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Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland

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ABSTRACT

Objectives: To evaluate the national regulatory, health technology assessment (HTA), and reimbursement pathways for public health care in Australia, Canada, England, and Scotland, to compare initial Canadian national HTA recommendations with the initial decisions of the other HTA agencies, and to identify factors for differing national HTA recommendations between the four HTA agencies. **Methods:** Information from the public domain was used to develop a regulatory process map for each jurisdiction and to compare the HTA agencies' reimbursement recommendations. Medicines that were reviewed by all four agencies and received a negative recommendation from only one agency were selected as case studies. **Results:** All four countries have a national HTA agency. Their reimbursement recommendations are guided by both clinical efficacy and cost-effectiveness, and the necessity for patient input. Their activities, however, vary because of different mandates and their unique political, social, and population needs. All have an implicit or explicit quality-adjusted life-year threshold. The seven divergent case studies demonstrate examples in which new medicine-indication pairs have been rejected because of uncertainties surrounding a range of factors including cost-effectiveness, comparator choice, clinical benefit, safety, trial design, and submission timing. **Conclusions:** The four HTA agencies selected for inclusion in this study share common factors, including a focus on clinical efficacy and cost-effectiveness in their decision-making processes. The differences in recommendations could be considered to be due to an individual agency's approach to risk perception, and the comparator choice used in clinical and cost-effectiveness studies.

Keywords: Australia, Canada, divergent recommendations, England, health technology assessment, Scotland.

Introduction

The growing availability of less expensive generics plus the rising costs of new medicines and limited health care budgets increase the need for rationalized allocation of public resources [1,2]. As a result, most public health providers require manufacturers to demonstrate the benefits of their new drug technology over existing treatments before reimbursement approval. The evaluations of treatments to guide health policy and reimbursement decisions are usually performed by health technology assessment (HTA) agencies. Generally, HTA agencies will evaluate the therapeutic value and cost-effectiveness of a health technology. The scope and methodologies used to conduct HTA can, however, vary greatly among agencies, because affordability and social and political factors are unique to each coverage population [3].

This study focuses on the HTA environments in Australia, Canada, England, and Scotland, because these four nations have an entwined history and share a common liberal, basic security welfare state ideology [4,5]. The study objectives were therefore to evaluate the national regulatory, HTA, and reimbursement pathways for public health care in the four regions to compare initial Canadian national HTA recommendations from January 2009 to May 2013 with the initial HTA decisions to identify factors for these differing national HTA recommendations.

Methods

Information for regulatory approval and HTA reimbursement recommendations was collected from the public domain directly

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from the Web sites of the European Medicines Agency (EMA) [6], the Canadian Agency for Drugs and Technologies in Health (CADTH) [7], Health Canada [8], the National Institute for Care and Health Excellence (NICE) in England [9], the Pharmaceutical Benefits Advisory Committee (PBAC) of the Pharmaceutical Benefits Scheme in Australia [10,11], the Scottish Medicines Consortium (SMC) [12–14], and the Therapeutic Goods Administration (TGA) in Australia [15]. This information facilitated the development of a process map for each jurisdiction using a previously developed mapping methodology [16]. These maps enabled the identification and relationships between the HTA agencies and the body responsible for the final reimbursement decision. Regulatory approval dates were identified from the regulatory authorities' online databases [6,8,15].

The CADTH Common Drug Review (CDR) program was selected as the primary agency for this study to complement a previous study evaluating the impact of CDR recommendations on provincial listing decisions [17]. A CDR listing recommendation issued from January 2009 to May 2013 was a criterion for the inclusion of a drug product in this study. New indication submissions were also included if the initial submission met the inclusion criteria. The proprietary name, generic name, indication, and recommendation were recorded from the online CDR database [7]. The corresponding HTA agency recommendations for Australia, England, and Scotland were identified by generic name and indication. Medicines marketed under a different brand name for the Australian or European market were included, provided they were listed for the same indications as the initial CDR recommendation. When an agency reviewed indications separately or issued different recommendations per indication within a single review, this was recorded as a medicine-indication pair for all four agencies. The first and latest recommendations issued up to September 2016 were recorded for all medicine-indication pairs across agencies and classified as either positive or negative recommendations. All recommendations to reimburse a medicine (with or without restrictions) were classified as positive recommendations and recommendations to not reimburse to any population were considered negative. Recommendations with restrictions have been combined with unrestricted recommendations because of the difficulty of actively comparing restrictions across agencies [18].

Statistical Analysis

HTA recommendations classified as positive or negative were numerically coded to calculate the quantity of concordant recommendations for each medicine between jurisdictional pairs. Not all HTA agencies will have reviewed the same medicines. Thus, reporting the total number of concordant recommendations alone could be misleading, and therefore the percentage agreement was calculated between jurisdiction pairs to report the proportion of concordant recommendations.

The 95% confidence interval (CI) was also calculated for each recommendation classification using the Wilson score method. This method was chosen because it is suitable for small n values and will not produce CIs with negative or larger than 100% value [19].

Results

HTA Processes in Australia, Canada, England, and Scotland

These four health care systems include a national HTA body to assess the added therapeutic value and cost-effectiveness of new medicines. There are, however, key differences between the mandates and processes of these agencies that should be considered when comparing their HTA recommendations. For example, Canada is the only region assessed in this study that has two national HTA programs: the pan-Canadian Oncology Drug Review for the assessment of oncology medicines and the CDR for the assessment of new medicines and indications (Fig. 1). Because this study was looking at reviews from only the CADTH CDR program, no oncology products were included in this research.

In the United Kingdom, the SMC reviews all new medicines to provide a reimbursement recommendation to the National Health Service (NHS) Scotland, but in England, NICE reviews only significant new medicines and indications that have a formal request for review from the Secretary of State for Health (Fig. 2). Therefore, the number of medicines with a recommendation issued by NICE will be much lower compared with the other three agencies.

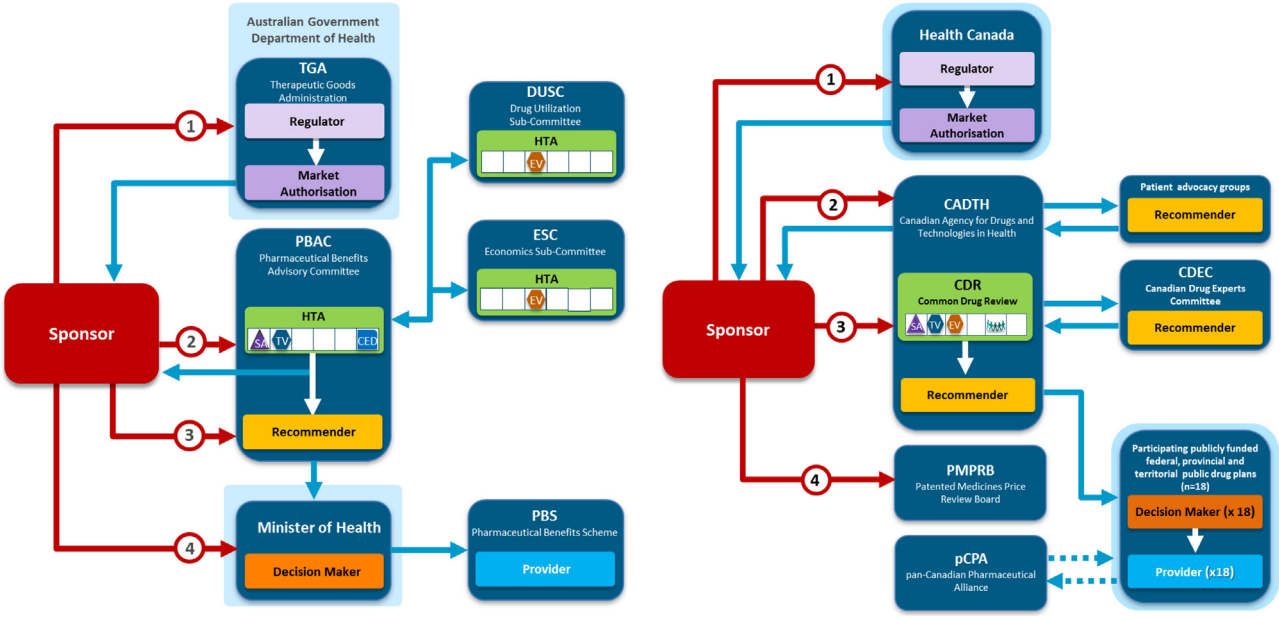


Fig. 1 – Process maps for Australia and Canada (Common Drug Review). HTA, health technology assessment.

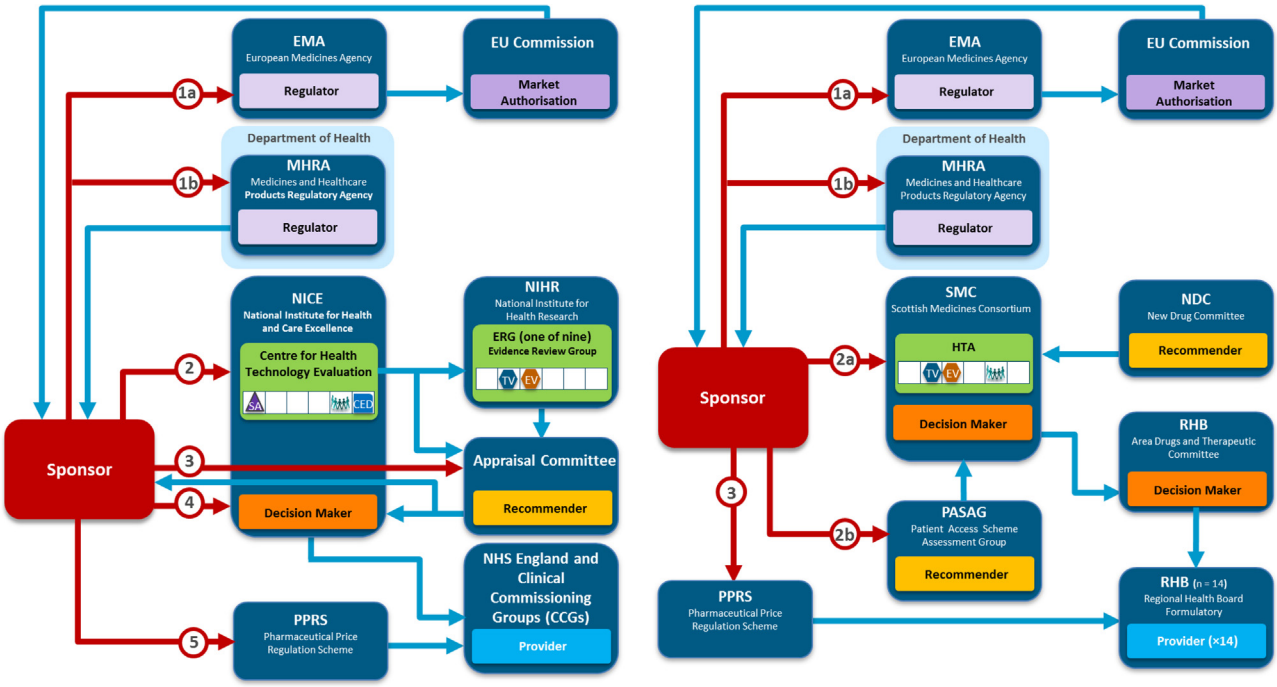


Fig. 2 – Process maps for England and Scotland. NHS, National Health Service.

The status of a listing decision varies by country. In Australia, the PBAC's primary role is to recommend which medicines should be subsidized. The Australian government determines the final listing decision, but can consider only medicines with a positive listing from the PBAC. In England, NHS England and commissioning groups must comply with positive recommendations by NICE and provide the medicines as advised by NICE within 3 months of the recommendation publication. Similarly, if the SMC provides a positive recommendation, Scottish NHS boards must provide the recommended medicine or an SMC-approved equivalent as soon as possible. In Canada, the recommendations issued by the CDR are not mandatory. The CDR was originally established to replace the independent review processes of 18 provincial, federal, and territorial drug plans, but the final reimbursement decision remains the responsibility of the 18 individual drug plans. These drug plans are also responsible for negotiating a price directly with the manufacturer. Therefore, the CDR does not negotiate prices with the manufacturer, but may issue a recommendation "do not list at the submitted price" to indicate when a lower price may have resulted in a positive recommendation. In England and Scotland, the price negotiation effectively takes place at the national level, in that manufacturers can submit a proposal for a patient access scheme (PAS) to improve the cost-effectiveness of medicines and lead to a positive recommendation on the basis of the conditions of the PAS.

These agencies also have varying approaches for incorporating patient input, from accepting online comments from patients and citizens (PBAC) to sending e-alerts to patient input groups for comments (CDR), including patients and laypersons at meetings (NICE) and hosting regular Public Involvement Network Advisory Group meetings and establishing a patient and clinician engagement process (SMC).

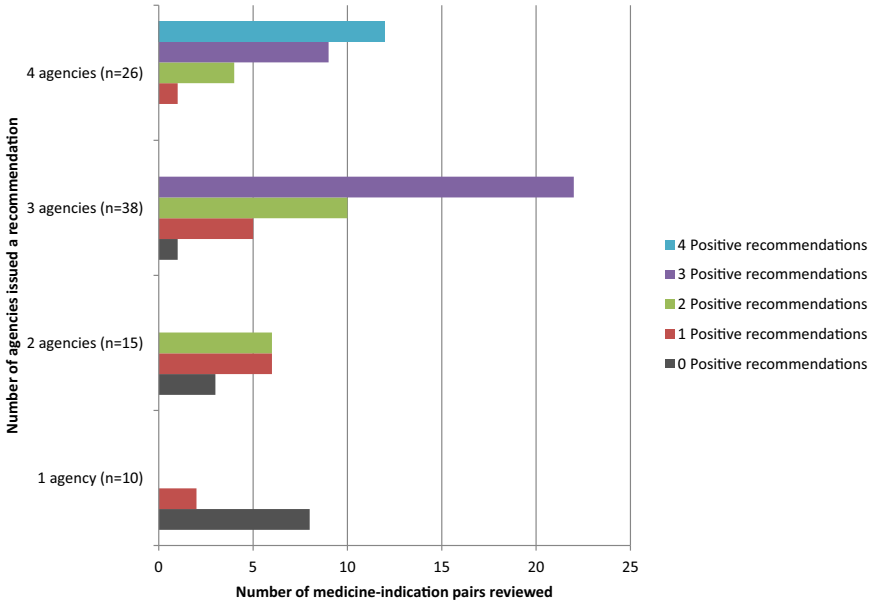
HTA Recommendations for New Medicine-Indication Combinations for Australia, Canada, England, and Scotland

Eighty-nine submissions for medicine-indication pairs met the inclusion criteria for an initial submission to CDR between January 2009 and May 2013. The most common therapeutic areas were the central nervous system (n = 19), followed by the cardiovascular system (n = 12) and the endocrine system (n = 11).

The latest HTA recommendations were classified as positive or negative and compared between each of the four HTA agencies. The percentage agreement was calculated for each agency pair and ranged from 48% (95% CI 0.32–0.65) for CDR and NICE to 87% (95% CI 0.71–0.95) for NICE and SMC. The second highest percentage agreement was 86% (95% CI 0.75–0.93) for PBAC and SMC, followed by 85% (95% CI 0.68–0.94) for NICE and PBAC. The percentage agreement calculated between the CDR and the PBAC was the second lowest at 62% (95% CI 0.50–0.73) and that between the CDR and the SMC was 64% (95% CI 0.52–0.74).

NICE issued the greatest proportion of positive recommendations (97%) and the lowest number of total recommendations (n = 31), because NICE does not review all new medicines and indications. The PBAC issued the second highest proportion of positive recommendations (89%) and reviewed 66 of the medicine-indication pairs. The SMC reviewed the second largest number of medicine-indication pairs (72) and issued the third highest proportion of positive recommendations (86%). The CDR issued the greatest number of negative recommendations (51%). It should, however, be recognized that the CDR provides a non-mandatory recommendation to guide regional decision makers and does not negotiate on price. Therefore, the negative HTA recommendations issued by the CDR include a recommendation not to reimburse at the submitted price, to indicate when a lower price could be negotiated to support a positive recommendation.

Of the 89 medicine-indication pairs evaluated in this study, only 26 were reviewed by all 4 HTA agencies (Fig. 3). Twelve of these medicines were granted a positive recommendation from all the agencies and no medicines received a negative recommendation from all the agencies. Interestingly, the proportion of negative reimbursement recommendations decreased as the number of agencies that received a submission increased (Fig. 4). This could be due to manufacturers being discouraged from seeking reimbursement for medicines that have already



0 positive recommendations represents the proportion of medicines that received all negative recommendations

Fig. 3 – Positive HTA recommendations for medicine-indication pairs. HTA, health technology assessment.*0 positive recommendations represent the proportion of medicines that received all negative recommendations.

received negative reimbursement recommendations. This may suggest that fewer markets will receive a submission for reimbursement as the number of negative HTA recommendations increases. Fewer submissions reduce potential opportunities for positive reimbursement recommendations and subsequently result in reduced access to these medicines. It could be argued that this may prevent the funding of low-value drugs, or prevent patients from receiving medications that may not allow them to achieve their desired outcome. If a manufacturer also anticipates that a medicine is unlikely to be reimbursed by HTA agencies with similar criteria, then the decision to not submit saves time as well as resources for both the manufacturer and the HTA agencies. The group of medicines initially reviewed by all four HTA agencies was evaluated to select medicine-indication pairs for case studies.

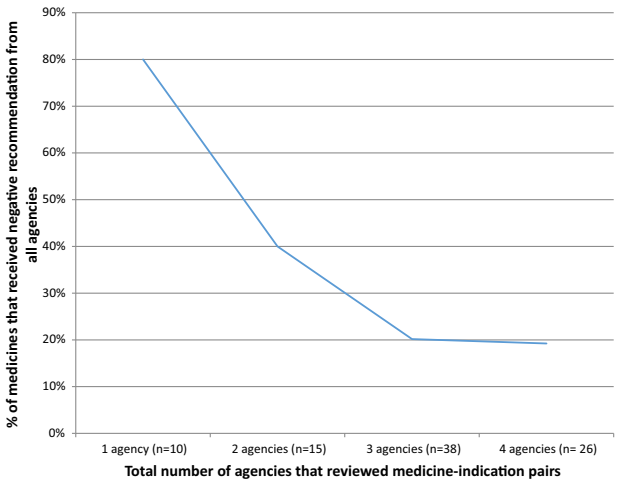


Fig. 4 – Proportion of medicines that received negative recommendations. Negative reimbursement recommendations were compared for 89 medicine-indication pairs that received a reimbursement recommendation issued by the CDR for an initial CDR submission from January 2009 to May 2013. The latest negative reimbursement recommendations for these medicine-indication pairs are compared from the following four agencies: CDR in Canada, NICE in England, PBAC of the Pharmaceutical Benefits Scheme in Australia, and SMC in Scotland. CDR, Common Drug Review; NICE, National Institute for Care and Health Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium.

Evaluation of Factors Influencing Discordant HTA Recommendations for Australia, Canada, England, and Scotland

The seven medicines that received a negative recommendation from one HTA agency are described in detail with their market access timelines shown in Figures 5 and 6. In the case study for ranibizumab, two indications were reviewed, despite only one of these meeting the inclusion criteria, because both indications were reviewed in the same submission on most occasions. Each case study is accompanied by a timeline that outlines the sequence of regulatory approvals and HTA recommendations.

Case study 1: Dabigatran for prevention of venous thromboembolism

Dabigatran was first granted marketing authorization by the EMA (March 2008) for the prevention of venous thromboembolism and was positively approved by the SMC and NICE within 6 months. The PBAC was the third HTA agency to issue a positive recommendation in November 2009. The CDR was the only HTA agency to issue a negative recommendation (January 2009) because noninferiority was not demonstrated to enoxaparin in the only trial that used the dose approved by Health Canada. The use of

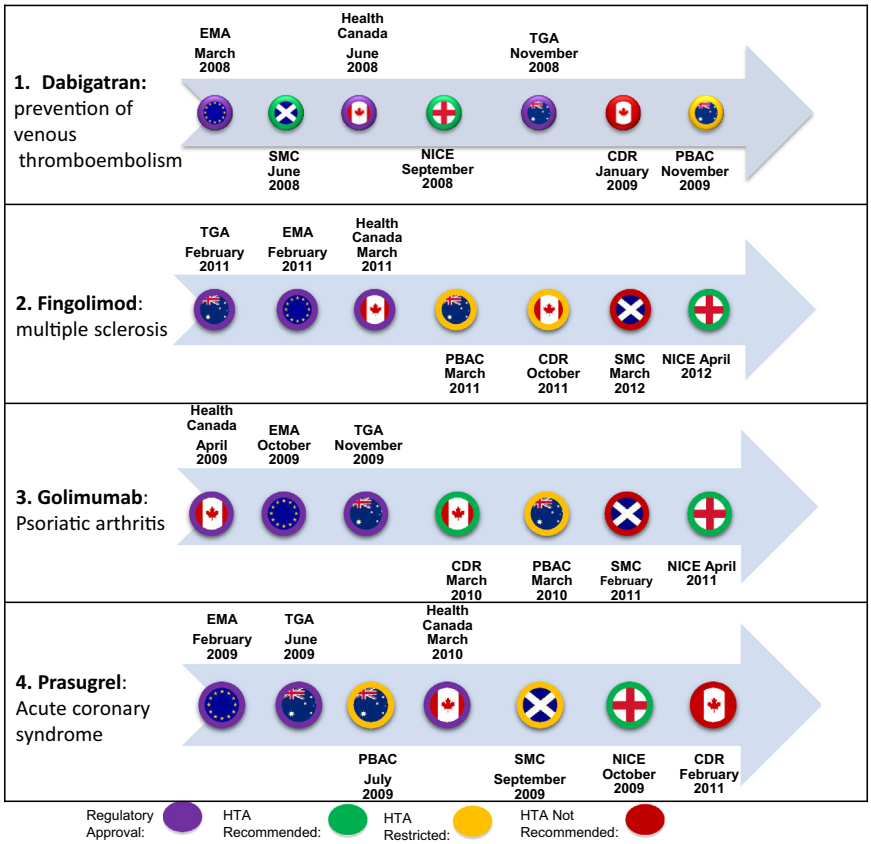


Fig. 5 – Market access timelines for case studies 1–4. CDR, Common Drug Review; EMA, European Medicines Agency; HTA, health technology assessment; NICE, National Institute for Care and Health Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium; TGA, Therapeutic Goods Administration.

dabigatran in this study was also associated with a statistically significant increase in a composite of deep vein thrombosis, nonfatal pulmonary embolism, and all-cause death. The CDR noted that there were some potential cost savings associated with dabigatran use versus enoxaparin use, but did not consider these to be sufficient to offset the increase in venous thromboembolism demonstrated in the trial.

The SMC, NICE, and PBAC all included enoxaparin as a comparator, and the SMC agreed that dabigatran was noninferior to enoxaparin and NICE determined that dabigatran was likely to have an equivalent clinical efficacy and cost-effectiveness. The SMC, NICE, and PBAC all noted cost-saving benefits of orally administering dabigatran compared with subcutaneous comparators as part of their recommendation rationale. For this case study, the CDR was the only agency to issue a negative recommendation despite other HTA agencies also expressing concerns over evidence supporting noninferiority with comparator. The CDR was also the only HTA agency that did not explicitly refer to the cost-saving benefits of dabigatran's oral route of administration.

Case study 2: Fingolimod for multiple sclerosis

Fingolimod was the first oral medicine available for the treatment of active, relapsing multiple sclerosis and was granted marketing authorization by the TGA in Australia, the EMA in Europe, and Health Canada within a 2-month period in 2011. All four HTA agencies reviewed fingolimod and concluded that it produced a significant reduction in annualized relapse rates and generally accepted that efficacy was comparable with IFN-β-1a, which was the main comparator included in all submissions. The submission to the PBAC also nominated IFN-β-1b and natalizumab as secondary comparators, which the PBAC considered to be informative. Both NICE and SMC, however, noted concerns regarding the manufacturer's choice of IFN-β-1a as the only comparator, because the submissions should include comparators that reflect clinical practice. The marketing authorization from the EMA specifies that fingolimod is to be used by patients with high disease activity despite treatment with at least one disease-modifying therapy. Health Canada also specified that fingolimod is generally recommended for patients who have had an inadequate response or are intolerant to one or more therapies for multiple sclerosis, but the TGA-licensed indication was not restricted to patients who are intolerant or nonresponders to current therapies.

The SMC was the only HTA agency to issue a negative listing recommendation, which was due to uncertainties regarding comparator choice for the initial submission in March 2012. The resubmission contained an additional comparator (natalizumab) and fingolimod was subsequently recommended for "restricted use" by the SMC in September 2012. The need for additional comparators from the SMC could be due to the different label population. Fingolimod was issued a positive listing recommendation by all four HTA agencies within 14 months of the first regulatory approval, despite the initial negative recommendation from the SMC because of comparator choice. Fingolimod is an example of a high-cost medicine that achieved positive listing

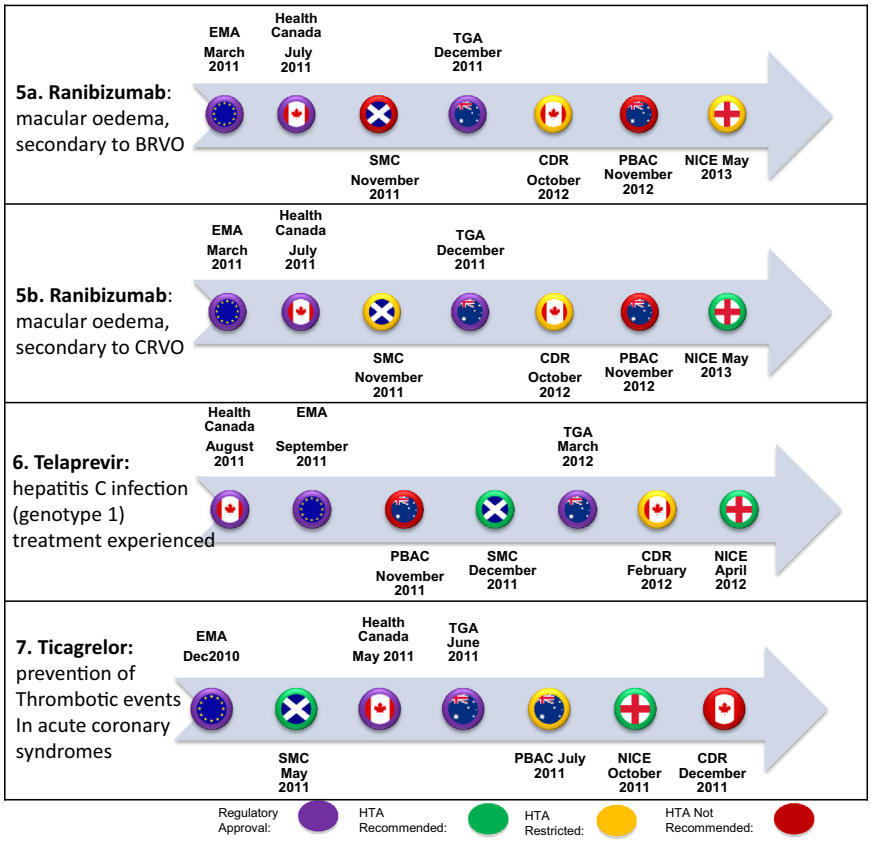


Fig. 6 – Market access timelines for case studies 5a–7. BRVO, branch retinal vein occlusion; CDR, Common Drug Review; CRVO, central retinal vein occlusion; EMA, European Medicines Agency; HTA, health technology assessment; NICE, National Institute for Care and Health Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium; TGA, Therapeutic Goods Administration.

recommendations from HTA agencies that consider cost-effectiveness and recognize innovative value.

Case study 3: Golimumab for psoriatic arthritis

Golimumab for the treatment of psoriatic arthritis received a reimbursement recommendation from all four agencies within 12 months of the first recommendation issued by the CDR (March 2010). All four HTA agencies noted a lack of trials with direct comparators, but accepted that golimumab was clinically superior to placebo (CDR, NICE, and SMC) and/or suggested similar efficacy to other tumor necrosis factor-alpha inhibitors (PBAC, NICE). All the four agencies accepted adalimumab and/or etanercept as comparators; in addition, the CDR, NICE, and SMC also included infliximab. Three agencies, the CDR, NICE, and PBAC, recommended golimumab for reimbursement and the SMC issued a negative recommendation because of an insufficiently robust economic analysis. Both the CDR and PBAC recommended golimumab on the basis of a cost-minimization approach and the SMC eventually granted a positive listing recommendation for golimumab after a resubmission including a cost-minimization analysis. Golimumab has also been reviewed for rheumatoid arthritis and for ankylosing spondylitis. Both submissions for new indications received positive initial recommendations from the SMC. These were, however, submitted after the initial golimumab submission for psoriatic arthritis, and it could be concluded that the manufacturer's experience detailed in this case study provided useful insights for future submissions.

Case study 4: Prasugrel for acute coronary syndrome

The first HTA recommendation for prasugrel was a restricted recommendation from the PBAC, followed by a restricted recommendation from the SMC and a "recommended" recommendation from NICE. The CDR issued the last HTA recommendation for prasugrel in February 2011, which was a negative "do not list" recommendation because of uncertainty over the applicability of the trial design to Canadian clinical practice for timing of administration of the comparator (clopidogrel). Concerns were also raised over safety because of trial results indicating a statistically significant increase in major bleeding events for prasugrel over clopidogrel. In June 2012, the CDR issued another "do not list" recommendation in response to the manufacturer's resubmission, which included a lower price. The comparator (clopidogrel), however, had since become available as a generic. The resubmission was based on a lower price but no new randomized controlled trials met the CDR requirements for the CDR systematic review, and the manufacturer's economic evaluation was limited because of CDR concerns over generalizability to the Canadian population. Nevertheless, the resubmission recommendation also stated that a positive listing could be achieved at a lower price for prasugrel. This case study provides an example of discordant HTA recommendations as a result of differing HTA agency mandates with regard to the ability to negotiate price.

Case study 5 (5a and 5b): Ranibizumab for macular edema

Case study 5 has been split into two parts because NICE and SMC issued different HTA recommendations for the two subpopulations

included in the licensed indication: macular edema secondary to branch retinal vein occlusion (BRVO) and macular edema secondary to central retinal vein occlusion (CRVO). All the four HTA agencies accepted laser photocoagulation as the comparator for macular edema secondary to BRVO. Macular edema secondary to CRVO, however, does not respond to laser photocoagulation and the CDR, PBAC, and SMC accepted "observation" as the main comparator and NICE accepted "best supportive care." Ranibizumab received positive recommendations from the CDR, SMC, and NICE for both BRVO and CRVO indications. The SMC recommendation for ranibizumab for the treatment of CRVO was, however, initially negative, but a resubmission with a PAS has since resulted in a positive recommendation. All three of these HTA agencies issued more restrictive recommendations for ranibizumab to treat BRVO, because this indication, unlike CRVO, has other potential treatment options and patients can spontaneously improve.

The submission to the PBAC was deferred because of ongoing concerns for comparator choice. Both the PBAC and NICE considered bevacizumab to be an appropriate comparator choice, despite no marketing authorization to treat CRVO and no intravitreal formulation available. Nevertheless, the PBAC does not consider reference to TGA-approved indications to be grounds for excluding a comparator when there are existing pharmaceutical analogues listed, and NICE also allows unlicensed medicines to be considered if they are part of established clinical practice. The PBAC's recommendation to reimburse ranibizumab for macular edema notes that it is likely that ranibizumab will replace a proportion of off-label bevacizumab use, and NICE recommended ranibizumab as a treatment option only if the manufacturer provides the discount agreed in a PAS. This case study highlights how varying agency approaches for the inclusion of an off-label comparator can result in different reimbursement recommendations.

Case study 6: Telaprevir for hepatitis C infection (genotype 1), chronic (treatment-experienced)

Telaprevir is licensed for the treatment of hepatitis C infection (genotype 1) with compensated liver disease. This case study focuses on the treatment-experienced population because this was the indication originally included in the submission to the PBAC in November 2011. The PBAC, however, rejected the original submission because information from the TGA was not available at the time of the review because the TGA did not approve market authorization until March 2012. The manufacturer's resubmission to the PBAC in July 2012 also included a request to review telaprevir for treatment-naive patients and the PBAC approved both indications for "authority-required" listing to be available only in specialized treatment centers.

The SMC was the second HTA agency to review telaprevir for patients with chronic hepatitis C and published two separate recommendations for treatment-naive and treatment-experienced patients in December 2011. Both indications were determined to have a statistically significant clinical benefit and cost-effectiveness compared with peginterferon-alpha and ribavirin. Nevertheless, the incremental cost-effectiveness ratio for telaprevir/peginterferon-alpha and ribavirin for treatment-experienced patients who were null responders was calculated to be as high as £73,600 per quality-adjusted life-year, but this was sensitive to many variables (e.g., age) and cost-effectiveness was accepted. Overall, telaprevir for hepatitis C infection in treatment-experienced patients achieved positive recommendations from all the four HTA agencies. The initial negative recommendation from the PBAC was due to the timing of the submission because the TGA final product information was not available at the time of the meeting. Australia has offered a parallel review process since 2011 that allows manufacturers to submit to the PBAC and the TGA at the same time. Manufacturers are, however, advised to wait until the fifth month of the TGA registration process because the PBAC review process is shorter and a medicine cannot be listed in the Pharmaceutical Benefits Scheme before its listing in the Australian Register of Therapeutic Goods. The process in Australia is different from those in the other countries included in this study because the CDR will accept submissions only up to 90 days before an expected notice of compliance and the SMC will accept submissions after a positive opinion from the EMA Committee for Medicinal Products for Human Use or approval from the Medicine and Healthcare products Regulatory Agency, but will not usually start a review until marketing authorization is granted.

Case study 7: Ticagrelor for acute coronary syndrome

Ticagrelor received the first positive HTA recommendation from the SMC in May 2011. In July 2011, the PBAC issued an "authority-required" recommendation and a "recommended" recommendation from NICE in October 2011. All three HTA reviews accepted ticagrelor as clinically superior to clopidogrel, but uncertainties were raised over comparative safety (PBAC). NICE decided that the potential benefits of ticagrelor outweighed the risks, and the SMC found that the increase in adverse events was not significant. The PBAC, NICE, and SMC reviews all accepted the increased cost per ICER for clopidogrel to be lower than the implicit or explicit thresholds. The CDR issued a "do not list" recommendation because a regional analysis did not provide evidence that ticagrelor would provide significant benefits over clopidogrel for the North American population, and the CDR could therefore not justify the increased cost of ticagrelor. Nevertheless, as with prasugrel, the CDR recommendation summary also stated that a positive recommendation would be more likely if the price was reduced. Once again, this is a divergent recommendation issued by the CDR, because price negotiation is not part of the CDR's remit.

Discussion

This study describes a comparison of HTA in Canada, Australia, England, and Scotland. These four jurisdictions were selected because of transparency and availability of data, including online summaries with rationale for reimbursement recommendations. The comparison of the full HTA recommendations data set provides a useful overview of recommendations for noncancer medicines issued over a period of more than 3 years.

Australia, Canada, England, and Scotland all provide universal health care funded by taxation and share a long history of HTA. At present, all four countries have a national HTA agency and reimbursement recommendations that are guided by both clinical efficacy and cost-effectiveness and have a framework that includes patient input. These agencies share common factors, such as considering clinical efficacy and cost-effectiveness of new medicines, and have an implicit or explicit quality-adjusted life-year threshold. Their activities, however, vary because of different mandates as well as unique political, social, and population needs. The divergent case studies presented in this research demonstrate examples of the rejection of new medicines because of uncertainties surrounding a range of factors including cost-effectiveness, comparator choice, clinical benefit, safety, trial design, and submission timing. In two of the case studies with divergent recommendations (case studies 1 and 5a and 5b), the rationale for the negative recommendation was also considered by the other three agencies, yet they issued a positive recommendation. Therefore, the differences in recommendations could be considered because of the agencies' approaches to risk perception. When one or more of these agencies issue a negative recommendation, it is possible that the manufacturer may decide

against further submissions to those agencies that consider similar factors. Case study 6 provides an example of a negative recommendation due to poor submission timing because the PBAC required a resubmission to allow consideration of final product information from the TGA. This example was a result of the PBAC's parallel submission process that enables manufacturers to submit to the PBAC at the same time as the TGA. Nevertheless, parallel review processes can provide benefits by speeding up the review process and patient access to medicines. In Canada, the introduction of a parallel review process cleared the backlog of CDR applications and removed the requirement for a separate priority review process [20].

The HTA recommendations for the 89 medicine-indication pairs have identified substantial variation between the first recommendations issued by the CDR, PBAC, NICE, and SMC because, unlike studies by Clement et al. [21] and Nicod and Kanavos [22], this investigation initially excluded resubmissions providing insights into how successful the initial submissions are for these four established and transparent HTA agencies. Nevertheless, the resubmissions were included to calculate percentage agreement across agencies because the latest recommendations are more relevant with regard to patient access. The case studies also include resubmission recommendations, because this can help identify the impact of the updates for the resubmissions. These case studies included trials that did not appropriately follow clinical practice for the country of submission (case study 4) or which had uncertainties surrounding comparator choice (case studies 2 and 5a and 5b). These findings support those by Spinner et al. [23] and demonstrate that factors such as comparator choice and varying clinical evidence influence an agency's decision, although this research did not focus on clinical evidence, but has identified other factors for divergent decisions. This includes an agency's ability to negotiate price or product listing agreements (case studies 4 and 7), which adds further evidence to the existing body of knowledge for understanding the impact of changes to health care systems, which is also supported by the findings of Clement et al. [21] and Nicod and Kanavos [22].

This study used information collected from the public domain to compare HTA recommendations and identify the rationale behind the decisions in the seven case studies. This is a limitation that could be overcome for future studies by working directly with HTA agencies, which might provide further insights. This study also builds on previous research that focused on the CDR, which resulted in the inclusion criteria being limited to only CDR-reviewed products [17]. This resulted in the exclusion of oncology products because these are reviewed by the pan-Canadian Oncology Drug Review, which was transferred to the CADTH in April 2014 to explore the potential for alignment with CADTH's CDR program [24]. Future research would benefit from the inclusion of oncology products to evaluate the rationale behind discordant recommendations as the systems to assess oncology products continue to evolve. This will be particularly useful for research focusing on the United Kingdom because the NICE board has approved a new technology appraisal process for the new Cancer Drugs Fund operating from April 2016. NICE will now appraise all new cancer medicines and will hold the initial appraisal committee meeting before the opinion of the Committee for Medicinal Products for Human Use is published to enable publication of NICE guidance within 90 days of marketing authorization [25]. Future studies could also investigate the hypothetical possibility that greater agreement may exist between HTA agencies if the medicine evaluated is from a class that already has previous approval and for which guidelines indicate that a full cost-effectiveness analysis is unlikely to be required. For example, the PBAC uses overt cost minimization in such circumstances.

The discordant recommendations are a result of varying factors including variations in the HTA agencies' practices. Unlike regulatory authorities, the HTA environment is still very fragmented and it is arguably more difficult to align. For example, Drummond [26] argues that to create a pan-European HTA agency there are three critical areas that require harmonization: economic evaluation guidelines, decision-making processes, and societal willingness to pay. There are, however, initiatives underway to help gain greater alignment among certain aspects of the HTA process between HTA agencies and also with regulators. The European Union supports cooperation on HTA through support of the joint action projects of the European network for Health Technology Assessment, which developed tools and supported cross-border collaboration, and by establishing a permanent HTA network in Europe. European HTA agencies have also been working with the EMA to pilot joint parallel scientific advice because evidence needs of multiple stakeholders can often be addressed in a single trial design or development program. The recently published EMA report on this pilot program indicates positive results and provides recommendations for a final sustainable model of parallel regulatory HTA advice [27]. On a global level, the Sixty-Seventh World Health Assembly resolution urges member states to strengthen the link between HTA, regulation, and management [28].

Conclusions

This study illustrates how multiple factors can impact HTA decision making and result in discordant recommendations. This emphasizes the challenging environment in which manufacturers need to navigate, and the results of this study have also shown that as the proportion of negative recommendations increases for a new medicine, the number of markets that receive a dossier decreases. As HTA agencies continue to evolve their processes, the proportion and rationale for discordant recommendations may also change.

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