VALUE IN HEALTH 18 (2015) 663–672

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Can a Joint Assessment Provide Relevant Information for National/Local Relative Effectiveness Assessments? An In-Depth Comparison of Pazopanib Assessments

Sarah Kleijnen, MSc[1,2,], Mohammed Fathallah, MSc[3], Michiel W. van der Linden, MD, PhD[1], Piet Vancraeynest, MD, MScBiostat[4], Bachir Dahmani, PhD[5], Angela Timoney, MSc, MPH[6], Anthonius De Boer, MD, PhD[2], Hubertus G. Leufkens, PharmD, PhD[2], Wim G. Goettsch, PhD[1,2]*

[1]*National Health Care Institute, Diemen, Netherlands;* [2]*Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands;* [3]*University of Utrecht, Utrecht, Netherlands;* [4]*National Institute for Health and Disability Insurance, Brussels, Belgium;* [5]*National Authority for Health, Paris, France;* [6]*Scottish Medicines Consortium and Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom*

ABSTRACT

Background: In many European jurisdictions, relative effectiveness assessments (REAs) of pharmaceuticals are performed during the reimbursement decision-making process. International collaboration in the production of these assessments may prevent the duplication of information in various jurisdictions. A first pilot of a joint REA (pazopanib for the treatment of renal cell carcinoma) was published in 2011. **Objective:** The objective was to investigate how well the methods used in the joint REA match the methods used in the national/local assessments on the same topic. **Methods:** National/local assessments from European jurisdictions, available in English language, were identified through a literature search and an e-mail request to health technology assessment organizations. Data were abstracted from joint and national/local assessments using a structured data abstraction form. Results were compared for differences and similarities. **Results:** In total, five national/local reports were included (Belgium, England/Wales, France, The Netherlands, and Scotland). The general methods (indication, main comparator, main end points, main trial) were similar. The details of the assessment (e.g., exact wording of indication, additional comparators, additional trials included, and method of indirect comparison), however, varied. Despite these differences, the joint REA included nearly all comparators, end points, trials, and methods of analysis that were used in national/local REA reports. **Conclusions:** This study has shown overlap in the methods national/local REA bodies in Europe have chosen for a pazopanib REA for renal cell carcinoma, except for the use and methods of indirect comparisons. Although some additional comparators and outcomes differed between national/local REAs, they can be captured in a comprehensive joint REA.

Keywords: comparative effectiveness, health technology assessment, pharmaceuticals, reimbursement.

Introduction

Because of continuous rising costs in health care and budget restraints, third-party payers often require that new, mostly expensive pharmaceuticals have a substantial added value compared with treatments that are already available [1,2]. One of the most common claimed values is an added clinical benefit and/or better safety profile. Comparing the clinical benefits and harms of a (new) technology with one or more (older) technologies used for the same condition is commonly referred to as *comparative effectiveness* in the United Stated, or *relative effectiveness* in Europe. In many European jurisdictions, relative effectiveness assessments (REAs) of pharmaceuticals are performed as part of the reimbursement decision-making process [3]. These REAs need to be performed in a limited time frame (rapid assessment) to achieve fast access for patients to new pharmaceuticals as was laid out in the Transparency Directive (Directive 89/105/EEC) [4]. An REA is a specific element of health technology assessment (HTA) that focuses on the clinical benefit of the intervention, whereas HTA is broader and can also include other aspects, such as ethical, organizational, and cost-effectiveness considerations [3].

In Europe, there is general consensus that the decision-making process on reimbursement decisions should be undertaken within national and local contexts in member states, also referred to as the subsidiarity principle. This does not preclude, however, collaboration on assessments because a clear separation of assessment and decision (or recommendation) is one of the key principles of conducting an HTA. It may very well be possible for the various parties to share a common assessment

* Address correspondence to: Sarah Kleijnen, Postbus 320, 1110 AH, Diemen, The Netherlands.
E-mail: skleijnen@zinl.nl.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2015.03.1790

using state-of-the-art methods, but to weight elements differently and thus arrive at different reimbursement decisions [5]. Increased sharing of information (e.g., methods, data requirements, and results) across jurisdictions may increase the quality and consistency of REAs in Europe. In addition, it may prevent the duplication of information in various jurisdictions and save resources accordingly [3,6].

In a multiple-country comparison, Kleijnen et al. [3] concluded that there are more similarities than differences in the methodology used for REAs in European jurisdictions, indicating that a standardized, joint production of REAs may be possible.

Workpackage 5 of Joints Action 1 (WP5JA1) of the European network for Health Technology Assessment published a first pilot joint REA in 2012 [7]. WP5JA1 was a 3-year collaboration between more than 30 European HTA organizations that was cofunded by the European Union and had the aim to develop methods for collaboration in the field of REA and to test these methods [8,9]. The topic of the first joint REA was "pazopanib for the treatment of advanced or metastatic renal cell carcinoma." The assessment was coproduced by 22 HTA organizations and tested the methods developed by the WP5JA1 as well as cross-border collaboration. Details of the production and evaluation of the assessment are described elsewhere [10].

Pazopanib, an antineoplastic agent that inhibits multiple receptor tyrosine kinases, received conditional marketing authorization in 2011 from the European Medicines Agency [11]. The approved therapeutic indication was for first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received cytokine therapy for advanced disease previously. It was concluded that there was a need to gain more understanding about the benefit/risk balance of pazopanib compared with other available medicinal products for the same indication. As a result, pazopanib received the conditional status, with the obligation to perform a postmarketing phase III study comparing pazopanib with sunitinib. After analysis of the results of the postmarketing phase III study, the conditional marketing authorization was switched to a full marketing authorization on July 1, 2013, without changing the wording of the approved indication [12].

Various national/local HTA reports have been produced on pazopanib for this indication. A comparison between the joint REA and national/local reports on the same subject could serve as a first indicator whether a joint REA can be informative for national/local assessments. The objective of this study was to investigate how well the methods used in the joint REA match the methods used in the national/local assessments.

Methods

Study Design and Selection of HTA Reports

A qualitative in-depth analysis was performed in which we compared HTA reports on pazopanib for the treatment of RCC. National/local reports were searched in the CRD database and PubMed and Web sites of HTA organizations. In addition, a query was sent to HTA organizations that were members of the European network for Health Technology Assessment WP5JA1 asking whether their agency has produced an English report on pazopanib. In case, a report only in the native language was available, the HTA organization was asked to translate the report into English for inclusion in this study. Inclusion was limited to full English HTA reports of pazopanib that were used for reimbursement decision making and published before March 2012. The joint REA was publicly available after February 2012. Therefore, national/local reports for which the recommendations were published after February 2012 were excluded because reports that were published after this date could potentially be influenced by the joint REA.

Data Abstraction

The data were abstracted from the joint and national/local assessment reports with a structured data abstraction form that contained 29 open questions. The questions are presented in Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.03.1790. The data were abstracted by one researcher and double-checked by a second researcher. For national/local reports, the abstracted data were sent to the respective organizations by e-mail asking them to 1) validate the abstracted data and 2) supplement the missing data that we were not able to find in the reports. After data abstraction was complete, results were processed as qualitative information and combined draft results were sent once more to the organizations for validation. Input received as a result of the two rounds of validation was processed accordingly.

Analysis and Synthesis of Data

A selection of the gathered information is presented in this article, with a focus on meta-data about the assessment and the methods that were used. Data gathered on, for example, the detailed process are not presented. The data that were selected for this article were grouped into 1) general information about the reports; 2) criteria included in the assessments; 3) methods used for the assessment (including the scope, the evidence included, and methods for assessing the evidence); and 4) outcome of the assessments and arguments used in the recommendations. The data were analyzed qualitatively and presented in tables. For the comparison of the methods, the analysis was a multistep process. First, the information included in the national/local reports was compared, which resulted in a set of common elements and a set of information that was not included in all national/local reports but in at least one of them, noncommon elements. Second, these information sets were compared with the information in the joint REA to identify whether the methods used were similar.

Direct comparisons were defined as randomized controlled studies (in this case placebo-controlled).

Indirect comparisons were defined as comparisons of at least two interventions for which no direct head-to-head evidence was available.

Results

General Information about the Reports

In total, HTA reports from five jurisdictions were included: Belgium, England/Wales, France, The Netherlands, and Scotland (see Fig. 1). One report was identified through the database search (England/Wales), one through searches on Web sites of the HTA organizations (Scotland), and three through the query that was sent to HTA organizations (Belgium, France, and The Netherlands). The reports from Belgium, France, and The Netherlands were translated by the respective organizations into English for inclusion in this study. In addition, the final version of the joint REA (version 4), which was published on the European network for Health Technology Assessment Web site, was included [7]. Further general information about the reports is presented in Table 1.

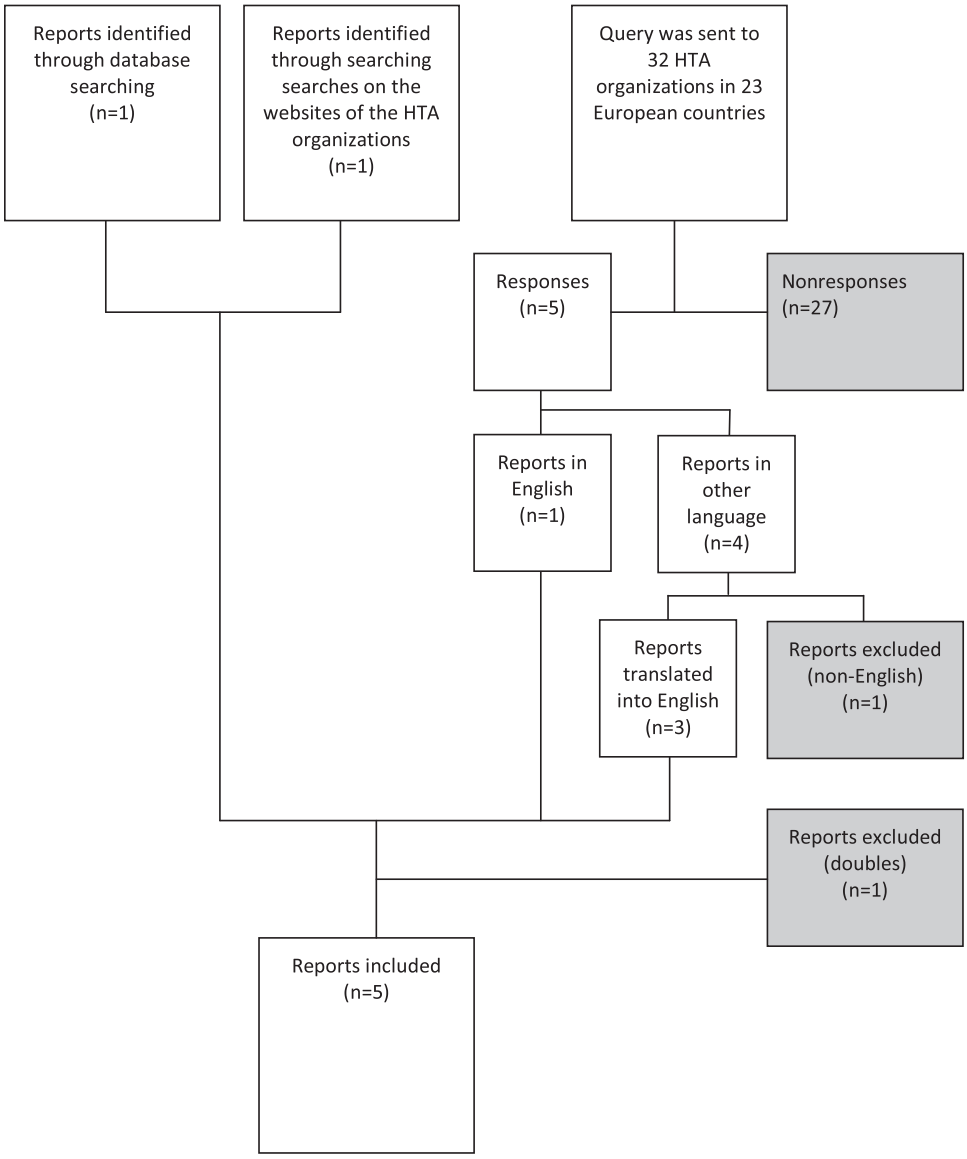

Fig. 1 – Flow chart of search for national/local pazopanib assessments. HTA, health technology assessment.

Criteria Included in the Assessments

The main results are summarized in Table 1. All assessment organizations included "efficacy/effectiveness" and "safety/harms/adverse events" in the REA. Also included in the REA in some jurisdictions were applicability (The Netherlands and Belgium), ease of use (The Netherlands and Belgium), experience (The Netherlands), and existence of therapeutic alternatives (France). In addition to relative effectiveness, some organizations included other criteria such as economic consideration (cost-effectiveness and budget impact) and/or patient or societal considerations (e.g., equity and equality). The joint REA included detailed information on organizational, social, ethical, and legal considerations.

In all jurisdictions, the criteria were not explicitly weighted to give a final recommendation. For the Dutch report, however, it was indicated that effectiveness and safety were usually more relevant for the outcome compared with the other criteria. For Belgium, it was indicated that efficacy, safety, and budget impact (and cost-effectiveness in case of claimed added value) take precedence over the other criteria.

Methods Used for the Assessment

Information included in all national/local reports, common elements, and information included in at least one of the national/local reports, noncommon elements, are presented in Table 2. In all reports, pazopanib was analyzed for first-line treatment of patients with advanced RCC. In Belgium, France, and The Netherlands, as well as in the joint REA, pazopanib was also analyzed for second-line treatment of patients with RCC who were already treated with cytokines. The indications were very similar with some variation in exact wording. For example, "metastatic" in addition to advanced was mentioned in the National Institute for Health and Care Excellence (NICE) report and the joint REA (see Table 2).

In all reports, sunitinib was chosen as a comparator for the first-line treatment and in case of second-line treatment sorafenib was always chosen as comparator. Other comparators included varied between jurisdictions for first- and second-line treatment.

In all assessments, progression-free survival (PFS) and overall survival (OS) were included as outcomes. Other outcomes that

Table 1 – General information on pazopanib reports, criteria included in the assessments, and outcome of the assessments.

Information element	BE	EN/WA	FR	NL	SC	Joint assessment
			General information about pazopanib reports			
Reference	[13]	[14][*]	[15][†]	[16]	[17]	[7]
Assessment organization	RIZIV	NICE	HAS	CVZ[‡]	SMC	WP5JA1
Date initiation assessment–Date final recommendation	Jun 2010–Oct 2010	Jul 2010–Feb 2011	Nov 2010–Feb 2011	July 2010–Jan 2011	Oct 2010–Feb 2011	May 2011–not applicable[§]
			Criteria included in the assessments			
Criteria evaluated as part of the REA	Efficacy, adverse events, applicability, ease of use	Efficacy, safety	Efficacy, adverse effects, therapeutic alternatives	Effectiveness, safety, experience, applicability, ease of use	Comparative efficacy, comparative safety, clinical effectiveness	Effectiveness and safety
Which other criteria have been evaluated?	Budget impact[‖]	Cost-effectiveness, acceptability, appropriateness and preference, feasibility and impact, equity and equality	No other criteria	No other criteria[‖]	Comparative health economic evidence	Organizational, ethical, social, and legal considerations
How were the criteria weighted?	No formal weighting was applied	No formal weighting was applied	Unknown	No formal weighting was applied	No formal weighting was applied	No formal weighting was applied
			Outcome of the assessment			
Final recommendation	Positive	Positive	Negative[¶]	Positive	Positive	Not applicable
Reimbursed/funded	Yes	Yes	Not in 2011[¶]	Yes	Yes	Not applicable

BE, Belgium; CVZ, College voor Zorgverzekeringen; EN/WA, England/Wales; EUnetHTA, European network for Health Technology Assessment; FR, France; HAS, Haute Autorité de Santé; NICE, National Institute for Health and Care Excellence; NL, The Netherlands; SC, Scotland; REA, relative effectiveness assessment; SMC, The Scottish Medicines Consortium; RIZIV, Rijksinstituut voor Ziekte-en Invaliditeitsverzekering; WP5JA1, Workpackage 5 of EUnetHTA Joint Action 1.

[*] A report of a reevaluation of pazopanib was published in EN/WA in November 2013.

[†] A report of a reevaluation of pazopanib was published in FR in June 2013.

[‡] The institution's name was changed to Zorginstituut Nederland (National Healthcare Institute) on April 1, 2015.

[§] A joint assessment does not include a recommendation (only a conclusion about the scientific evidence) because recommendations are considered a national/local competence in Europe. The joint report was published in December 2012.

[‖] In case the manufacturer would have claimed an added value, cost-effectiveness would also have been one of the criteria; however, no added value was claimed in BE and NL.

[¶] The reevaluation (June 2013) changed the recommendation into positive for first-line treatment of advanced renal cell carcinoma. For second-line treatment, the recommendation remained negative.

Table 2 – Methods: Common versus noncommon elements in jurisdiction-specific pazopanib assessments and comparison with joint assessment.

Information element	Common elements: Information included in all jurisdiction- specific assessments (BE, EN/WA, FR, NL, and SC)	Noncommon elements: Other information (not common) included in at least one jurisdiction- specific assessment	Elements included in joint assessment	Are common/noncommon elements included in the joint assessment?
Indication(s)	*First-line* Advanced RCC *Second-line*[*] Patients with advanced RCC who formerly have been treated with cytokines	Advanced and/or metastatic RCC (EN/WA)	Advanced and/or metastatic RCC Patients with advanced and/or metastatic RCC who formerly have been treated with cytokines	Common: Yes Noncommon: Yes Common: Yes Noncommon: Not applicable
Comparators	*First-line* Sun *Second-line*[*] Sor	Placebo (BE, FR), best supportive care (EN/WA, SC), IFN-α (BE, EN/WA, SC), Bev + IFN-α (BE) Sun (FR, NL)	Sun, IFN-α + Bev, IFN-α, best supportive care Sor, best supportive care	Common: Yes Noncommon: Yes Common: Yes Noncommon: No
Outcomes	PFS, OS, RR, QOL	TR/RT (BE, FR), DoR (BE, SC), AE (BE, EN/WA, SC), FAE (BE, EN/WA, NL), SerAE (FR), WDAE (FR), ORR (Nl), SevEA (NL)	OS, QOL, PFS, ORR, RR (CR&PR), TTP, RT, DoR, patient preference, AE, WDAE, SerAE, SevAE, and FAE	Common: Yes Noncommon: Yes
Direct and/or indirect comparison included	Direct	Indirect[†]: BE[‡], EN/WA, NL, SC	Direct and indirect	Common: Yes Noncommon: Yes
Type of analysis for indirect comparison		Bucher method (BE[‡], SC), naive indirect comparison (NL), not specified (EN/WA)	Bucher method	Common: Not applicable Noncommon: No, naive indirect comparison is not included
Studies included	VEG105192	RCT: Lorenzo Di et al. [18] (NL) Observational: VEG102616 (BE, EN/WA, FR, NL), VEG107769 (BE, EN/WA, NL, SC) Set of studies for indirect comparison: BE: not specified[‡]; EN/WA: 8 studies; NL: 10 studies; SC: not specified	RCT: VEG105192 Observational: VEG102616, VEG107769, Hurwitz 2009 [19] Set of studies for indirect comparison: 10 studies Other: Balagula 2011 [20][§]	Common: Yes Noncommon: No, Lorenzo Di et al. [18] (NL) was not included in the cross-border assessment. In addition, the set of studies for the indirect comparison was not identical to the jurisdiction-specific sets

continued on next page

Table 2 – *continued*

Information element	Common elements: Information included in all jurisdiction- specific assessments (BE, EN/WA, FR, NL, and SC)	Noncommon elements: Other information (not common) included in at least one jurisdiction- specific assessment	Elements included in joint assessment	Are common/noncommon elements included in the joint assessment?
PFS considered as an indicator for OS?	No		No	Common: Yes Noncommon: Not applicable
Internal validity of the studies assessed?	Yes		Yes	Common: Yes Noncommon: Not applicable
External validity addressed		Yes: EN/WA, FR, NL, SC No: BE[‖]	Yes	Common: Not applicable Noncommon: Yes

AE, adverse event; BE, Belgium; Bev, bevacizumab; CR, complete response; DoR, duration of reponse; EN/WA, England/Wales; FAE, frequent adverse event; FR, France; NL, The Netherlands; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QOL, quality of life; RCT, randomized controlled trial; RR, response rate; RT/TR, response time; SC, Scotland; SerAE, serious adverse event; SevAE, severe adverse event; Sor, sorafenib; Sun, sunitinib; TTP, time to progression; WDAE, withdrawal due to adverse events.

[*] Not applicable to EN/WA and SC because second-line treatment was not assessed for these jurisdictions.

[†] The applicant had included an indirect comparison; however, the analysis was not considered relevant in the assessment in FR.

[‡] The applicant had included an indirect comparison with sunitinib, sorafenib, IFN-α, and bevacizumab in the BE submission file. The results were presented in the BE assessment report with the explicit caveat that it should be very cautiously interpreted and that in essence this evidence was not considered for the conclusion.

[§] Systematic review and meta-analysis of the risk of hand foot skin reaction to pazopanib. Used as input for safety evaluation.

[‖] Although the external validity is not explicitly addressed in the assessment, it may be addressed by the reimbursement committee.

were reported in multiple assessments were quality of life (QOL), response rate, adverse events, and frequent adverse events. In the joint REA, OS, QOL, PFS, response rate, serious adverse events, and severe adverse events were included in the main report, whereas other outcomes were included in the appendix of the pilot assessment.

In none of the assessments PFS was considered an indicator for OS. England/Wales considered PFS a relevant independent outcome because it is considered a relevant outcome for patients. In the joint REA it was mentioned that "there are different opinions regarding the surrogacy of PFS for OS in RCC."

A submission file provided by the marketing authorization holder was used as a basic source for all assessments included. Because no template for a submission file was available yet at the time of the assessment, the submission file used for the joint REA was based on the submission file for NICE plus an addendum presenting the final OS data from the pivotal study together with associated analyses to adjust for the effects of crossover, which were not available yet at the time of the NICE submission.

The number of studies included in the assessments varied between 2 (France) and 14 (joint REA). The only direct comparison that was included in all assessments was the VEG105192 study. This study was a double-blind, placebo-controlled randomized controlled trial of pazopanib versus placebo. All assessments included observational studies.

All jurisdictions used a direct comparison, and all jurisdictions, except France, used an indirect comparison in their REA. For Belgium, however, the indirect comparison performed by the applicant was presented with the explicit caveat that it should be very cautiously interpreted and that in essence this evidence was not considered for the conclusion. The number of studies included in the indirect comparison varied. The Bucher method (adjusted indirect comparison in which the indirect comparison of A and B is adjusted according to the results of their direct comparisons with a common intervention) was used in at least two indirect comparisons.

All jurisdictions assessed the internal validity of the studies included in their assessment; however, only the Evidence Review Group report for England/Wales and the joint REA reported the assessment systematically. For the other assessments, the reports refer only to the most relevant shortcomings of the data.

In all reports, except in the Belgian report, the external validity of data was explicitly addressed to some extent. In general, this means that one or two sentences that refer to external validity of (some of) the studies were included. In the joint REA, external validity was assessed and reported systematically. The joint REA included all methodological elements that were identified as common elements across the national/local reports. Furthermore, the joint REA included almost all non-common methodological elements that were included in at least one of the national/local reports except for one comparator for second-line treatment (sunitinib) and one study (Lorenzo Di et al. [18]). In addition, the set of studies for the indirect comparison was not identical to the national/local-specific sets.

Outcome of the Assessments and Arguments Used in the Recommendations

Except for the French authority, all organizations recommended that pazopanib should be reimbursed/funded for the indications that had been assessed (first-line in Belgium, England/Wales, The Netherlands, and Scotland and second-line in Belgium and The Netherlands). In all jurisdictions, the reimbursement decisions corresponded with the recommendation. For France, a reevaluation was published in June 2013. It was recommended to include pazopanib on the reimbursement list for the first-line treatment of advanced RCC. Inclusion for the second-line treatment of advanced RCC was not recommended. The joint REA did not have a recommendation (only a conclusion about the scientific evidence). Recommendations are considered a national/local competence in Europe; therefore, a joint REA does not include one.

The length of the recommendation sections varies considerably between the different reports. Discussion items in multiple assessments were the (un)certainty of the evidence from the indirect comparison, unmet need for patients who cannot tolerate currently available treatments, the relevance of the OS data, the relevance of PFS, different toxicity profiles, and the need for head-to-head data. The most common argument used for a positive recommendation was that pazopanib is considered to be as effective as its comparators, and might have a different and/or more favorable toxicity profile than its comparators. The most relevant argument for the negative recommendation (France) was the uncertainty as to whether pazopanib is non-inferior to sunitinib and may therefore result in a loss of opportunity for the patient. It was indicated that results from the ongoing comparative trial (pazopanib vs. sunitinib) were necessary to address the current uncertainty around the comparative efficacy and safety of pazopanib and sunitinib.

Discussion

Some other studies have been published that compared HTA reports for a specific topic [21–24]; however, this is the first study to explore differences between national/local REA reports and a joint REA report. Moreover, this study adds to the existing evidence base by having a detailed look at the methods used in the REA reports.

Jurisdiction-Specific Reports versus the Joint REA

We conclude that for this topic the main methodological elements for the assessment (main comparators, end points, and studies) on which the recommendations seem to be based are similar between the jurisdictions except for the indirect comparison. Not all jurisdictions included an indirect comparison, the studies selected for the indirect comparison varied, and the method for indirect comparison varied. Furthermore, there were some differences in additional comparators (IFN-α, bevacizumab + IFN-α, best supportive care), additional outcomes (response rate, duration of reponse, response time), and the additional evidence included. In contrast to the main methodological elements, these additional methodological elements did not seem to have a relevant weight in the recommendation of the jurisdictions.

The joint REA covered most methodological elements included in the national/local reports, except for sunitinib as second-line treatment, which was included in the Dutch and French reports, and also different sets of studies have been used for the indirect comparisons. The latter can partly be explained by the fact that the indirect comparison in the joint REA included the highest number of comparators for first-line treatment, which results in a wider evidence base as input for the indirect comparison. We conclude that despite some variance in national/local reports, the joint REA could inform the national/local reports, due to the wide range of included comparators, the end points, studies, and the methods of analysis. To be useful in various national/local settings, it seems necessary to include both direct and indirect evidence (if available) because there is variance in the acceptance of indirect evidence. We also think that it is recommendable for a joint assessment to present a relatively high level of detail because it seems easier for national/local organizations to summarize on the basis of an extensive joint

assessment compared with having to add additional details. For example, all countries assessed the internal validity of the studies; however, the level of detail varied. Although the internal validity was reported systematically in only one of the national/local reports, it is strongly recommendable to report it systematically in the joint REA (as currently included). This will add to the credibility and transparency of the joint REA report, but also maintain efficiency by ensuring that national/local organizations do not have to add this level of detail themselves. Furthermore, it is relevant to present outcomes for which different jurisdictions may have different opinions regarding the relevance, in a neutrally and balanced way, leaving room for interpretation by individual countries. This was, for example, applicable to PFS. Some organizations considered the difference in terms of PFS versus placebo as a patient-relevant outcome, whereas other organizations indicated that a difference in terms of PFS is considered patient relevant (in absence of OS data) only in case of improved QOL. Finally, one of the comparators of the national/local report (sunitinib for second-line treatment) was not included in the joint REA. An extensive consultation of European countries about possible comparators in an early stage in the process can help to define the most appropriate comparators for a joint assessment. In addition, it would be helpful for the jurisdictions to include information in the joint REA report on why possible comparators were (not) selected. For example, sunitinib is not recommended as second-line treatment in European guidelines [25].

To further investigate to what extent the joint REA can serve as a basis for national/local assessments, it may be suggested to match the content of the single information elements. For example, is a similar level of detail presented about the pivotal phase three study (e.g., number of patients included, exclusion criteria, and information on comedication)?

Comparison of Our Findings with Published Literature

Others have raised questions about the extent to which HTA evidence requirements can be harmonized [21,24]. Trueman et al. [24] studied assessments of a medical device (drug-eluting stent) and concluded that the demand for evidence that is relevant to local practice means that the core data set is relatively small and that significant efforts are required to generate additional data to inform local coverage decisions. However, they also indicated that probably the effectiveness of medical devices is more susceptible than pharmaceuticals to differences in local practice patterns [24]. Our study confirms that pharmaceutical trials are considered more generalizable across settings, and as a result, there may be less need for reliance on local (registry) data. Our study results demonstrate that there is a set of methodological elements for pharmaceuticals that is sharable (see Table 2). In addition, the study confirms the findings of Kristensen and Gerhardus [21] that even when an assessment is built on similar evidence, the final recommendations can differ. The difference occurs because of different interpretation of the data. We were able to identify three key differences in the interpretation of the same evidence between jurisdictions: the relevance of PFS as a patient-relevant outcome, the uncertainty around the evidence (can pazopanib be considered noninferior compared with other treatments on the basis of available evidence?), and the relevance of the indirect comparison.

The results of the present study in general confirm the results of a previous study that we published on an investigation of 30 countries, including the countries of this case study, assessing similarities and differences in major methodological aspects of REA [4]. There were, however, some interesting differences between the current and previous findings on the selection of the comparator and the use of indirect comparisons. First, in the review by Kleijnen et al. [4], only Belgium indicated that besides other comparators, the pharmaceutical can be compared with "whatever is used in registration trials," which is placebo in this case. Other countries indicated in the survey to include only the best possible or best standard care as comparator. In our current case study, however, results relative to placebo were mentioned in all HTA reports included in this analysis. The results from this analysis indicate that although the main emphasis of the HTA reports is on comparative data, placebo-controlled data are also very relevant, especially in the absence of comparative data. However, it is not clear from the reports (except for England/Wales) whether the placebo arm is considered best possible/standard care because these patients often receive usual palliative care. Second, our previous study indicated that in Belgium, England/Wales, France, The Netherlands, and Scotland, indirect comparisons are included in the assessment if evidence from head-to-head trials is not available. This case study, however, illustrated that this is not always applicable. In this specific case, France did not include an indirect comparison and for Belgium it was indicated that the indirect comparison should be considered with a lot of caution. Although indirect comparisons have become more common in reimbursement applications for new pharmaceuticals, many HTA organizations struggle with the uncertainty surrounding these analyses.

The comparison of the two studies and the identified exemptions illustrate that for some areas general principles for assessments are challenging to define because the exact approach for the assessment depends on the topic under assessment. For example, the willingness to include indirect data may increase when there are multiple comparators leading to a "network" of evidence because it is not realistic to request comparative trials with multiple comparators. However, when there is only one clearly identified comparator, it becomes more realistic to demand direct comparative data. Despite many recent efforts to produce methodological guidelines on indirect comparisons [26,27], further development of uniform standards is relevant for international collaboration.

Comparison of REA Reports with Committee for Medicinal Products for Human Use Report

There has been a discussion to which extent the REA part of HTA reports directly after market authorization differs from the report produced as part of the marketing authorization process, which is the Committee for Medicinal Products for Human Use (CHMP) assessment report in Europe [1]. Some indicate that these differences may be minor and that the additional value of REA assessments is limited [1]. Others from HTA organizations, however, argue that REA reports substantially differ [28] because of different decision criteria for licensing decisions and reimbursement/funding decisions. Possible differences are that HTA assessors always prefer comparative data [28], place more emphasis on clinically relevant outcomes and health-related QOL outcomes [1], perception of what is considered clinically relevant, stronger emphasis by HTA assessors on external validity of data, and, finally, a higher level of acceptance, by at least some HTA assessors, of modeling and observational data [29]. When comparing the pazopanib REA reports with the CHMP risk/benefit assessment of pazopanib [30], some of these differences are confirmed. Most REA reports put more emphasis on indirect evidence and QOL data compared with the CHMP report. In addition, the CHMP considered the difference in terms of PFS versus placebo as clinically relevant, whereas, as discussed

above, opinions differed between the HTA organizations. In general, however, the REA reports did not address the external validity intensively. In addition, both the CHMP report and the REA reports identified the lack of direct comparative data as a relevant evidence gap. For most licensing assessments, placebo-controlled data are sufficient; however, for pazopanib, the CHMP indicated that direct comparative data are relevant to rule out that the use of the pharmaceutical would mean a loss of opportunity for the patients.

It is increasingly recognized that there is considerable scope for better, coordinated interactions between regulators and payers [29,31]. Although the end conclusion may differ, the examples above confirm the relevance of regulator-payer interaction because it is very likely that they face similar evidence dilemmas for the same compound. Further research to investigate the differences between regulatory assessments and REAs could facilitate the interaction.

Study Limitations

The research methods used in this study have some limitations. The data that were abstracted from national/local reports were validated and completed by representatives from assessment organizations, which may be prone to difference in interpretation by the individuals. To minimize the chance, we sent queries if difference in interpretation was suspected. In addition, five jurisdictions were included for this study and only one topic (pazopanib for RCC) was compared. The limited number of national/local REA reports that could be included in this analysis can be explained by the fact that 1) no REA report was produced by a specific jurisdiction (before March 2012); 2) the REA report is not publicly available; or 3) the report was not available in English and there was not enough time or resources to translate the report. To get a wider picture, it would be desirable to include more jurisdictions and multiple subjects. The extent to which these findings apply to different subjects and other jurisdictions is still uncertain.

The pazopanib pilot joint REA was coproduced by 22 HTA organizations, whereas more recent joint REA pilots have been produced according to a different collaboration model involving only a few authoring organizations (two or three) [32,33]. Despite this change in the organizational model, we think that the content of the pazopanib REA is similar to that of most recent joint REAs. For this reason we think that results from this comparison may also be indicative for the most recent joint assessments.

By excluding national/local reports that have been published after February 2012, we have prevented that national/local reports could be influenced by the joint REA. This may imply, however, that the joint REA could have been influenced by the already available national/local reports. For example, the submission file used for the joint REA was a submission file based on the NICE submission file. The joint REA was a collaboration of 22 countries, for which an independent assessment was done by all the authors. Moreover, there was no overlap between the main authors of the joint REA and the authors of the included national/local reports. Therefore, we think that this limitation does not have a substantial effect on the results of this study.

Conclusions

This study has shown overlap in the methods national/local REA bodies in Europe have chosen for a pazopanib REA for RCC, especially in the evidence that was considered relevant in the formulation of the recommendations (main comparators, outcomes, and studies). The most relevant difference seems to be the acceptance of and methods used for the indirect comparison. Because of the increasing relevance of indirect evidence for reimbursement decisions in absence of direct comparative data, further development of uniform standards for indirect comparisons will be relevant for harmonization of methods. Although inclusion of additional comparators and additional outcomes differed between national/local REAs, because of variance in health systems, they can be captured in a comprehensive joint REA.

Source of financial support: This work was produced by the European network for Health Technology Assessment Joint Action 1, which was cofunded by the European Union (grant no. 20092302) and the participating HTA organizations.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2015.03.1790 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Eichler HG, Bloechl-Daum B, Abadie E, et al. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 2010;9:277–91.
[2] Franken M, Nilsson F, Sandmann F, et al. Unravelling drug reimbursement outcomes: a comparative study of the role of pharmacoeconomic evidence in Dutch and Swedish reimbursement decision making. Pharmacoeconomics 2013;31:781–97.
[3] Kleijnen S, George E, Goulden S, et al. Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions. Value Health 2012;15:954–60.
[4] Kleijnen S, Goettsch W, d'Andon A, et al. EUnetHTA JA WP5: relative effectiveness assessment (REA) of pharmaceuticals. Background review. July 2011. Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Final%20version%20of%20Background%20Review%20on%20Relative%20Effectiveness%20Assessment%2Bappendix.pdf. [Accessed September 19, 2013].
[5] Drummond MF, Schwartz JS, Jönsson B, et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care 2008;24:244–58: discussion 362–8.
[6] Huić M, Nachtnebel A, Zechmeister I, et al. Collaboration in health technology assessment (EUnetHTA joint action, 2010–2012): four case studies. Int J Technol Assess Health Care 2013;29:323–30.
[7] EUnetHTA WP5. Pazopanib for the treatment of advanced renal cell carcinoma: pilot assessment using the draft HTA Core Model for Rapid Relative Effectiveness Assessment model. December 2012. Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/WP5%20JA1%20Pilot%20Pazopanib%20Report+Appendix.pdf. [Accessed September 19, 2013].
[8] Kleijnen S, Pasternack I, Casteele Van de M. Casteele Van de M, et al. Standardised reporting for rapid relative effectiveness assessments of pharmaceuticals. Int J Technol Assess Health Care 2014;30:488–96.
[9] Pavlovic M, Teljeur C, Wieseler B, et al. Endpoints for relative effectiveness assessment (REA) of pharmaceuticals. Int J Technol Assess Health Care 2014;30:508–13.
[10] Kleijnen S, Pasternack I, Peura P, et al. Piloting international production of rapid relative effectiveness assessments of pharmaceuticals. Int J Technol Assess Health Care 2014;30:521–9.
[11] Nieto M, Borregaard J, Ersbøll J, et al. The European Medicines Agency review of pazopanib for the treatment of advanced renal cell carcinoma: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. Clin Cancer Res 2011;17:6608–14.
[12] European Medicines Agency. European Public Assessment Report, summary for the public. Votrient, pazopanib. EMA/445271/2012, EMEA/H/C/001141. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001141/WC500094273.pdf. [Accessed March 3, 2014].
[13] RIZIV—Rijksinstituut voor Ziekte—en Invaliditeitsverzekering. Dienst voor Geneeskundige Verzorging. Commissie Tegemoetkoming

Geneesmiddelen. Dossier 3570: VOTRIENT. Evaluatierapport Dag 60 van 13-09-2010 (Koninklijk besluit van 21 December 2001).
[14] National Institute for Health and Clinical Excellence. Pazopanib for the first-line treatment of advanced renal cell carcinoma. February 2011. Available from: http://www.nice.org.uk/guidance/ta215/chapter/1-guidance. [Accessed September 19, 2013].
[15] Haute Autorité de Santé. TRANSPARENCY COMMITTEE OPINION: re-examination of the proprietary medicinal products: VOTRIENT 200 mg, film-coated tablets B/30 (CIP: 491 313 4), VOTRIENT 400 mg, film-coated tablets B/30 (CIP: 491 315 7), VOTRIENT 400 mg, film-coated tablets B/60 (CIP: 491 316 3). February 2011. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-06/votrient_ct_8713.pdf. [Accessed September 19, 2013].
[16] College voor Zorgverzekeringen. Pharmacotherapeutic Report of Pazopanib (Votrient®) for the Indication 'Locoregionally Advanced and/or Metastatic Renal Cell Carcinoma'. Diemen, The Netherlands, January 2011.
[17] The Scottish Medicines Consortium. Pazopanib 200mg, 400mg film-coated tablets (Votrient®) SMC No. (676/11). February 2011. Available from: http://www.scottishmedicines.org.uk/files/advice/pazopanib_Votrient_FINAL_February_2011.doc_for_website.pdf. [Accessed September 19, 2013].
[18] Lorenzo Di G, Cartenì G, Autorino R, et al. Phase II study of sorafenib in patients with sunitinibrefractory metastatic renal cell cancer. J Clin Oncol 2009;27:4469–74.
[19] Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res 2009;15(12):4220–7.
[20] Balagula Y, Wu S, Su X, et al. The risk of hand foot skin reaction to pazopanib, a novel multikinase inhibitor: a systematic review of literature and meta-analysis. Invest New Drugs 2012;30(4):1773–81.
[21] Kristensen FB, Gerhardus A. Health technology assessments: what do differing conclusions tell us? BMJ 2010;341:c5236.
[22] Spinner DS, Birt J, Walter JW, et al. Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in-depth case series across three jurisdictions. Clinicoecon Outcomes Res 2013;5:69–85.
[23] Clement FM, Harris A, Li JJ, et al. Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. JAMA 2009;302:1437–43.
[24] Trueman P, Hurry M, Bending M, Hutton J. The feasibility of harmonizing health technology assessments across jurisdictions: a case study of drug eluting stents. Int J Technol Assess Health Care 2009;25:455–62.
[25] Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67:913–24.
[26] EUnetHTA WP5. Methodological guideline for REA of pharmaceuticals: comparators and comparisons – direct and indirect comparisons. February 2013. Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf. [Accessed February 15, 2015].
[27] Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health 2014;17:157–73.
[28] European Medicines Agency. EMA-HTA workshop. Bringing together stakeholders for early dialogue in medicines development. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/05/WC500166228.pdf. [Accessed October 9, 2014].
[29] Tsoi B, Masucci L, Campbell K, et al. Harmonization of reimbursement and regulatory approval processes: a systematic review of international experiences. Expert Rev Pharmacoecon Outcomes Res 2013;13:497–511.
[30] European Medicines Agency. CHMP assessment report. Votrient, pazopanib (EMA/CHMP/248579/2010). June 14, 2010. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001141/human_med_001337.jsp&mid=WC0b01ac058001d124. [Accessed March 3, 2014].
[31] Wonder M, Backhouse ME, Hornby E. Early scientific advice obtained simultaneously from regulators and payers: findings from a pilot study in Australia. Value Health 2013;16:1067–73.
[32] EUnetHTA WP5 JA2. Zostavax® for the prevention of herpes zoster ('zoster' or shingles) and herpes zoster related postherpetic neuralgia. September 2013. Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Zostavax_main%20report%20including%20appendices_20130922.pdf. [Accessed February 16, 2015].
[33] EUnetHTA WP5 JA2. Canagliflozin for the treatment of type 2 diabetes mellitus. February 2014. Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/WP5_SA-2_canagliflozin_for_the_treatment_of_diabetes_mellitus.pdf. [Accessed February 16, 2015].