Working Paper No: 42/2015 January 2015 LSE Health

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An analysis of HTA decisions for orphan drugs in Canada and Australia

THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

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Working Paper No. 42/2015

First published in January 2015 by:
LSE Health
The London School of Economics and Political Science
Houghton Street
London WC2A 2AE

British Library Cataloguing in Publication Data. A catalogue record for this publication is available from the British Library.
ISSN 2047-8879

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1. Executive Summary

1.1. Background and aims

In a landscape of increasing budgetary constraint, HTA is increasingly used to help make or influence pricing and reimbursement decisions about healthcare products. However, existing evaluation criteria are not suitable for all products, including orphan drugs. Consequently, some health systems have implemented orphan drug policies to ensure optimal patient access to these drugs. This study aimed to compare value drivers of HTA decision making for orphan drugs in Australia and Canada and to better characterise the factors that feed into their evidence assessments.

1.2. Methods

17 drug-indication pairs were selected for the analysis. Pragmatic literature reviewing was undertaken to characterise the orphan drug reimbursement landscape, current orphan drug assessment processes in Canada and Australia, and reimbursement decisions made for the drug-indication pair sample. Descriptive analysis was used to examine key drivers of decision making and the factors that feed into the evidence assessment for orphan drugs in Canada and Australia.

1.3. Results

More drug-indication pairs achieved marketing authorisation in Canada than Australia, but fewer drugs were assessed. Considerably more drug-indication pairs achieved positive outcomes in Australia than in Canada, although processing times to national decisions were longer. Australia's orphan drug programme did not appear to have a major impact, with no notable differences in outcomes between drug-indication pairs with and without official orphan designation. Inconsistency was observed between national and provincial level decisions in Canada. Key drivers of decision-making and evidence requirements were similar in both countries.

1.4. Conclusions

Despite the narrow scope of this study, the findings suggest existing / impending orphan drug policies in Australia and Canada need to be better tailored to the unique nature of these drugs to ensure equality and equity of access to treatment for patients with rare diseases. Future studies should adopt a broader scope and assess a wider range of orphan drug-indication pairs in order to validate the findings of this study.

2. Introduction

In response to increasing budgetary constraints, many healthcare systems globally have begun to use health technology assessment (HTA) to help make or influence pricing and reimbursement decisions about healthcare products[1]. HTA is widely recognised as an important tool to aid evidence-based decisions[2] to ensure optimally efficient healthcare resource allocation. However, recently there have been growing concerns that the evaluation criteria traditional HTA is based on – often reliant on clinical evidence from randomised controlled trials (RCTs) and economic evidence through cost-effectiveness analysis – are not appropriate for all types of healthcare products[1]. This is particularly true for orphan drugs – those designed to manage rare diseases and conditions – that are associated with the same high cost of research and development as other healthcare products, but are less commercially viable as they have a lower profit potential due to their small patient numbers[3, 4].

2.1. The challenge of assessing orphan drugs

The basic principles of HTA have been focused around the need for rational, evidence-based decision-making in healthcare – which was primarily driven by a limitation of resources to allocate to healthcare in many countries[5]. In most markets, HTA involves a formal assessment of the clinical efficacy/effectiveness, safety and economic impacts of a new product[6], while legal, social and ethical aspects may also be considered[7] (although often informally)[8, 9]. In terms of evidence requirements, broadly speaking, there are similarities across HTA agencies and countries. RCTs are typically considered the "gold standard" for demonstrating clinical attributes of a new product, although in the absence of RCTs, HTA may involve systematic review of data from studies of varying designs[6]. In terms of economic evidence, the results of cost-effectiveness and budget impact analyses are common evidence requirements for many HTA agencies[6].

Orphan drugs, however, have two key characteristics which pose a challenge to traditional methods of assessment[1, 4, 7]:

- Low patient numbers

- High cost of development (which, combined with low patient numbers, contributes to the high prices of orphan drugs as manufacturers attempt to recoup the research and development costs[1])

These characteristics mean it is difficult to demonstrate two core requirements of many HTAs – cost-effectiveness (because it is challenging to offset high cost drugs with efficacy benefits) and clinical evidence from RCTs (because the low patient numbers mean it is difficult to recruit sufficient participants to perform them)[1, 7]. Consequently, orphan drugs do not tend to do well under traditional HTA[1].

2.2. Orphan drug policies

More than 5,000 rare diseases exist globally but, for many, treatments do not exist[4]. Consequently, and in recognition of the barriers traditional HTA can pose to orphan drug access, many countries (e.g. the US, Singapore, Australia) have established orphan drug policies to ensure equitable access to orphan drugs that is better aligned with the wider patient access to non-orphan drugs[1]. Such policies aim to encourage innovation and investment into rare diseases by a variety of measures, including reduced taxes for research and development, different reimbursement assessment process to non-orphan drugs (e.g. reduced fees, fast-track applications etc) and market exclusivity[1]. The success of such policies at securing patients equitable access to orphan drugs, however, is unclear. Consequently, there is a need to better understand and characterise the value drivers of HTA decision making for orphan drugs so that policies can be designed to ensure an appropriate balance between encouraging investment in orphan drug resources, efficient allocation of scarce healthcare resources and optimal patient access.

The purpose of this study was to explore the value drivers of HTA decision making for orphan drugs in a cost-effectiveness driven market with an established orphan drug policy (Australia) and a cost-effectiveness driven market without an established orphan drug policy (Canada). Furthermore, given the lack of published literature on orphan drug HTA and reimbursement in

[1] The market exclusivity designated to orphan drugs in many countries also contributes to high prices as it essentially creates a monopoly, allowing manufacturers to set high prices in the absence of alternative, "competitor" treatments[7]

Australia and Canada, this study also sought to better characterise the factors that feed into assessments of the evidence for orphan drugs in these countries. Prior to undertaking this study, a series of research objectives were formulated to guide the analysis:

- To summarise the current HTA process for orphan drugs in Canada and Australia
- To discuss the key challenges related to HTA of orphan drugs (vs. non-orphan drugs)
- To assess the reimbursement decisions made for a sample of orphan drug–indication pairs in Canada and Australia
    - To establish the length of time from initial marketing authorisation to HTA processing/decision for orphan drugs in Canada and Australia
    - To examine the key drivers for decision making for orphan drugs in Canada and Australia
    - To examine the similarities/differences in decision making at a national and provincial level in Canada
    - To explore the factors that feed into the assessment of evidence for orphan drugs in Canada and Australia
- To discuss the potential policy implications of the research findings

3. Methodology

3.1. Sample selection

To ensure a manageable scope for the project, the focus of the analysis was narrowed to two countries and 15-20 specific drug-indication pairs. Australia and Canada were chosen as, although they are both developed, cost-effectiveness markets, Australia has a formalised orphan drug policy but Canada does not. Additionally, HTA governance in Australia is centralised while in Canada it is both centralised and provincial. Comparing two such countries should provide insight into the impact of orphan drug policies on patient access and highlight any differences in decision drivers, in addition to enabling a comparison of how two health systems with different HTA governance work in practice.

To determine the orphan drug-indication pairs to be included in the analysis, a review of orphan designation approvals (for drugs with marketing authorisation) by the European Medicines

Agency (EMA) between January 2000 and December 2012 was conducted[10]. Of these, 17 orphan drug-indication pairs were selected to ensure an appropriate balance of oncology and non-oncology drugs (see Table 1).

Table 1: Drug-indication pairs selected for analysis

Active ingredient	Brand name	Indication	Year of EMA orphan designation	Oncology drug?
Pasireotide diaspartate	Signifor	Cushing's disease	2009	N
Pirferidone	Esbriet	Idiopathic pulmonary fibrosis	2004	N
Tafamadis	Vyndaqel	Neuropathic heredofamilial amyloidosis	2012*	N
Sorafenib tosylate	Nexavar	Hepatocellular carcinoma (HCC)	2006	Y
Levodopa/carbidopa monohydrate	Duodopa	Parkinson's disease	2001	N
Pazopanib hydrochloride	Votrient	Renal cell carcinoma (RCC)	2006**	Y
Imatinib mesylate	Glivec	Chronic myeloid leukaemia (CML)	2001***	Y
Imatinib mesylate	Glivec	Gastrointestinal stromal tumours (GISTs)	2001***	Y
Sunitinib	Sutent	Malignant GISTs	2005†	Y
Sunitinib	Sutent	RCC	2005†	Y
Azacitidine	Vidaza	Myelodysplastic syndromes	2002	Y
Dasatinib	Sprycel	CML	2005	Y
Everolimus	Afinitor	RCC	2007††	Y
Muramyl tripeptide phosphatidyl ethanolamine	Mepact	Osteosarcoma	2004	Y
Eculizumab	Soliris	Atypical haemolytic uremic syndrome (aHUS)	2009	N
Eculizumab	Soliris	Paroxysmal nocturnal haemoglobinuria (PNH)	2003	N
C1 esterase inhibitor	Cinryze	Hereditary angioedema (HAE)	2009††	N

**Indication expansion; **Removed from Community Register of Designated Orphan Medicinal Products in 2010 at the manufacturer's request; ***Removed from Community Register of Designated Orphan Medicinal Products in 2011 following patent expiry; †Removed from Community Register of Designated Orphan Medicinal Products in 2008 at the manufacturer's request; ††Removed from Community Register of Designated Orphan Medicinal Products in 2011 at the manufacturer's request*

3.2. Analytical framework

To address the aforementioned research objectives, a combination of pragmatic literature reviewing and descriptive analysis was adopted.

3.3. Orphan drug landscape overview

A targeted literature review of PubMed and the grey literature was conducted between May and July 2014 to understand the challenges associated with orphan drug reimbursement and access, and to characterise national HTA processes for both orphan (where relevant) and non-orphan drugs in Australia and Canada. Varying combinations of broad search terms were used in the targeted review to ensure all potentially relevant literature were identified (see Table 2). 16 sources were deemed relevant and included in this report.

Table 2. Search terms used in targeted literature searching

#	Search terms
1	Australia OR Canada
2	Orphan OR rare
3	Drug OR pharmaceutical
4	#2 AND #3
5	Health technology assessment OR HTA
6	Evaluation OR assessment
7	#5 OR #6
8	#1 AND #4 AND #7

3.4. Orphan drug-indication pair reimbursement decisions overview

Targeted searches were conducted in May 2014 to identify the date of marketing authorisation and national reimbursement status of the orphan drug-indication pairs in Australia and Canada (see Table 3). Additional searches were conducted in July 2014 to identify the provincial reimbursement status of the orphan-drug indication pairs in Canada, using Ontario and British Columbia as representative provinces.

Table 3: Sources for HTA outcomes data in Australia and Canada

Source	Description	Study application
Australia		
Pharmaceutical Benefits Advisory Committee (PBAC)	• Downloadable list of all national recommendations by product from PBAC on eligibility for new medicines to be listed on the Pharmaceutical Benefits Scheme (PBS)[11]	To identify national HTA decisions for orphan drug indication-pairs
Australian Register of Therapeutic Goods (ARTG)	• Contains searchable database of therapeutic goods that can be lawfully supplied in Australia (i.e. have marketing authorisation)[12]	To identify dates of marketing authorisation for orphan drug-indication pairs
Canada		
Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review (CDR)	• Searchable database of all national recommendations by product from the CDR on eligibility for new medicines to be listed on the national Drug Benefit List[13]	To identify national HTA decisions and dates of marketing authorisation for orphan drug-indication pairs
Pan-Canadian Oncology Drug Review (pCODR)[14]	• Searchable list of all national recommendations by product from the pCODR on the eligibility of new oncology products to be listed by provincial / territorial formularies[14] • Established in 2010 so only reports decisions for products assessed since then	To identify national HTA decisions for oncology-specific orphan drug-indication pairs
Ontario Drug Benefit Formulary	• Searchable database of provincial-level recommendations in Ontario for eligibility of new medicines to be listed on the formulary[15]	To identify provincial listing decisions for orphan drug-indication pairs
Ontario Exceptional Access Program (EAP)	• List of all drugs not available through the Drug Benefit Formulary that are funded through the Exceptional Access Program[16]	To identify provincial listing decisions for orphan drug-indication pairs
British Columbia Drug Formulary	• Searchable database of provincial-level recommendations in British Columbia for eligibility of new medicines to be listed on the PharmaCare formulary[17]	To identify provincial listing decisions for orphan drug-indication pairs
British Columbia Cancer Agency (BCCA)	• List of all oncology drugs available in British Columbia via the Financial Support Drug Program (FSDP) for cancer patients drug benefit list[18]	To identify provincial listing decisions for oncology-specific orphan drug-indication pairs

3.5. Analysis of HTA decisions and drivers

In order to identify any differences/similarities in the level and timing of availability of, and access to, orphan drugs in Australia and Canada, a descriptive analytic approach was used on the resulting HTA decisions to identify key trends in the number of drugs assessed, the pattern of assessment outcomes and the time lag between marketing authorisation (see Table 4).

Table 4. Analysis endpoints

Endpoint	Description
National HTA decision	• Based on outcome of HTA to determine the number of positive/negative decisions within each country • Categorised as negative (i.e. do not list), positive (list either with or without criteria) or defer (Australia only)
Provincial HTA decision (Canada only)	• Based on drug listings in Ontario and British Columbia provinces to determine if variation exists between provincial and national outcomes • Categorised as positive (listed) or negative (not listed)
Timing	• Time from marketing authorisation to final decision was analysed in Canada and Australia, and time from federal to provincial decision was analysed in Canada only, to assess how long the HTA decision-making process timings/time to patient access is • As Australia has an appeals process, time from marketing authorisation to first decision was analysed to assess HTA processing times
Decision drivers/evidence requirements	• The rationale for each HTA decision in Canada and Australia was analysed to assess the key drivers for positive and negative decisions in each country

3.6. Limitations

As with any analysis, this study is not without limitation and it is important to take this into account when interpreting the results. Firstly, due to the narrow scope of this analysis a relatively small sample size of orphan drug-indication pairs was used which limits the ability to draw firm conclusions – particularly at the national level for Canada, where so few drug-indication pairs were appraised. Future studies with broader scopes should concentrate on a larger sample size of orphan drugs to strengthen the robustness of any trends observed and conclusions drawn. Similarly, to remain within scope, only two provinces were selected to compare national and provincial level decisions in Canada. While useful to illustrate any difference between national and provincial level decisions, given that each province has its own assessment rules caution should be taken not to generalise the findings – to do this, future studies are needed involving a comprehensive analysis of decisions made across all provinces. Finally, the national HTA appraisal documents available in the public domain for both countries only provide brief summaries of the rationale for decisions, while no rationale is available for decisions made at the provincial level in Canada. Consequently, the conclusions drawn regarding decision drivers are based on limited evidence. Future studies could incorporate primary research with key decision makers at a national level in both countries, and a provincial

level in Canada, to validate this study's findings and to strengthen the evidence base on which to assess the key drivers of decision making.

4. Results

4.1. HTA processes in Australia and Canada

4.1.1. Australia

In Australia, traditional pharmaceuticals are centrally assessed via the PBAC[19, 20]. Once a new drug has applied for marketing authorisation from the Therapeutic Goods Administration (TGA) and successfully been added to the ARTG it undergoes HTA by PBAC. PBAC then makes reimbursement recommendations to the Minister for Health and Ageing – who makes final coverage decisions – based on an appraisal of the drug's comparative safety, clinical effectiveness and cost-effectiveness[19]. Only drugs receiving a positive recommendation by PBAC can be listed by the PBS and be publicly funded[19].

Drugs for rare diseases – defined in Australia as those not affecting more than 2,000 people at any time – can apply for orphan designation from the TGA[21] in order to be considered under the orphan drug programme, which was established in 1997[22]. To be eligible, they must not have been registered for use in the particular disease/condition prior to January 1, 1998 nor been rejected by any of the following organisations on the grounds of safety[21]:

- TGA
- Food and Drug Administration (FDA) in the US
- EMA in Europe
- Therapeutic Products Directorate (TPD) in Canada
- Medicines and Healthcare Product Regulatory Agency (MHRA) in the UK
- Medical Products Agency (MPA) in Sweden
- Medicines Evaluation Board (MEB) in the Netherlands or the EMEA

The orphan drug programme aims to promote access to drugs achieving orphan status by waiving the registration fees associated with HTA and enabling priority evaluation[21, 22].

4.1.2. Canada

In Canada, pharmaceuticals can be assessed at both a central and provincial level. Once a new drug has successfully received marketing authorisation (notice of compliance; NOC) from Health Canada, it is assessed by CADTH via the CDR process on a first-come-first-served basis[23]. The CDR was established in 2003 and makes recommendations to federal, provincial and territorial level drug plans based on the assessment of the clinical and cost-effectiveness of new (non-oncology) drugs[23, 24]. In 2007, the Joint Oncology Drug Review (JODR) was established to assess oncology drugs separately, and subsequently became the pCODR in 2010[24]. The pCODR – now a specialist body within CADTH[2] - assesses new oncology drugs "*by reviewing clinical evidence, cost-effectiveness, and patient perspectives, and using this information to make recommendations to Canada's provinces and territories (except Quebec) in guiding their drug funding decision*"[25].

HTA by the CDR is primarily driven by assessment of a new drug's comparative therapeutic benefit and cost-effectiveness relative to an existing therapy. Three outcomes are possible – list without condition, list with conditions or do not list[23]. The decisions made by the CDR/pCODR at a federal level are not binding and, once reached, each drug plan makes its own final decision[23, 24] – consequently, it is possible for a drug to achieve one decision at a federal level but a different decision at a provincial level and vice versa. No explicit policy currently exists for orphan drugs – defined as those used to treat rare diseases affecting less than 5 in 10,000 persons – in Canada which makes it one of a very small number of developed countries that do not have any provision for promoting access to and incentivising manufacturer investment in orphan drugs[26]. However, Health Canada is currently finalising a proposed framework for an orphan drug policy which will soon be targeted for public consultation[27].

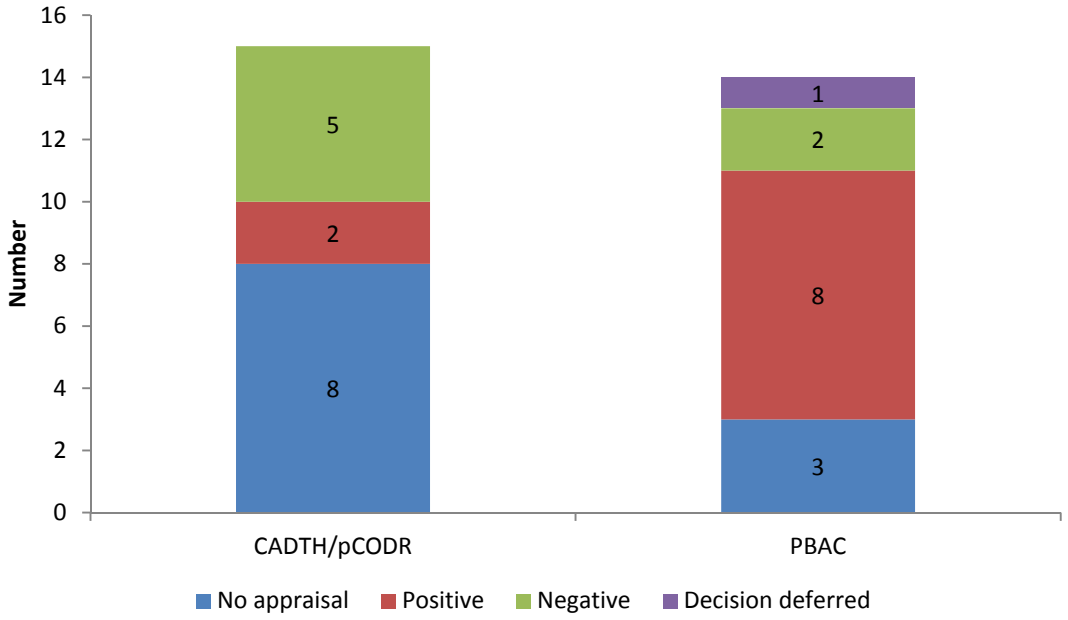
4.1.3. Reimbursement decision overview

Of the 17 drug-indication pairs analysed, 15 had marketing authorisation in Canada compared with 14 in Australia. Overall, CADTH and pCODR assessed considerably fewer drug-indication pairs (7) than PBAC (11). At a national level, just 2 drugs were provided with positive

[2] Originally an independent body established in 2010, pCODR was transferred to CADTH in April 2014

recommendations in Canada – 1 by CADTH (list with criteria) and the other by pCODR – while PBAC provided positive recommendations for 8 drugs (see Figure 1). Of the 9 drug-indication pairs with official orphan designation by the TGA, 7 were assessed by PBAC. Of these, 4 received a positive recommendation, 2 a negative recommendation and for 1 the decision was deferred. In scenarios where PBAC feel insufficient evidence has been submitted to evaluate a product, they may defer decisions *"pending the provision of specific additional information that would be relevant and important to the decision"*[28]. Of the 4 out of 5 drug-indication pairs without official orphan designation that were assessed by PBAC, all received a positive recommendation.

Figure 1. Overview of HTA outcomes



Of the 6 drugs assessed by both agencies, a discrepancy in recommendations existed in 3 cases, with CADTH providing negative recommendations, while PBAC provided positive recommendations (2 cases) or deferred the decision pending additional evidence (1 case; see Table 5).

Table 5. Outcomes for drugs assessed by both CADTH/pCODR and PBAC

Drug	Indication	Recommendation	
		CADTH/pCODR	PBAC
Duodopa	Parkinson's disease	Negative	Positive
Votrient	RCC	Positive*	Positive
Sutent	GIST	Positive (LWC)	Positive
Sutent	RCC	Negative	Positive
Soliris	PNH	Negative	Defer**
Soliris	aHUS	Negative	Negative

**Assessed by pCODR; **Decision deferred pending provision of additional information; LWC=list with criteria*

In addition to national-level decisions, provincial-level assessments from Ontario and British Columbia were also analysed in Canada to determine any variation between national and provincial decisions. Of the 8 drug-indication pairs with marketing authorisation that were not appraised by CADTH or pCODR, 2 were not appraised in either province, 5 were listed in both provinces and 1 (Vidaza) was listed in British Columbia only, by the BCCA (see Table 6). Negative decisions at the federal level were upheld by one or both provinces in only 2 out of 5 cases; the two positive decisions at the federal level (Sutent, malignant GIST; Votrient, RCC) were upheld in both provinces.

4.2. Timing

At face value, the time from marketing authorisation to final decision was – in general – shorter in Canada than Australia – despite the limited sample for Canada (see Table 6 and Figure 2). However, unlike in Canada, manufacturers can appeal in Australia if their products are rejected by PBAC – consequently, the time from marketing authorisation to first assessment was also analysed to get a better understanding of how quickly the orphan drug-indication pair submissions were processed in Australia (see Table 7). With the exception of 1 drug-indication pair which had a lengthy time to first decision (Soliris, aHUS; 42 months), the processing times ranged from -4–6 months, suggesting that time to assessment is relatively quick in Australia but that appeals add considerably to the timings of orphan drug assessment. Official orphan designation seemed to have minimal impact on processing times, with the time to first decision

for these drug-indication pairs ranging from -4–5 months (excluding Soliris, aHUS at 42 months).

In Canada, the timing of provincial decisions in British Columbia ranged from 23 months before the federal-level decision (Votrient) to 20 months after the federal-level decision; when Votrient was excluded, they ranged from 3-20 months post federal-level decision (see Table 8). The dates of provincial decisions in Ontario were not reported. Given the limited sample size of both outcomes and provinces, further conclusions cannot be drawn.

Table 6. Date of marketing authorisation and final decision, by country

Drug	Indication	AUSTRALIA			CANADA					BC decision	BC outcome
					Federal level			Provincial level			
		MA	Final decision	Outcome	MA	Final decision	Outcome	Ontario decision	Ontario outcome		
Signifor	Cushing's disease	1/11/2013	-	-	23/09/2013	-	-	-	-	-	-
Esbriet	Idiopathic pulmonary fibrosis	-	-	-	01/10/2012	18/04/2013	Negative	-	-	14/01/2014	Negative (Pharmacare non-benefit)
Vyndaqel	Neuropathic heredofamilial amyloidosis	-	-	-	-	-	-	-	-	-	-
Nexavar	HCC	25/02/2008	Jul 2008	Positive (LWC)	28/01/2008	-	-	N/R	Positive (EAP)	01/01/2008 (date activated)	Positive (BCCA Compassionate Use Program)
Duodopa*	Parkinson's disease	27/02/2008	Nov 2010	Positive	01/03/2007	22/07/2009	Negative	-	-	31/03/2011	Negative (Pharmacare non-benefit)
Votrient	RCC	30/06/2010	Mar 2012	Positive	27/05/2010	29/08/2013**	Positive***	N/R	Positive (EAP)	01/09/2011	Positive (BCCA Compassionate Use Program)
Glivec*	CML	17/12/2013	-	-	20/09/2001	-	-	N/R	Positive (Drug Benefit Formulary)	01/07/2002	Positive (BCCA class II)
Glivec*	GISTs	17/06/2009	Mar 2011	Positive	07/08/2002	-	-	N/R	Positive (EAP)	01/01/2008	Positive (BCCA class II)
Sutent	Malignant GISTs	14/09/2006	Jul 2009	Positive	26/05/2006	28/03/2007	Positive (LWC)	N/R	Positive (EAP)	01/08/2007	Positive (BCCA class II)
Sutent	RCC	14/09/2006	Jul 2008	Positive	17/08/2006	26/04/2007	Negative	N/R	Positive (EAP)	01/07/2007	Positive (BCCA Compassionate Use Program)

Vidaza*	Myelodysplastic syndromes	30/11/2009	Sept 2009	Positive	23/10/2009	-	-			01/07/2010	Positive (BCCA Compassionate Use Program)
Sprycel*	CML	15/01/2007	Mar 2007	Positive	26/03/2007	-	-	N/R	Positive (EAP)	01/11/2007	Positive (BCCA Compassionate Use Program)
Afinitor*	RCC	6/08/2009	Nov 2011	Negative	14/12/2009	-	-	N/R	Positive (EAP)	01/02/2011	Positive (BCCA class II)
Mepact*	Osteosarcoma	-	-	-	-	-	-	-	-	-	-
Soliris*	aHUS	20/03/2009	Mar 2013	Negative	28/01/2009	19/02/2010	Negative at submitted price	N/R	Positive (EAP)	-	-
Soliris*	PNH	03/03/2008	Jul 2010	Deferred	01/03/2013	18/07/2013	Negative	-	-	-	-
Cinryze*	HAE	05/04/2012	-	-	19/10/2012	-	-	-	-	-	-

**Designated orphan status by TGA in Australia; **Submitted to pCODR 20/02/2013; ***Assessed by pCODR*

Figure 2: Time from marketing authorisation to final national-level decision

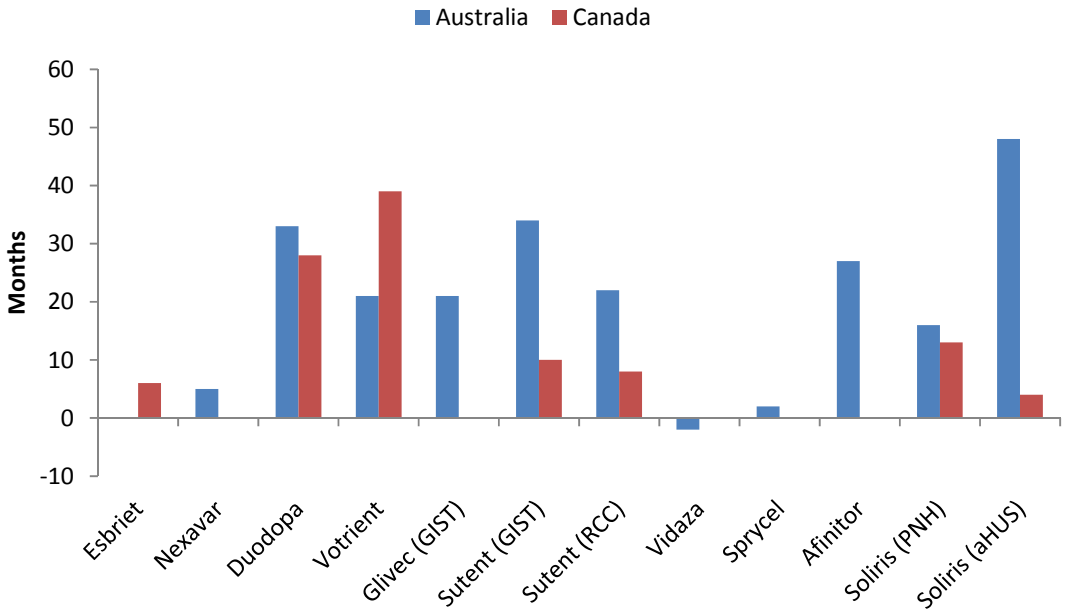


Table 7. Time from marketing authorisation to first assessment for relevant drug-indication pairs in Australia

Drug	Indication	MA	First assessment	Final assessment	Time from MA to first assessment (months)	Time from first to final assessment (months)
Nexavar	HCC	25/02/2008	Jul 2008	Jul 2008	5	-
Duodopa	Parkinson's disease	27/02/2008	Mar 2008	Nov 2010	1	32
Votrient	RCC	30/06/2010	Jul 2010	Mar 2012	1	20
Glivec	GIST	17/06/2009	Nov 2009	Mar 2011*	5	16
Sutent	Malignant GISTs	14/09/2006	Mar 2007	Jul 2009	6	28
Sutent	RCC	14/09/2006	Mar 2007	Jul 2008	6	16
Vidaza	Myelodysplastic syndromes	30/11/2009	Jul 2009	Sept 2009	-4**	2
Sprycel	CML	15/01/2007	Mar 2007	Mar 2007***	2	-
Afinitor	RCC	6/08/2009	Nov 2009	Nov 2011	3	24
Soliris	aHUS	20/03/2009	Mar 2013	Mar 2013	42	-
Soliris	PNH	03/03/2008	Jul 2008	Jul 2010	4	28

**First approval received in March 2011 followed by an additional request in March 2012 (with approval in November 2012) for extending approval to include a maximum duration of treatment of 3 years; **First assessment prior to NOC; ***First approval received in March 2007 followed by an additional indication expansion in July 2011*

Table 8. Time from federal decision to provincial assessment (British Columbia) for relevant drug-indication pairs in Canada

Drug	Indication	Federal assessment (CADTH / pCODR)	Provincial assessment (British Columbia)	Time from federal to provincial assessment (months)
Esbriet	Idiopathic pulmonary fibrosis	18/04/2013	14/01/2014	9 months
Duodopa	Parkinson's disease	22/07/2009	31/03/2011	20 months
Votrient	RCC	29/08/2013	01/09/2011	-23 months
Sutent	Malignant GISTs	28/03/2007	01/08/2007	5 months
Sutent	RCC	26/04/2007	01/07/2007	3 months

4.3. Drivers of decision making

In Canada, clinical effectiveness and cost-effectiveness were the key drivers of decision making at the federal level, with all 4 rejections attributed to unacceptably high ICERs and / or uncertainty around clinical effectiveness (often associated with poor clinical trial design) (see Table 9). Similar trends were observed in Australia, regardless of official orphan designation status.

Table 9. National-level decision drivers in Australia and Canada

Drug	Indication	National-level decision and driver(s)	
		Australia	**Canada**
Esbriet	Idiopathic pulmonary fibrosis	-	Negative • Uncertainty of clinical effect due to inconsistent clinical trial results • Unacceptably high ICER ($143,617 per QALY)
Nexavar	Hepatocellular carcinoma	*Positive (LWC)* • High but acceptable ICER due to high unmet need in patient population because of lack of alternative treatments ($45,000-75,000 per LYG/>$75,000 per QALY) • 2 well-designed clinical trials (double-blind RCTs) • Low financial impact (<$10 million in year 5)	-
Duodopa	Parkinson's disease	*Negative (Mar 2008)* • Unacceptably high and uncertain ICER ($130,000-150,000 per QALY) • Lack of inclusion of all relevant comparators in submission • Major concerns over adverse events *Negative (Mar 2009)* • Uncertain clinical benefit • Unacceptably high and uncertain ICER ($75,000-105,000 per QALY) *Positive (Nov 2010)* • High but acceptable ICER vs. standard medical care including DBS ($45,000-75,000 per QALY) • High clinical need in patient population	*Negative* • Unacceptably high ICER (not reported) • Clinical trial quality issues

Drug	Indication	National-level decision and driver(s)	
		Australia	**Canada**
Votrient	RCC	*Negative (Jul 2010)* • Uncertain clinical benefit *Positive (LWC; Mar 2012)* • Cost-minimisation vs. sunitinib	*Positive (Aug 2013)* • Similar efficacy vs. current standard (sunitinib) • Different toxicity profile vs. current standard • Patient need for alternative treatment options • Cost effective vs. current standard
Glivec	GIST	*Negative (Nov 2009)* • Uncertain clinical benefit • Unacceptable high and uncertain ICER (range: $45,000-75,000 per QALY but could be much higher)	-
		Negative (Jul 2010) • Uncertain clinical benefit • Unacceptable high and uncertain ICER (range: $45,000-75,000 per QALY but could be >$100,000 per QALY)	-
		Positive (Mar 2011) • Acceptable ICER vs. placebo ($15,000-45,000 per QALY) • Price decrease offered by manufacturer	-
		Negative (extension to listing; Mar 2012) • Uncertain magnitude of survival benefit • Unacceptably high ICER (range: $150,000-200,000 per QALY)	-

Drug	Indication	National-level decision and driver(s)	
		Australia	**Canada**
		Positive with price reduction (extension to listing; Nov 2012) • Acceptable ICER provided price reduction brings it down from $45,000-75,000 to $15,000-45,000 per QALY)	-
Sutent	GIST	*Defer (Mar 2007)* • Insufficient economic evidence to appraise cost-effectiveness *Negative (Mar 2008)* • Unacceptably high and uncertain ICER ($105,000-200,000 per QALY) *Positive (Jul 2009)* • High but acceptable ICER vs. BSC ($45,000-75,000 per QALY) • High clinical need	*Positive (LWC)* • Established clinical benefit • Acceptable costs (similar to alternative)
Sutent	RCC	*Defer (Mar 2007)* • Insufficient economic evidence submitted *Negative (Mar 2008)* • Unacceptably high and uncertain ICER ($75,000-105,000 per QALY) *Positive (Jul 2008)* • Acceptable ICER vs. BSC at new price proposed ($45,000-75,000 per QALY)	*Negative* • Uncertainty of clinical effect, due to no RCT data in licensed patient population • Uncertainty around ICER (manufacturer estimate: $56,000 per QALY)
Vidaza	Myelodysplastic syndromes	*Defer (Jul 2009)* • Insufficient economic evidence submitted *Defer (Aug 2009)* • Price negotiation required for ICER to be	-

Drug	Indication	National-level decision and driver(s)	
		Australia	**Canada**
		considered reasonable	
		Positive (Sept 2009) • High but acceptable ICER ($45,000-75,000 per QALY)	
Sprycel	CML	*Positive (Mar 2007)* • Cost-effectiveness – less costly and more effective than imatinib	-
		Positive (Jul 2011) • Cost-minimisation basis vs. imatinib	
Afinitor	RCC	*Negative (Nov 2009)* • Uncertain clinical benefit • Unacceptably high and uncertain ICER ($105,000-200,000 per QALY)	-
		Negative (Jul 2010) • Uncertain clinical benefit • Unacceptably high and uncertain ICER ($45,000-105,000 per QALY)	
		Negative (Nov 2011) • Unacceptably high and uncertain ICER ($45,000-75,000 per QALY)	
Soliris	PNH	*Negative (Jul 2008)* • Unacceptably high and uncertain ICER (>$200,000 per additional death avoided) [section 100] • Currently no means of identifying relevant patient subgroup [Life Saving Drugs Program; LSDP]	*Negative at submitted price* • Unacceptably high ICER ($2.4 million per QALY)
		Negative (Mar 2009) [Section 100]	

Drug	Indication	National-level decision and driver(s)	
		Australia	**Canada**
		Independent review for LSDP • Unacceptably high and uncertain ICER (>$200,000 per additional death avoided)	
Soliris	aHUS	*Negative (Mar 2013)* • Uncertain clinical benefit • Unacceptably high ICER ($1-4 million per QALY)	*Negative* • Uncertainty of clinical effect due to limitations of clinical trials

LWC=list with criteria

5. Discussion

Although the drivers of national-level decision making in each country were similar, overall, the results suggest that the assessment of, and access to, orphan drugs varies considerably in Australia and Canada.

5.1. HTA processes

Unsurprisingly, the assessment processes for orphan drugs differed in Australia and Canada, due to the presence and absence of an orphan drug programme in each country, respectively. In Australia, drugs applying, and successfully meeting, the eligibility criteria for orphan designation by the TGA do not have to pay the registration fees typically associated with HTA and are enabled a priority evaluation.

5.2. Reimbursement decisions overview

Although a similar number of drugs had marketing authorisation in both countries, only 46.7% of the eligible drug-indication pairs were assessed at the national level in Canada compared with 78.6% in Australia. One reason for this discrepancy may be due to CADTH's reputation for being a challenging country to achieve positive HTA recommendations in at the national level compared with HTA agencies in other countries, such as France and Sweden[29], so manufacturers may choose not to submit their products for HTA in Canada. This is reflected by the results of this study, where only 2 drug appraised by CADTH/pCODR achieved a positive recommendation (compared with 8 by PBAC). Furthermore, unlike in Australia, the lack of orphan drug programme in Canada means there is no incentive for manufacturers of new drugs for rare diseases to undergo the costly HTA submission process.

Despite the literature widely acknowledging that new drugs in Canada must undergo assessment at a national level by the CDR or pCODR prior to assessment at a provincial or territorial level[23, 24], our findings indicated some potential discrepancies. Of the 8 drug-indication pairs with marketing authorisation for which no national level outcomes appear to have been made by CADTH/pCODR, 6 were assessed and received positive decisions in both Ontario and British Columbia, and 1 was assessed and received a positive decision in British Columbia alone. While

the exact reasons for this remain unknown, several hypotheses can be made when the decisions are explored in more detail. Firstly, it is important to note that all 6 drugs were for oncology indications and were assessed prior to 2010 when the pCODR was established (and 2011 when it began accepting submissions). Secondly, 4 drug-indication pairs received marketing authorisation prior to the establishment of the pCODR in 2010, while the remaining 2 received marketing authorisation prior to 2003 when the CDR was established. Based on these observations, it appears the latter drug-indication pairs (Glivec CML/GIST) may have applied directly to provincial/territorial plans prior to the establishment of the CDR – hence no documentation of outcomes at a national level. Similarly, if the other 4 drug-indication pairs had been assessed at a national level, it would likely have been by the JODR between 2007 and 2010 – as the JODR did not publish its outcomes[30] it is not possible to determine if national decisions were made for these products through secondary research alone. Finally, as access to most of these drug-indication pairs at a provincial level were via exceptional access or compassionate use programmes these data suggest high cost oncology drugs may be accessible to patients at a provincial level on a case by case basis, with national level recommendations of lower importance in the decision-making process.

The official orphan designation system existing in Australia did not seem to have a major impact on recommendations by PBAC – in fact, the only negative recommendations received were for 2 drugs with official orphan designation status. These data suggest that, beyond the reduced fees for submission/eligibility to fast-track assessment, orphan designation does not appear to impact how the drug is assessed versus non-orphan designation drugs.

5.3. Timing

Despite the limited sample size, the time from marketing authorisation to final decision appeared to be shorter in Canada than Australia. However, given the high number of negative outcomes for the small sample of drugs assessed at the national level in Canada, these faster processing times did not appear to translate into faster treatment access for patients. At a provincial level, however, where decision making is independent to that at the federal level, the results suggest access patient to orphan drugs may be more favourable. While the time from marketing authorisation to final decision in Australia seemed much longer than in Canada, this is likely due

to the appeals process that exists to enable manufacturers to appeal negative outcomes. In this study, only 3 orphan drug-indication pairs had a single assessment by PBAC (Soliris, aHUS – negative; Nexavar, HCC and Sprycel, CML – both positive) – all others underwent at least one appeal and, in the majority of cases, negative decisions were overturned to positive decisions. There were only two exceptions to this – Afinitor, RCC which received three negative decisions on the basis of cost, and Soliris, PNH which received 2 negative decisions, before a final deferral of decision in July 2010 pending additional information on survival gain. Although not explicitly stated, given a primary driver of negative decisions was unacceptably high ICERs, the overturned decisions are likely attributable to risk-sharing agreements or significant price reductions. When time from marketing authorisation to first decision was analysed, the processing times were similar to those in Canada (where the final decision is the first and only decision). Collectively, these data suggest that the likelihood of patient access to orphan drugs at a federal level is generally better in Australia than Canada, although this access may be subject to significant delays due to the lengthy appeals process. While the provincial level findings highlight that treatment access can vary from the federal level, the limited sample size means it is not possible to draw firm conclusions about provincial patient access to drugs in Canada.

5.4. Drivers of decision making

Overall, the rationale for positive and negative decisions for the assessed orphan drug-indication pairs was consistent in Canada and Australia and centred on clinical and cost effectiveness. In Australia, given the relatively large number of orphan drug-indication pairs assessed, combined with the high number of appeals, provide a relatively large sample from which trends can be inferred – these are outlined below.

It is well documented that PBAC decisions for non-orphan drugs are driven primarily by clinical evidence and cost-effectiveness[29]. Surprisingly, despite having an official orphan drug programme, the key decision drivers identified in this study for orphan drug-indication pairs were consistent with those of non-orphan drugs. For clinical evidence, our results suggest PBAC maintained the high quality standards they exert for non-orphan drugs with Phase III randomised controlled trials being favoured over other types of study design. Additionally, the appeals process that was prevalent for many of the orphan drug-indication pair analyses following a

negative outcome appears, in an overwhelming majority of cases, to have been driven solely on cost-effectiveness, suggesting manufacturers may have to make substantial price cuts or commit to risk sharing agreements to achieve positive decisions for orphan drugs. The majority of positive decisions were driven by acceptable cost-effectiveness data, with the typical 'acceptable' range being $45,000-75,000/QALY provided perception of unmet need for the patient population was high and/or no other treatment options were available. Interestingly, this range is similar to the implicit willingness to pay threshold for non-orphan drugs estimated for PBAC in the literature ($42,000-76,000)[31], suggesting PBAC does not make exceptions for orphan drugs with regards to economic evidence requirements. In contrast, negative decisions were typically driven by uncertain clinical benefit and unacceptably high and uncertain cost-effectiveness data, with a much broader range of 'unacceptable' costs observed ($45,000-4 million/QALY).

Given the limited number of outcomes for the study sample in Canada, it is difficult to draw firm conclusions. However, as the two drugs receiving positive recommendations were assessed by different bodies (CADTH and pCODR), a couple of points of interest are worth noting. Firstly, cost-effectiveness data were considered by both bodies and influenced the decision outcomes – given the lack of official orphan drug policy in Canada this reliance of traditional HTA economic evidence requirements is unsurprising. Secondly, while CADTH officially states patient input is considered in its assessment process[32], the prominence of this in the pCODR assessment report was far greater, indicating that patient value is now recognised to have some weight in the assessment of the value of oncology products in Canada. While analysis of a greater volume of decisions by both bodies is necessary to draw robust conclusions from this, given the high unmet need surrounding orphan diseases, this preliminary finding is promising as it reflects a shift in attitude and increasing recognition of the need to consider patient impact when assessing high cost drugs for high unmet need populations.

5.5. Implications for orphan drug policy

This study highlights the need for, and importance of, orphan drug policies to ensure fair assessment and equitable access to treatment for rare diseases. In Australia, although an orphan drug programme exists, the time from marketing authorisation to final decision and implied

reliance on risk sharing agreements/price reductions suggest new economic evidence requirements that are less reliant on cost-effectiveness may be needed to ensure patients suffering from rare diseases have rapid and equitable access to orphan drugs. The recent agreement between the TGA and the EMA to share full assessment reports related to marketing authorisation[33] indicates a dedication from Australia to strengthen their orphan drug assessment approach and it will be interesting to monitor the downstream implications of this collaboration on the existing orphan drug programme/assessment approach.

Similarly, in Canada, the limited number of assessments conducted (and subsequent positive outcomes) at the national level, combined with the lack of documentation at the national level for some oncology drugs and the corresponding inconsistency between national- and provincial-level decisions highlight the need for an established orphan drug program that can encompass both oncology and non-oncology drugs in a consistent and equitable manner. Such a program would help ensure manufacturers are incentivised to submit the products to CADTH/pCODR, patients have greater access to orphan drugs and that the risk of a 'provincial-level' lottery with inequitable access to treatment for patients with rare diseases living in different provinces is minimised. Consequently, the orphan drug framework currently in development by Health Canada[27] will be of great value to those citizens currently living with rare diseases in Canada. Given Health Canada has had the benefit of being able to observe the existing orphan drug policies adopted globally it will be interesting to see how it has designed their framework and what, if any, lessons have been learned.

6. Conclusion

In conclusion, despite the narrow scope of this study, some interesting observations have been made regarding the assessment of orphan drugs in Canada and Australia. While Australia assessed and provided access to a greater number of orphan drug-indication pairs at a national level than Canada, the separate provincial-level assessment powers add an additional layer of complexity – and opportunity – for orphan drug assessment and access in Canada. The HTA decision drivers and evidence requirements in both countries were similar and, with the exception of an emphasis on unmet need, not wholly different to the traditional criteria for HTA of non-orphan drugs documented in the literature for both countries. Given the challenges of

'traditional' evidence generation for drugs for rare diseases in terms of both their clinical trials and economic aspects, these findings suggest the existing orphan drug policy in Australia and impending policy in Canada need to be better tailored to the unique nature of these drugs to ensure equality and equity of access to treatment for patients with rare diseases. Future studies should adopt a broader scope and assess a wider range of orphan drug-indication pairs in order to validate the findings of this study.

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