 732–737.

Scottish Medicines Consortium (SMC), 2012. SMC Modifiers Used in Appraising New Medicines.

Scottish Medicines Consortium (SMC), 2018. Interim acceptance decision option [WWW Document]. URL. https://www.scottishmedicines.org.uk/how-we-decide/interim-acceptance-decision-option/.

Scottish Medicines Consortium (SMC), 2021. Availability of medicines in the NHS following SMC decisions [WWW Document]. URL. https://www.scottishmedicines.org.uk/how-we-decide/.

Services Scotland, National, 2020. Patient Access Scheme (PAS) Guidance.

Simoens, S., 2011. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet J. Rare Dis. 6, 1–8.

Simoens, S., Picavet, E., Dooms, M., Cassiman, D., Morel, T., 2013. Cost-effectiveness assessment of orphan drugs. Appl. Health Econ. Health Pol. 11, 1–3.

Tafuri, G., Bracco, A., Grueger, J., 2022. Access and Pricing of Medicines for Patients with Rare Diseases in the European Union: an Industry Perspective. Expert review of pharmacoeconomics & outcomes research.

Vreman, R.A., Bouvy, J.C., Bloem, L.T., Hövels, A.M., Mantel-Teeuwisse, A.K., Leufkens, H.G.M., Goettsch, W.G., 2019. Weighing of evidence by health technology

assessment bodies: retrospective study of reimbursement recommendations for conditionally approved drugs. Clin. Pharmacol. Ther. 105, 684–691.
Vreman, R.A., Mantel-Teeuwisse, A.K., Hövels, A.M., Leufkens, H.G., Goettsch, W.G., 2020. Differences in health technology assessment recommendations among European jurisdictions: the role of practice variations. Value Health 23, 10–16.
Ward, L.M., Chambers, A., Mechichi, E., Wong-Rieger, D., Campbell, C., 2022. An international comparative analysis of public reimbursement of orphan drugs in Canadian provinces compared to European countries. Orphanet J. Rare Dis. 17, 113. https://doi.org/10.1186/s13023-022-02260-6.
Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz, J., Garau, M., 2019. Comparing access to orphan medicinal products in Europe. Orphanet J. Rare Dis. 14, 1–12.