EUnetHTA WP5, Relative effectiveness of pharmaceuticals

PAZOPANIB FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA

Pilot assessment using the draft rapid REA model

Version 3, 6 June 2012
Public Consultation

Disclaimer:
The purpose of the pilot was to test the usability of the draft HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals and draft guidelines. As the main purpose of the pilot was not to produce an actual HTA report for decision making it is emphasised that the results of this assessment are not suitable for drawing conclusions for decision making.

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Summary of relative effectiveness of pazopanib

This summary covers the assessment phase of the pilot, reported in the 'Results' section of the main report. The organisational aspects of the pilot and recommendations for future rapid REA project are discussed in Section 4 of the main report.

The assessment element ID codes in brackets (e.g. A0001) refer to the result cards in Appendix 1, which give details of the relevant results.

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Scope

Population	Treatment-naïve patients (first-line treatment) and cytokine pre-treated patients (second-line treatment) with advanced or metastatic (stage III-IV) renal cell carcinoma (patients ≥ 18 years or older; no restrictions according to performance status)
Intervention	Pazopanib
Comparison	Medicines in the same therapeutic category: tyrosine kinase inhibitors: sunitinib, sorafenib medicines with similar therapeutic aims, a) monoclonal antibodies: bevacizumab b) cytokines: interferon-alfa, aldesleukin and their combinations, and best supportive care
Outcome(s)	Benefits: Overall survival, quality of life, progression free survival Harms: Serious adverse events, Severe adverse events (Grade 3-4), Frequent adverse events of any severity grade

Introduction

Health problem

In 2008 kidney cancer was the tenth most common cancer in Europe. The average European incidence of renal cell carcinoma was 7.1 for women and 15.8 for men (age-standardised rate per 100,000) in 2008.[1,2] The incidence of renal cell carcinoma varies geographically and is highest between age 40 and 60 (A0023). Smoking, obesity and hypertension are risk factors for renal cell carcinoma (A0003). Every fourth new renal cell carcinoma diagnosed is already at an advanced or metastatic stage. Specific symptoms at diagnosis include haematuria, flank pain and palpable abdominal mass. Half of the patients present no or non-specific symptoms at diagnosis.

Renal cell carcinoma is predominantly diagnosed by abdominal ultrasound or computed tomography. Renal biopsy is performed to confirm the diagnosis and to determine the disease stage (A0024).[1,3,4,] The current standard of care for renal cell carcinoma is nephrectomy followed by systemic therapy for metastatic disease.[1] In patients with resectable tumours and a good performance status the resection of metastases is recommended.[1,3] Radiotherapy has a role in palliation in some patients (A0025) . [1,3]The

1 overall median survival from time of diagnosis of metastatic renal cell carcinoma is
2 about 1 year and the 5-year survival rate ranges from 5% to 15% (A0004).[1,5,6]
3
4 **Description of technology**
5 In June 2010, the European Medicines Agency granted conditional approval for pazopanib
6 (Votrient ®) for the treatment of advanced and/or metastatic renal cell carcinoma as first-line
7 treatment or after initial cytokine based therapy has failed, and requested further evidence
8 of effects with respect to other drugs for the same indication (B0003).[7]
9
10 Pazopanib inhibits multiple tyrosine kinase-coupled receptors, which are involved in
11 angiogenesis, tumour growth and metastatic progression of cancer (B0003).[8] Other targeted
12 therapies currently available include: sunitinib, sorafenib, bevacizumab plus interferon alfa,
13 temsirolimus and everolimus. Sunitinib and sorafenib belong to the same category of
14 tyrosine kinase inhibitors as pazopanib. According to most treatment guidelines sunitinib,
15 bevacizumab plus interferon alfa and pazopanib are recommended for the first-line therapy
16 in low and intermediate risk patients (defined according to the Memorial Sloan-Ketttering
17 Cancer Center risk system); in high-risk patients temsirolimus is recommended.[9] Sorafenib
18 and pazopanib are recommended as second-line treatment after cytokine (interferon alfa and
19 aldesleukin) failure, and everolimus is recommended as second-line treatment following
20 tyrosine kinase inhibitors (A0025).[1,9,10]
21
22 The recommended dose of pazopanib is 800 mg/day (B0001). The Summary of Product
23 Characteristics recommends discontinuation if liver enzymes or blood pressure are
24 persistently elevated, and in patients who develop Grade 4 proteinuria or wound dehiscence.
25 In the pivotal trial, pazopanib was discontinued upon disease progression.[7]
26
27 No specific organisational changes are required when implementing therapy with pazopanib.
28 All targeted therapies should be initiated by a physician experienced in the administration of
29 anti-cancer drugs. Oral administration of pazopanib allows delivery in an outpatient setting
30 (G0003).[11] Frequent monitoring of liver and thyroid function, blood pressure and
31 electrocardiogram monitoring are required to prevent serious adverse events (C0062).[12] The
32 manufacturer's risk management plan proposes additional pharmacovigilance activity for
33 collecting data on liver chemistry and ischaemic events (C0007b).[7] Oral administration is
34 generally perceived as a benefit for the patient, carer and health system, as it may reduce the
35 number of clinic visits or stays. However, the resulting reduced contact with health
36 professionals may have negative effects on motivation and compliance (F0011).[13-15]
37
38 ## *Results*

39 **Available evidence**
40 There is one randomised comparative trial of pazopanib versus placebo (best supportive
41 care) and no trials comparing pazopanib to any of the comparators.[8] There are two additional
42 single-arm trials examining pazopanib.[16,17] Applicability of the body of evidence might differ
43 in different clinical settings due to differences in the distribution of the effect modifiers.

44 **Upcoming evidence**
45 Ongoing trials include a phase III clinical study comparing pazopanib and sunitinib in the
46 treatment of treatment-naïve patients with locally advanced and/or metastatic renal cell
47 carcinoma (COMPARZ) and a head to head randomised trial (PISCES) comparing patient
48 preference between pazopanib and sunitinib.[18,19]
49
50 **Clinical effectiveness**
51 Pazopanib extends progression free survival statistically significantly compared with best
52 supportive care: in treatment-naïve patients from 3 months to 11 months (median), and in
53 cytokine pre-treated patients from 4 months to 7 months (median; D0006).[8] However, there
54 is insufficient evidence to determine the effect of pazopanib on overall survival and quality
55 of life (D0001, D00012 & D0013). There are no studies directly comparing pazopanib with
56 the comparators listed in the scope (except best supportive care). For that reason, pazopanib

was indirectly compared with interferon alfa through one common comparator (best supportive care), and with sunitinb and bevacizumab plus interferon alfa through two common comparators (best supportive care and interferon alfa) in the treatment-naïve population. In the cytokine pre-treated population pazopanib was indirectly compared with sorafenib through one common comparator (best supportive care). Data from five interferon alfa studies[20-24], one sunitinib study[25], 2 bevacizumab plus interferon alfa studies[26,27] and one sorafenib study[28] were utilised in the indirect comparisons. There were no statistically significant differences in overall survival between pazopanib and its comparators (D0001). For progression free survival, there was a statistically significant difference only between pazopanib and interferon alfa (D0006). There was no significant difference in the quality of life of patient treated with pazopanib vs best supportive care. For other comparators no comparative data on quality of life are available (D00012&D0013).

Safety

Twelve percent of patients on pazopanib had serious pazopanib related adverse events such as brain or myocardial ischaemia and liver failure. Fatal adverse events include pulmonary haemorrhage and gastrointestinal perforation (C0001).[7,8] Every third patient using pazopanib experienced severe adverse events such as vomiting, abdominal pain and fatigue in the trials. Diarrhoea and hypertension were the most common reasons for lowering the dose of the medication. There was no consistent significant difference in frequency of adverse events between pazopanib and the comparators in quantitative indirect comparisons with two methods (C0008a, C0008b).[29] However, some qualitative differences in the adverse event profiles have been identified in indirect comparisons. For sunitinib (first line) (C0008a)[7,29] and sorafenib (second line) (C008b)[7,29,31] higher rates of decreased blood cell count, hypothyroidism, stomatitis and palmar-plantar erythrodysesthesia syndrome were reported compared (indirectly) with pazopanib. Aldesleukin (first line) showed a higher rate of headache, dizziness, confusion, hypotension, erythema, thrombocytopenia, pyrexia and pruritus (C0008b)[7,26] compared (indirectly) with pazopanib. Interferon alfa (first line) and combined therapy with interferon alfa plus bevacizumab (first line) showed higher rates of nausea and asthenia compared (indirectly) with pazopanib; the combination therapy had a discontinuation rate of 1 out of 4 patients because of proteinuria, headache, haemorrhage and dyspnoea (C0008b)[7,26,27].

Reimbursement

Pazopanib is reimbursed in fourteen out of seventeen investigated countries. In some of the countries where it is not reimbursed specials arrangements, such as approval on a case by case basis, can lead to reimbursement in exceptional cases. In addition, in many of the countries in which it is reimbursed restrictions (such as indication restrictions) are applicable (A0021).

1 *Summary table of relative effectiveness of pazopanib*

First line (treatment-naïve patients) *The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.*						
	Health benefit			**Harm**		
	OS HR (95% CI)	**QoL**	**PFS** HR (95% CI)	**Serious AEs**	**Severe AEs (Grade 3-4)** RR (95% CI)	**Frequent AEs of any severity grade** RR (95% CI)
Pazopanib / **Sunitinib**	HR=0.97 (0.36-2.61) ***D0001***	No comparative data available ***D0012& D0013***	HR=0.95 (0.58-1.57) ***D0006***	No compara-tive data available ***C0008a***	No comparative data available ***C0008a***	Fatigue: RR 0.21 (0.06, 0.77) **.in favour of pazopanib** Diarrhoea RR 0.16 (0.04, 0.58).**in favour of pazopanib** Other AEs P>0.05 ***C0008a***
Quality of body of evidence	*Very low (GRADE) HR derived from indirect comparison*	*NA*	*Very low (GRADE) HR derived from indirect comparison*	*NA*	*NA*	*Quality of body of evidence was not assessed. Significance is based on one of the two routes of indirect comparison.*
Pazopanib / **IFN-α + Bevacizu-mab**	HR=0.73 (0.20, 2.65) ***D0001***	No comparative data available ***D0012& D0013***	HR=0.79 (0.50, 1.25) ***D0006***	Death 4% vs 2%. study discontinuation due to mostly diarrhoea or liver disturbances 12% vs 28%. ***C0008b***	Grade 3 AEs 37% vs 57% (IFN-2 α). Grade 4 AEs 6% vs 6% (IFN-2 α) No significant differences in two quantitative indirect comparisons. ***C0008b***	Diarrhoea 49% vs 20%, hypertension 38% vs 26%, fatigue 24% vs 33%. ***C0008b***
Quality of body of evidence	*Very low. (GRADE) HR derives from an indirect comparison*	*NA*	*Very low. (GRADE) HR derives from an indirect comparison*	*Quality of body of evidence was not assessed. Percentages derive from placebo controlled trials: for pazopanib VEG105192 trial and for Bevaci-zumab plus IFN-α Avoren trial (Escudier 2007)*	*Quality of body of evidence was not assessed. Percentages derive from placebo controlled trials: for pazopanib VEG105192 trial and for Bevaci-zumab plus IFN-α Avoren trial (Escudier 2007)*	*Quality of body of evidence was not assessed. Percentages derive from placebo controlled trials: for pazopanib VEG105192 trial and for Bevaci-zumab plus IFN-α Avoren trial (Escudier 2007)*

Abbreviations: AE=adverse event; HR=hazard ratio; IFN-α=interferon-alpha; NA=not applicable; OS=overall survival; PFS= progression free survival; QoL=quality of life; RR=relative risk

1

First line (treatment-naïve patients) *continued* *The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.*						
	Health benefit			**Harm**		
	OS HR (95% CI)	**QoL**	**PFS** HR (95% CI)	**Serious AEs**	**Severe AEs (Grade 3-4)** RR (95% CI)	**Frequent AEs of any severity grade** RR (95% CI)
Pazopanib / **IFN-α**	HR 0.63 (0.17, 2.27) ***D0001***	No comparative data available	HR 0.51 (0.33, 0.80) **in favour of pazopanib** ***D0006***	Death 4% vs 2%. Study discontinuation due to mostly diarrhoea or liver disturbances 12% vs 12%. ***C0008b***	Grade 3 AEs 37% vs 42% (IFN-2a). Grade 4 AEs 6% vs 4% (IFN-2a) No significant differences in two quantitative indirect comparisons. ***C0008b***	Diarrhoea 49% vs 15%, hypertension 38% vs 9%, fatigue 24% vs 27 % ***C0008b***
Quality of body of evidence	*Very low (GRADE) HR derives from indirect comparison*	*NA*	*Low (GRADE) HR derives from indirect comparison*	*Quality of body of evidence was not assessed. Percentages derive from placebo controlled trials: for pazopanib VEG105192 trial and for IFN- α Avoren trial (Escudier 2007).*	*Quality of body of evidence was not assessed. Percentages derive from placebo controlled trials: for pazopanib VEG105192 trial and for IFN- α Avoren trial (Escudier 2007).*	*Quality of body of evidence was not assessed. Percentages derive from placebo controlled trials: for pazopanib VEG105192 trial and for IFN- α Avoren trial (Escudier 2007)*
Pazopanib / **Best supportive care**	HR 0.50 (0.14, 2.35) ***D0001***	P>0.05 in EQ-5D and EORTC-QLQ-C30 scores at all time point (weeks 6-48) ***D0012& D0013***	Median 11.1 mo (7.4, 14.8) vs 2.8 mo (1.9, 5.6) HR=0.40 (0.27, 0.60) **in favour of pazopanib** ***D0006***	Serious AEs 24% vs19% Serious AEs due to pazopanib 12% Fatal AEs 4% vs 3% Treatment-related fatal AEs according to investigators 1%: Leading to withdrawal 15% vs 6%: ALT and AST increase, diarrhoea and asthenia ***C0001***	Grade 3 AEs 33% vs 14% Grade 4 AEs 7% vs 6% ***C0001***	Diarrhoea 52% vs 9%; RR 5.77 (3.39-9.81); Hypertension 40% vs10%; RR 3.83 (2.33-6.32); Hair colour changes 38% vs 3%; RR 13.63 (5.13-36.22); Nausea 28% vs 9%; RR 2.85 (1.63-4.96); Anorexia 22% vs 10%; RR 2.32 (1.35-3.99); Vomiting 21% vs 8%; RR 2.77 (1.51-5.10); **All are in favour of BSC.** ***C0001***

2 Abbreviations: AE=adverse event; HR=hazard ratio; IFN-α =interferon-alpha; NA=not applicable; OS=overall survival; PFS=
3 progression free survival; QoL=quality of life; RR=relative risk
4

1

First line (treatment-naïve patients) *continued* *The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.*						
	Health benefit			**Harm**		
	OS HR (95% CI)	**QoL**	**PFS** HR (95% CI)	**Serious AEs**	**Severe AEs (Grade 3-4)** RR (95% CI)	**Frequent AEs of any severity grade** RR (95% CI)
Quality of body of evidence	*Low (GRADE) HR derives from direct head- to-head comparison within the VEG105192 trial. HR is adjusted for the effects of the cross over using weighted unadjusted RPSFT.*	*High (GRADE) Result derives from a mixed-model repeated measures analysis for change from baseline within the VEG105192 trial.*	*High (GRADE) HR derives from direct head- to-head comparison within the VEG105192 trial*	*Quality of body of evidence was not reported. Percentages and RRs derive from direct head- to-head comparison within the VEG105192 trial.*	*Quality of body of evidence was not reported. Percentages and RRs derive from direct head-to-head comparison within the VEG105192 trial.*	*Quality of body of evidence was not reported. Percentages and RRs derive from direct head- to-head comparison within the VEG105192 trial.*

2 Abbreviations: AE=adverse event; HR=hazard ratio; IFN-α =interferon-alpha; NA=not applicable; OS=overall survival; PFS=
3 progression free survival; QoL=quality of life; RR=relative risk

1

Second line (cytokine pre-treated patients) *The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.*						
	Health benefit			**Harm**		
	OS HR (95% CI)	**QoL**	**PFS** HR (95% CI)	**Serious AEs**	**Severe AEs (Grade 3-4)** RR (95% CI)	**Frequent AEs of any severity grade** RR (95% CI)
Pazopanib **Sorafenib**	No comparative data available ***D0001***	No comparative data available ***D0012&*** ***D0013***	HR 1.00 (0.62, 1.60) ***D0006***	No comparative data available ***C0001a&b***	Grade 3 and 4 AEs merged: sorafenib RR 0.41 (0.11, 1.50); P>0.05 in all investigated Grade 3-4 AEs. ***C0008b***	All AEs RR 0.81 (0.6, 1.09) ***C0008b***
Quality of body of evidence	*NA*	*NA*	*Low.(GRADE) HR derives from an indirect comparison*	*NA*	*Quality of body of evidence was not assessed. Significance is based on Indirect comparison**	*Quality of body of evidence was not assessed. Significance is based on one of the two routes of indirect comparison**
Pazopanib **BSC**	HR 0.82 (0.57-1.16) ***D0001***	No comparative data available ***D0012&*** ***D0013***	Median 7.4 mo vs 4.2 mo HR=0.54 (0.35, 0.84) **in favour of pazopanib** ***D0006***	Serious AEs 24% vs19% Serious AEs due to pazopanib 12% Fatal AEs 4% vs 3% Treatment-related fatal AEs according to investigators 1%: Leading to withdrawal 15% vs 6%: ALT and AST increase, diarrhoea and asthenia ***C0001***	Grade 3 AEs 33% vs 14% Grade 4 AEs 7% vs 6% ***C0001***	Diarrhoea 52% vs 9%; RR 5.77 (3.39-9.81); Hypertension 40% vs10%; RR 3.83 (2.33-6.32); Hair colour changes 38% vs 3%; RR 13.63 (5.13-36.22); Nausea 28% vs 9%; RR 2.85 (1.63-4.96); Anorexia 22% vs 10%; RR 2.32 (1.35-3.99); Vomiting 21% vs 8%; RR 2.77 (1.51-5.10); **All are in favour of BSC.** ***C0001***
Quality of body of evidence	*Low (GRADE) HR derives from direct head- to-head comparison within the VEG105192 trial. HR is adjusted for the effects of the cross over using weighted unadjusted RPSFT.*	*NA*	*High (GRADE) HR derives from direct head- to-head comparison within the VEG105192 trial*	*The quality of body of evidence was not reported. Percentages and RRs derive from direct head-to-head comparison within the VEG105192 trial.*	*The quality of body of evidence was not reported. Percentages and RRs derive from direct head- to-head comparison within the VEG105192 trial.*	*The quality of body of evidence was not reported. Percentages and RRs derive from direct head- to-head comparison within the VEG105192 trial.*

2 **Abbreviations:** AE=adverse event; HR=hazard ratio; IFN-α=interferon-alpha; NA=not applicable; OS=overall survival;
3 PFS= progression free survival; QoL=quality of life; RR=relative risk
4

1 *Discussion*

Reliable results showing an overall survival effect can be difficult to obtain due to insufficient duration of follow-up. Patients in the control arm may be allowed to crossover to the treatment arm to receive the active agent or they can be treated with similar second or third line agents that may lead to dilution of the overall survival benefit. As early as only 5 or 10 months post-randomisation many of the best supportive care subjects had crossed over to receive pazopanib therapy or another anti-cancer therapy in the VEG105192 study. At the time of the clinical cut-off (15 March 2010) 64% of the treatment-naïve patients in the best supportive care arm and 34% of those in the pazopanib arm had received further anti-cancer therapies. Crossover between therapies in the VEG105192 study made the interpretation of overall survival data comparing pazopanib and best supportive care challenging since various statistical techniques and other methodological approaches were applied to deal with the crossover. However, irrespective of the approach or technique used, there is no clear evidence that pazopanib would differ from best supportive care in terms of overall survival.

Progression free survival is commonly used as a surrogate to predict overall survival in cancer. In addition to avoiding the shortcomings of overall survival measurements caused by subsequent treatments or crossovers, it has the advantage of shortening the duration of the trial. Progression free survival is considered to be an important intermediate endpoint, provided that it predicts overall survival in metastatic renal cell carcinoma or it is substantiated that health-related quality of life in progression free patients is significantly higher than in patients with progression. However, a robust comparison of survival and progression free survival is difficult, and opinions differ regarding the validity of progression free survival as a surrogate for overall survival in the treatment of renal cell carcinoma.

There are no studies directly comparing pazopanib with its comparators (except for best supportive care). Therefore, methods of indirect comparison were used in the evidence synthesis. The validity of the indirect comparison rests on the assumption of similarity. If the trials included in the evidence synthesis differ, however, and the differences are modifiers of relative treatment effect, the results of the indirect comparison are biased. For example, for the overall survival analysis, the studies included patients with different Eastern Cooperative Oncology Group (ECOG) performance statuses. If the performance status modifies the relative effect, the assumption of similarity is not valid. However clinical trials often differ in design but these differences do not always imply effect modification. The indirect comparisons of safety data need to be treated with particular caution due to the lack of primary safety endpoints in studies, associated multiplicity issues (risk of Type I error), the difficulty of valuing different adverse effects against each other and the differences in follow-up duration between the different trials. On the other hand, meta-analyses of pooled safety data can facilitate the interpretation of results that are generally underpowered in single trials.

The evidence on the effects of pazopanib in patients with advanced and/or metastatic renal cell carcinoma is from randomised controlled trials. In the current assessment process, no data from so called “real life” studies were identified. Therefore judgments about whether the available research evidence reflects the expected results in “real life” practice are based on the results of randomised controlled trials. This was done by assessing the applicability of these studies. Because the applicability of the body of evidence might differ in different clinical settings (due to differences in the distribution of the effect modifiers), judgements about major limitations of the applicability of individual studies should be made on a national level. To facilitate this, evidence on current treatment practices should also be assessed and reported at a national level.

1 *Conclusion*

There is insufficient evidence to determine whether pazopanib increases the overall survival or quality of life of patients with advanced renal cell carcinoma compared with best supportive care. It extends progression free survival compared with best supportive care, both in treatment-naïve patients (median 8 months longer) and in cytokine pre-treated patients (median 3 months longer). There are different opinions regarding the surrogacy of progression free survival for overall survival in the treatment of renal cell carcinoma. Progression free survival may be considered to be an important intermediate endpoint if it predicts overall survival in metastatic renal cell carcinoma or if it is substantiated that health-related quality of life in progression free patients is significantly higher than in patients with progression. However, a robust comparison of overall survival and progression free survival is difficult. When compared with the other systemic therapies currently used, pazopanib seems to be superior to interferon alpha (first line), both in terms of progression free survival and severe adverse events. Compared with sunitinib and bevacizumab (first line), pazopanib has fewer adverse events associated with it but no evidence of more health benefits. Compared with sorafenib (second line) there is no evidence of differences in either benefits or harms. Due to the lack of direct head-to-head trials all differences between pazopanib and its active comparators are based on indirect comparison. This, together with limited evidence on the comparators, makes confidence intervals wide. Randomised controlled trials directly comparing the agents would provide more evidence, potentially enabling more robust conclusions. The report of a clinical phase III study that compares treatment with pazopanib and sunitinib in treatment-naïve patients with locally advanced and/or metastatic renal cell carcinoma (COMPARZ) is expected to be available by June 2013.

1 List of abbreviations

AETSA	Andalusian Agency for Health Technology Assessment
AGREE	The Appraisal of Guidelines for Research and Evaluation. An instrument which evaluates the process of practice guideline development and the quality of reporting.
AHTAPol	Agency for Health Technology Assessment in Poland
AIFA	Italian Medicines Agency
CAHIAQ	Catalan Agency for Health Information, Assessment and Quality
CAST	Centre for Applied Health Services Research and Technology Assessment
CRD	Centre for Reviews and Dissemination
CVZ	Dutch Health Care Insurance Board
EPAR	European public assessment report
FIMEA	Finnish Medicines Agency
FINOHTA	Finnish Office for Health Technology Assessment at the National Institute for Health and Welfare
GÖG	Health Austria GmbH
GYEMSZI	Hungarian National Institute for Quality- and Organizational Development
HAS	French National Authority for Health
HBV	Association of Austrian Social Insurance Institutions
HPCU	Health problem and current use domain
HR	Hazard ratio
IQWIG	German Institute for Quality and Efficiency in Health Care
NIPH	National Institute of Public Health of the Republic of Slovenia
KCE	Belgian Healthcare Knowledge Centre
KELA	The Social Insurance Institution of Finland
MedDRA	Medical Dictionary for Regulatory Activities
MHEC-DPA	Directorate for Pharmaceutical Affairs (DPA) at the Ministry of Health, the Elderly and Community Care in Malta
MoH CZ	Ministry of Health - Czech Republic
MoH Spain	Ministry of Health Spain
mRCC	Metastatic renal cell carcinoma
MSPCI	Ministerio de Sanidad, Politica Social e Igualdad
NHS	National health services
NICE	National Institute for Health and Clinical Excellence, UK
NNH	Number needed to harm
NOKC	Norwegin Knowledge Center for the Health Services
OS	Overall survival
PDGFR	Platelet-derived growth factor receptor
PFS	Progression free survival
PICO	Patient problem, intervention, comparison, outcome
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RIZIV	National Institute for Health and Disability Insurance
SPC	Summary of Product Characteristics
STROBE	Strengthening the reporting of observational studies in epidemiology
THL	National Institute for Health and Welfare
TNM	Tumour- node- metastasis. A staging system for cancer.
TLV	Dental and Pharmaceutical Benefits Agency
TNM	Tumour node metastasis
UETS	HTA Unit Agencia Laín Entralgo
VEC	Centre of Health Economics in Latvia
VEGFR	Vascular Endothelial Growth Factor Receptors
WP	Work package

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1 1. Introduction to pilot assessment

EUnetHTA Joint Action (JA) is a joint action between the European Commission and Member States. Its aim is to develop a sustainable network of health technology assessment (HTA) and information resources to inform health policy making. EUnetHTA Joint Action builds on the earlier EUnetHTA Project 2006-08 and several other European projects.

The task of the Work package 5 (WP5) of EUnetHTA was to develop a model for the relative effectiveness assessment (REA) of pharmaceuticals, according to the structure of the EUnetHTA HTA Core Model (see Appendix 2 for definitions). Two earlier HTA Core Model applications were developed during the EUnetHTA Project 2006-08; one for medical and surgical interventions, and another for diagnostic technologies. A third application, the model for screening technologies, was developed in the WP4 of EUnetHTA Joint Action.

Within WP5 it was decided that two different model applications were to be developed for REA of pharmaceuticals.

- Model for Full REA: suitable for REA of pharmaceutical(s) considering all domains (except cost-effectiveness) and assessment elements of the HTA Core Model.
- Model for Rapid REA: suitable for a (single) rapid REA of a pharmaceutical. E.g. for the assessment of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions. The Model for Rapid REA contains a subset of the assessment elements included in the full model, and specific methodological guidance for rapid assessment.

Additionally, a set of methodological guidelines have been prepared within WP5 to complement the methodologies presented in the REA models.

The lead partner of the WP5 of EUnetHTA Joint Action is the Dutch Health Care Insurance Board (CVZ) and the co-lead partner is the French National Authority for Health (HAS).

1.1. Objective of the pilot

The objective of this pilot was to test the usability of the draft Model for Rapid REA and draft guidelines developed by WP5.

Primary outcome of pilot:

- HTA doers' perceptions about the model and guidelines: Is the model structure helpful? Is the guidance helpful in the assessment?

Secondary outcomes:

- duration of the assessment
- workload (in terms of working hours)
- feasibility of international cooperation
- readers' perceptions about the format of the pilot report, adaptability of information for national purposes, and its readability.

In summary, WP5 aims to get more insight into how the concept model/guidelines work in daily practice. Based on the input from this pilot the draft Model for Rapid REA and draft guidelines will be revised in 2012. The overall aim of WP5 is to produce products that are useful for daily practice in order to facilitate international collaboration on the assessment of the relative effectiveness of pharmaceuticals in future.

Disclaimer:

The purpose of the pilot was to test the usability of the draft HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals and draft guidelines. As the main purpose of the pilot was not to produce an actual HTA report for decision making it is emphasised that the results of this assessment are not suitable for drawing conclusions for decision making.

1.2. Topic selection

The pharmaceutical to be assessed within the pilot was selected on the basis of the preferences of WP5 members. First, a list was produced of all the pharmaceuticals that received market authorization between 1 June 2010 and 1 February 2011. A number of exclusion criteria (see Box 1) were defined for the selection of the pilot pharmaceutical and the related indication. This resulted in a list of eight pharmaceuticals, from which all WP5 members were asked to indicate their preference for assessment (first, second and third choices). Based on these preferences a shortlist of four suitable pharmaceuticals was generated. The WP5 Stakeholder Advisory Group and the European Medicines Agency were consulted about the suitability of the four pharmaceuticals as topics for the pilot.

Box 1. Exclusion criteria for pharmaceuticals to be selected as the topic of this pilot:

1. Generic pharmaceuticals
2. Orphan drugs (often no comparator, therefore less suitable for testing the model)
3. Vaccines
4. Extension of indications
5. Medicinal product for diagnostic use only

Next, the manufacturers of the four pharmaceuticals were approached about their willingness to provide information on the pharmaceutical (a submission file) based on the work that had already been done for the national reimbursement authorities, and the feasibility of doing so. A submission file compiled by the market authorisation holder is important basic information for most national rapid assessments of pharmaceuticals. The availability of such a file would, therefore, increase the resemblance of this pilot to daily practice in most countries.

Finally, out of the list of four pharmaceuticals, *pazopanib for the treatment of advanced renal cell carcinoma* (RCC) was chosen because

- this was the most common first choice of WP5 members,
- there were no objections from the stakeholder advisory group and European Medicines Agency, and
- the marketing authorisation holder was willing to provide a submission file.

1.3. Organisation of the pilot

Table 1 shows the timetable of the WP5 pilot.

The pilot was organised in eight domain teams (Table 2). Each team had a domain lead, and one or several authors and reviewers. The domain teams were based on individual preferences for domain content and included a total of 45 individuals from 21 agencies in 14 countries. The coordination team consisted of the project coordinator, and the leads of each domain team. The role of the coordination team was to discuss and decide upon methods and project coordination related issues that were common to all domain teams.

There was an additional team for developing the summary of relative effectiveness of pazopanib. This “summary team” included volunteers from WP5 member organisations who had been active in REA model development and in the pazopanib pilot. The authors of the effectiveness and safety domain were not included in this team because it was considered beneficial for the members have a fresh view on the data.

The project team in CVZ consisted of a project leader and two project coordinators, whose tasks were project management, editing and quality assurance in all phases of the project. The co-lead partner, HAS, was consulted about coordination issues at several stages.

1 *Table 1. Timetable of the WP5 pilot 2011-2012*

Step	Period
Selecting the topic	May 2011
Protocol phase	May-June 2011
Assessment and reporting	July-October 2011
First draft of the report for consultations to marketing authorisation holder and WP5 members	November-January 2011
Second draft of the report for consultation to stakeholder advisory group	March 2012
Third draft of the report for public consultation	June 2012
Final version of the reports	September 2012

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3 *Table 2. Pazopanib pilot team*

Project leader	Wim Goettsch, CVZ
Project coordinators	Iris Pasternack, CVZ Sarah Kleijnen, CVZ

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Domain lead	Author	Reviewer
Health problem and current use of the technology		
AIFA (Agnese Cangini)	AIFA (Agnese Cangini)	CAHIAQ (Núria Paladio)
	KCE (C. de Laet)	a Gemelli (Marco Marchetti)
	GÖG (Alexander Eisenmann)	
Description and technical characteristics of technology		
MHEC-DPA (Isabelle Zahra Pulis/Bernardette Rossi)	MHEC-DPA (Isabelle Zahra Pulis, Bernardette Rossi, Sylvana Magrin,Diane Balzan)	GYEMSZI (Áron Vinczicz ki)
	HBV (Anna Bucsics, Eva Zebedin)	CAST (H. Vondeling)
Safety		
RIZIV (Marc Van de Casteele)	RIZIV (Marc Van de Casteele)	FOPH (Ameli Kruselerf)
	AETSA (M Auxiliadora Castillo)	GYEMSZI (Zoltan Huszti)
	AIFA (Luisa Muscolo)	NOKC (Marianne Klemp)
Clinical effectiveness		
FIMEA (Pertti Happonen)	FIMEA (Pertti Happonen, Piia Peura, Vesa Kiviniemi, Tuomas Oravilahti)	MoH Spain (Mercedes Martínez Vallejo)
	HAS (Pauline Vitre)	UETS (Juan Blasco)
	AIFA (Simona Montilla)	AETSA (Belen Corbacho)
Ethical analysis		
A.Gemelli (Rossella Di Bidino)	A.Gemelli (Rossella Di Bidino)	NOKC (Ingvil Sæterdal)
	A.Gemelli (Dario Sacchini)	VEC (Daiga Behmane)
	A.Gemelli (Pietro Refolo)	

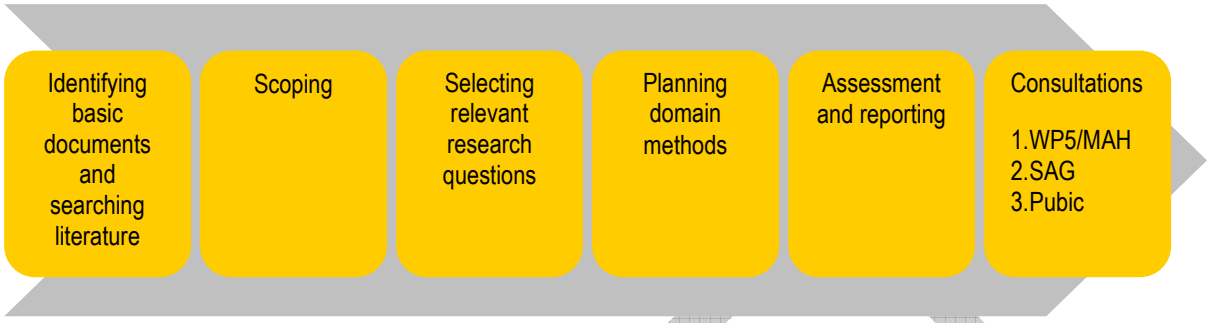
Domain lead	Author	Reviewer
	A.Gemelli (Roberta Minacori)	
Organisational aspects		
A.Gemelli (Rossella Di Bidino)	A.Gemelli (Rossella Di Bidino)	GYEMSZI (Bence Nagy)
	NIPH (Marjetka Jelenc)	A.Gemelli (Marco Marchetti)
	A.Gemelli (Matteo Ruggeri)	
Social Domain		
CVZ (Payaam Abrishami)	CVZ (Payaam Abrishami, Wim Goettsch)	NOKC (Tove Ringerike)
	Finohta/THL (Sinikka Sihvo)	RIZIV (André De Swaef)
Legal domain		
THL (Sirpa Soini)	THL (Sirpa Soini) FIMEA (Paavo Autere)	HBV (Hans Seyfried)
		RIZIV (Francis Arickx)
Summary team		
	Anna Bucsics (HVB), Pietro Folino Gallo (AIFA), Elisabeth George (NICE)	Wim Goettsch (CVZ), Marianne Klemp (NOKC), Mira Pavlovic (HAS), Beate Wieseler (IQWIG), Jana Žížalová (Czech MoH)

1

2. Methods of pilot assessment

This chapter describes the methods of the various phases of the project. An overview of the project phases is shown in Figure 1.

Figure 1. Overview of project phases



Abbreviations: MAH=marketing authorisation holder; SAG=stakeholder advisory group; WP5=work package 5

2.1. Basic documents and literature search

The basic documents that guided the content and methods of the pilot were[a]:

- The draft HTA Core Model for the relative effectiveness assessment of pharmaceuticals (Model for Rapid REA)
- The collection of draft methodological guidelines that are being developed within WP5 during Joint Action (Box 2)

Box 2. Methodological guidelines that are being developed by WP5 during EUnetHTA Joint Action

- Clinical Endpoints
- Composite endpoints
- Surrogate endpoints
- Health-related quality of life
- Safety
- Criteria for the choice of the most appropriate comparator(s)
- Direct and indirect comparison
- Internal validity
- Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals

The pilot followed the structured method of producing and reporting HTA information proposed by the Model for Rapid REA. There was a project manual and the project coordinators provided the domain teams with guidance and tools on how to proceed in each phase of the pilot. The two main phases were the protocol and assessment phases.

- The protocol phase included scoping, searching for information, formulating research questions, and planning methodologies. The objective of this phase was for each domain team to create a list of all the relevant questions to be answered, and present the methodologies they intended to use in the assessment.

[a] These documents will be subject to public consultation in spring and summer 2012. The final versions of these documents will be publicly available by the end of 2012.

- The assessment phase included finding answers to the questions using the methods defined in the protocol phase, the methodological guidance provided in the Model for Rapid REA, and the methodological guidelines. The objective of this phase was for each domain team to provide a domain report including the result cards.

Basic search for the project

The basic search was conducted in the coordinating office (CVZ) using three reference databases, Medline, Embase and the Centre for Reviews and Dissemination (CRD) database, European Medicines Agency web pages and direct communication with the marketing authorisation holder of pazopanib. This is described in more detailed below and in Appendices 3-5.The aim of the basic search was to provide central information for all domain teams, and to assist the authors in the preparation of the protocol, i.e. defining the research questions and methods to be used in the assessment. Most domain teams complemented the basic search with their own domain-specific searches during the assessment phase (see details in the methods sections of each domain report).

Documentation by marketing authorisation holder and European Medicines Agency

The submission file for pazopanib (Votrient) was provided by the marketing authorisation holder GlaxoSmithKline to be used specifically in this project. The European Public Assessment Report (EPAR) of pazopanib was the other essential base document to be distributed to all domain teams.[7]

Search from reference databases (published, peer reviewed literature)

Simple search strategies were used for Medline, Embase and the CRD database (Appendix 3). There was no need to create strict inclusion criteria in this phase, in which the requirements related to the type of information and research methodologies were different in all domains. Instead of restricting the search to specific outcomes, comparisons, or methodologies only, any article or document that was considered likely to be helpful for any of the domains was included. Exclusion criteria for studies are presented in Appendix 4, and the final selection of articles for possible inclusion in Appendix 5.

Process for study selection

- One coordinator screened the titles, excluded those articles that were clearly not relevant by reading the title, and documented the number of included titles.
- Two coordinators independently screened all abstracts of the included titles, and proposed inclusion or exclusion based on reading the abstract only. Coordination team members commented on these proposals. The number of included abstracts is documented.
- Full texts were retrieved for the included abstracts and placed in the electronic workroom available for all domain teams.

2.2. Scoping the project

The scope of the assessment was developed using a table template which required defining

- Technology
- Indication
    - target condition
    - target population
    - purpose of the use of the technology, and

- Comparison

Endpoints were not defined in this phase; it was left for the domain teams to decide on them in the protocol phase when formulating the research questions.

Coordinators prepared the first version of the scoping table, which was circulated for comments to all team members, both authors and reviewers, and was discussed in an e-meeting. Further adjustments were made after discussions in a face-to-face meeting. The final scope is presented at the beginning of the results section. The scope, structured according to PICO, is included in the summary of the report.

2.3. Selecting relevant research questions

Each domain team selected relevant assessment elements from the Model for Rapid REA. Each assessment element contains a generic question relevant to the rapid assessment of the relative effectiveness of pazopanib. Estimates of relevance were based on the authors' own expertise, the literature retrieved from the basic search, and consultations with experts. A brief justification was provided for those elements that were regarded as not relevant for this assessment (see Appendix 6 excluded generic questions).

The domain teams translated the generic questions they had selected as relevant into answerable research questions. One generic question translates into one or several answerable research questions (The list of research questions is presented at the beginning of each domain report).

In a brief ethical discussion in the beginning of this phase, the domain authors considered whether there were ethical issues that might affect the selection of issues or their formulation into research questions.

2.4. Plan of domain-specific methods

The domain teams planned and reported the methodologies they intended to use in the assessment phase, within their particular domain. In this exercise the authors were encouraged to use the domain-specific methodology sections in the Model for Rapid REA, and the WP5 guidelines (see Box 2).

The following items were required for the plan.

- Plan for information retrieval: sources and search terms for locating domain-specific information, inclusion/exclusion criteria for studies or other information, in terms of content, methods and quality.
- Plan for handling the published data: do a systematic review, cite recent reviews, "screen until saturated" etc.
- Plan for finding information when there is no published data: from web sites of organisations, discussion forums, registers; by performing surveys (questionnaire, interview); other types of domain-team research (analysis of primary data, modelling etc).
- Quality assessment tools or criteria to be used.
- Plan for synthesis: evidence table, plan for meta-analysis or narrative synthesis etc.

The plans are not reported in this document. Instead, the methods sections of each domain report describe the methods actually used in the assessment.

2.5. Assessment and reporting

Preparing the domain reports

The domain authors shared the research questions among them and did the assessment and reporting. They were encouraged to use the methods sections of the Model for Rapid REA

and the new methodology guidelines to support the assessment task. The results were to be reported in a structured format represented by the result card. One result card contains one research question, the methods for finding the answer to it, and the answer to the question, with references (see Box 3). The result cards of the domains are included in Appendix 1. Additionally, each domain team provided a summary of main findings and a section discussing the work done in their domain.

Box 3. Result cards

A result card is a template that contains fields for

- the research question,
- the methods that have been used to answer the question,
- the answer itself (the result),
- a possible discussion, and
- the references used to answer the question.
- an estimate of importance and transferability of the information

Preparing the project summary

An expert team (see summary team in Table 2) was called to prepare a meaningful overview for the summary about the relative effectiveness by presenting the balance between benefits and harms of pazopanib compared with relevant comparators. Additionally, coordinators abbreviated the individual domain summaries into even shorter paragraphs and compiled them as part of the report summary.

2.6. Planned consultations on the draft pilot report

The draft pilot report is subject to several consultation rounds: first to the marketing authorisation holder and WP5 members, then to the stakeholder advisory group and public in order to receive input on the validity and applicability of the report. Additionally the authors and reviewers of the pilot project were asked to respond to questions related to feasibility and workload and to propose improvements for the Model for Rapid REA and guidelines. The responses from these consultations will provide the pilot team with the answers needed to address the main objectives.

3. Results of the pilot assessment of pazopanib

3.1. Scope

Technology	• Pazopanib (Votrient, GlaxoSmithKline). A tyrosine kinase inhibitor which inhibits multiple receptors: vascular endothelial growth factor (VEGFR-1, VEGFR-2, VEGFR-3), platelet-derived growth factor (PDGFR-a/β), and c-kit. Tyrosine kinase inhibitors are protein kinase inhibitors, and are also described as targeted anticancer agents. • Dosage/administration: orally administered • Duration: until disease progression or unexpected toxicity • MeSH: none • ATC: L01XE11 - Pazopanib
Indication	**Target condition** • Advanced or metastatic (stage III-IV) renal cell carcinoma. Other terms used for renal cell carcinoma: RCC, renal adenocarcinoma, hypernephroma. • The primary tumour is usually unresected but can also be resected after initiation of systemic therapy. • No need to restrict to certain cancer variants. • ICD-10: C64 • MeSH: Carcinoma, Renal Cell **Target population** • All patients with the target condition who are 18 years or older. No restrictions according to performance status. **Purpose of use** • As first-line treatment, and as a treatment after prior cytokine therapy

Comparison	• Medicines in the same therapeutic category,
	  ○ Tyrosine kinase inhibitors: sunitinib, sorafenib
	• medicines with similar therapeutic aims,
	  ○ b) monoclonal antibodies: bevacizumab
	  ○ c) cytokines: interferon-alpha (IFN-α), interleukin
	• and their combinations
	• best supportive care.
	• MeSH terms: angiogenesis inhibitors; antibodies, monoclonal; cytokines; immunosuppressive agents; protein kinase inhibitors; IFN-α; interleukin-2;

3.2. Health problem and current use of the technology

Authors: Agnese Cangini, Chris de Laet, Alexander Eisenmann

3.2.1. Methods

Research questions

Element ID	Research question
A0001	What are the main features of advanced and/or metastatic renal cell carcinoma (RCC)?
A0003	What are the known risk factors for acquiring advanced and/or metastatic renal carcinoma?
A0004	What is the natural course of advanced and/or metastatic RCC?
A0005	What are the main signs and symptoms of advanced and/or metastatic RCC and its consequences for the patient?
A0023	What is the incidence and prevalence of advanced and/or metastatic RCC?
A0006	What is the burden of advanced and/or metastatic RCC?
A0009	What aspects of the burden of disease of advanced and/or metastatic RCC are targeted by the technology?
A0011	How much is the technology being used?
A0012	What kind of variations are there across countries /regions /settings?
A0024	How is the disease/health condition currently diagnosed/identified: according to published guidelines and in practice?
A0025	How is advanced and/or metastatic RCC currently managed,according to published guidelines and in practice? Is the use of pazopanib currently included in the guidelines?
A0017	What are the differences in management for different stages of disease?
A0019	In which phase is the development of the technology?
A0020	What is the market authorisation status of the technology in different countries, or international authorities?
A0021	What is the reimbursement status of the technology across countries?

Sources

- Manufacturer's submission (GlaxoSmithKline)
- Assessments from European Medicines Agency and Food and Drug Administration
- Reference databases: Cochrane Central, CRD, Medline, Embase, Pharmline; Guidelines reference databases (e.g. Guidelines Network International, guideline producers websites)
- Registries and statistics on prevalence, incidence, mortality and morbidity-disability
- For information on regulatory status: national health services' websites or by directly contacting the agencies

Search terms: RCC/cancer

Inclusion/exclusion criteria: The inclusion and exclusion criteria were those used for the basic search as detailed in Appendices 3-5.

There was reliable published information available in reference databases or other established sources to answer most health problem and current use (HPCU) research questions (e.g. on disease mechanism, natural course, prevalence, incidence, risks factors and prognosis of RCC). However, published data on the utilisation of pazopanib were less readily available; hence data from IMS Health (prescription data) was considered.

Quality appraisal

The Appraisal of Guidelines for Research and Evaluation (AGREE) checklist was used to assess the guidelines included (http://www.agreecollaboration.org/instrument/). For some information (e.g. data from registers and statistics about utilisation of pazopanib) there are no established methods of quality assessment.

Analysis
Due to the variety of the issues and the multiple sources of information available only a non-systematic review of literature and other information sources was feasible for many issues, although systematic review would have been preferred. A descriptive synthesis was used to report the results.

3.2.2. Summary of main results

In 2008 kidney cancer was the tenth most common cancer in Europe, and the yearly increase in incidence is about 2%. RCC represents about 90% of all kidney cancers. The prevalence of RCC shows considerable geographical variations and is twice as common in men compared with women, with a peak in incidence in the fifth and sixth decades of life (A0023).[1,32] The aetiology of RCC is still unclear (A0001).[1] Established risk factors for RCC are smoking, obesity, the von Hippel Lindau syndrome and hypertension.(A0003).[1]

RCC can be graded into stages I to IV using the American Joint Committee on Cancer tumour node metastasis (TNM) system. Stage III is characterised as the stage in which the tumour is either locally advanced and/or has spread to regional lymph nodes. In metastatic RCC, referred to as stage IV, the tumour has spread beyond the regional lymph nodes (A0024). According to the WHO classification about 80-90% of RCCs are clear cell RCC. Other less common cell types include papillary, chromophobe, and collecting duct (Bellini duct) tumours (A0001).[33]

Despite notable variations in disease progression of untreated metastatic RCC, the prognosis for RCC is very poor. The overall median survival period from time of diagnosis of metastatic RCC is about 1 year, and the 5-year survival rate ranges from 5% to 15% (A0004).[1,5,6] About 25-30% of RCCs are diagnosed in an advanced and/or metastatic stage of the disease[5] and another 20-30% of patients with localised RCC who had undergone nephrectomy develop metastases within a 3-year follow-up (A0001).[34]

Half of the patients diagnosed with RCC have no or non-specific symptoms. The most frequent symptoms are gross haematuria, flank pain and palpable abdominal mass.[1,35,36] Anaemia, hepatic dysfunction, persistent fatigue, and weight loss occur in approximately 20-50% of patients with advanced and/or metastatic RCC at the time of diagnosis (A0005).[35,37]

The renal cancers are predominantly diagnosed by abdominal ultrasound or computed tomography.[1] Renal biopsy is performed to confirm the diagnosis and to determine the type and grade of malignancy (A0024).[1,3,4] The current standard of care for RCC is nephrectomy followed by systemic therapy of metastatic disease. Chemotherapy as monotherapy is not considered an effective alternative.[1] Patients with lung-only metastases, good prognostic features and good performance status are more likely to benefit from cytoreductive nephrectomy.[4] In patients with resectable tumours and a good performance status the resection of metastases is recommended.[1,3] Radiotherapy can have a role in palliation in selected patients with brain and osseous lesions.[1,3]

There are six targeted agents available for the treatment of advanced or metastatic RCC: sunitinib, sorafenib, bevacizumab plus IFN-α, pazopanib, temsirolimus and everolimus. According to most treatment guidelines[3,9,38], sunitinib, bevacizumab plus IFN-α and pazopanib are indicated for the first-line therapy in patients at low and intermediate risk (according to the Memorial Sloan-Ketttering Cancer Center risk system) whereas

temsirolimus is recommended as first-line treatment in high risk patients. Sorafenib and pazopanib are recommended as second-line treatment after cytokine failure (even if sunitinib is also recommended by the National Comprehensive Cancer Network in these patients– see result card A0025) and everolimus is recommended as second-line treatment following tyrosine kinase inhibitors.[1,9,10] Monotherapy with IFN-α or high-dose bolus interleukin 2 should be administered for selected patients (A0025).[1,4]

The future consumption of pazopanib in Europe, considering the scenario with the highest level of penetration (40%) and the scenario with the lowest level (10%) was estimated to be respectively 452 mg and 113 mg per 100,000 inhabitants (A0011). It was not possible to analyse variations in use across countries. However variations in use are expected according to the different coverage decisions (A0012).

Pazopanib is in an early approval phase; it was granted conditional authorisation on 14 June 2010 in Europe.[39] In the USA, the Food and Drug Administration granted approval to pazopanib for the treatment of advanced RCC on 19 October 2009.[40] It has also been approved in Canada, Australia and New Zealand (A0020).[41-43] Pazopanib is reimbursed in 14 of the 17 countries investigated. In some of the countries where it is not reimbursed special arrangements, such as reimbursement on a case by case basis, can lead to reimbursement in exceptional cases. In addition, in many of the countries in which it is reimbursed restrictions (such as indication restrictions) are applicable (A0021).

By December 2012 the data collection for the primary outcome measure (progression free survival) of a clinical phase III study, which compares directly pazopanib and sunitinib in the treatment of locally advanced and/or metastatic RCC (COMPARZ) will be concluded and the study will be completed by December 2014 (A0019).[18] .

3.2.3. Discussion

The two hypothesised scenarios of future pazopanib consumption may be affected by:

- the different disease incidence rates across countries
- the market penetration of other therapies for the same indications
- reimbursement decisions for the other therapies for the same indications (in the UK sorafenib and bevacizumab obtained a negative recommendation in 2009 thus sunitinib is considered the standard of care)
- reimbursement decisions for pazopanib in terms of level of coverage and recommended therapeutic indications (in the UK pazopanib is recommended only as first-line treatment for advanced metastatic RCC)

It should also be taken into account that the incidence of the disease increases yearly by about 2% (See research question A0023-Target condition). Moreover the results of the ongoing trials could have an impact on the future penetration of pazopanib.

Because of the recent approval and the different time of coverage decisions it was not possible to analyse the variations in use across countries/regions/settings but this could be done when more data on consumption become available.

3.3. Description and technical characteristics of technology

Authors: Diane Balzan, Anna Bucsics, Sylvana Magrin Sammut, Bernardette Rossi, Isabelle Zahra Pulis, Eva Zebedin-Brandl

3.3.1. Methods

Research questions

Element ID	Research question
B0001	What is this technology which is to be assessed?
B0002a	What is the approved therapeutic indication of pazopanib and what is its main scope of use?
B0002b	What are the main potential advantages of pazopanib compared with standard treatment for metastatic renal cell carcinoma? (mode of action, treatment compliance, safety profile)
B0003	What is the stage of development of pazopanib? (Introduction into clinical setting, indication, regulatory status, awaiting clinical trials, potential uses apart from approved indication, combination treatment)
B0004a	Who can decide to initiate pazopanib treatment?
B0004b	For which patients can the treatment be initiated?
B0005	At which level(s) of health care (self-care, primary, secondary, tertiary) and in which setting (inpatient, outpatient) will the technology be used?
B0010	What kind of data and records (patient level) are needed to monitor the use of the technology?
B0011	What kind of register (population level) is needed to monitor the use of the technology? Are there existing registries that should be used, or should a registry be established, to collect the necessary data?

Sources

- Literature from basic search
- Manufacturer's submission file
- Summary of Product Characteristics (SPC) pazopanib
- European Public Assessment Report (EPAR) pazopanib
- Guidelines for the treatment of RCC

For some issues e.g. RCC treatment guidelines, RCC staging, and RCC registries, a more specific search was done, such as a search for articles in peer-reviewed journals. This was done in order to confirm the results obtained earlier.

The databases used for more specific searches were PubMed, Cochrane, Database Google Scholar and EMBASE.

Search terms and sources used to answer some research questions:

- European Medicines Agency site, Pazopanib – Votrient-SPC and Marketing Approval
- Pazopanib reviews
- Pazopanib +metastatic renal cell carcinoma
- Pazopanib vs sunitinib +RCC
- Pazopanib vs interferon alpha + RCC
- Pazopanib + advantages + RCC
- Pazopanib + ongoing studies (what phase of studies will be used and including how many participants, done in which countries, etc.)
- NICE guidance + pazopanib (and then search for prescriber criteria recommended)
- Pazopanib + cautions + RCC
- Pazopanib + monitoring + RCC

- Pazopanib + therapy initiation + RCC
- Combination treatment + RCC + Pazopanib
- Pazopanib + monotherapy + RCC
- Pazopanib + monotherapy vs combination therapy + RCC
- Pazopanib vs sunitinib clinical trial
- Pazopanib sunitinib sorafenib mechanism of action
- Pazopanib signal transduction
- Pazopanib pharmacokinetics
- Pazopanib interaction
- Pazopanib dose finding
- Pazopanib toxicity
- Pazopanib tumour models
- Pazopanib sunitinib sorafenib dose response

Quality appraisal

- The Jadad scale was used to assess the quality of some published clinical trials with regard to random assignment, double blinding and flow of patients.
- On the other hand - as most research questions could be answered directly by using the SPC and EPAR - no further formal quantitative or qualitative method to appraise the data was used.
- For quality assessment of pre-clinical data, the following criteria were applied:
  - Peer-reviewed publication
  - Conventional hierarchy of evidence (impact points)
  - Date of publication
  - Is the methodology suitable to reliably answer the research question?
  - Is the result statistically significant?
  - What is the clinical relevance of the result?
  - Is there more than one publication to answer research questions? If yes, data needs to be synthesised and discrepancies resolved
  - List of publications of corresponding author (which serves as an indicator of the level of involvement/expertise of the author)
  - Independently financed studies were preferred.

Synthesis

Most of the research questions could be answered in plain text format. In addition, evidence tables were used in some instances. The data volume by itself was minimal and therefore there was no need to use the European Medicines Agency format.

3.3.2. Summary of main results

- Pazopanib is an orally administered antineoplastic agent that targets multiple tyrosine kinase-coupled receptors, which are involved in angiogenesis, tumour growth and metastatic progression of cancer. Thus pazopanib is regarded as a typical tyrosine-kinase inhibitor. In particular, it inhibits vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR) and c-KIT (B0003).[8]

- The recommended daily dose of pazopanib is 800mg administered orally once daily as a film-coated tablet. Pazopanib should be taken without food, at least 1 hour before or 2 hours after a meal and should be taken whole with water and not broken or crushed. To date pazopanib is approved only for adult patients.[44]

- In June 2010, the European Medicines Agency granted conditional approval of pazopanib (Votrient®) for the treatment of advanced and/or metastatic RCC as first-

line treatment or after initial cytokine-based therapy has failed. This has been renewed for another year from June 2011. In the meantime the marketing authorisation holder will complete a number of clinical trials the results of which will be taken into account in the risk–benefit balance during the assessment of the renewal application (B0003).[7]

- The current standard of care for RCC is nephrectomy followed by systemic therapy for metastatic disease (B0002a). [7] Cytokines and targeted agents are used as treatment in RCC patients.

- Current therapeutic alternatives to pazopanib are:
    - Sunitinib (indicated for the treatment of advanced and/or metastatic RCC in adults[45]
    - Sorafenib (indicated for the treatment of patients with advanced RCC who have failed prior IFN-α or interleukin-2 based therapy or are considered unsuitable for such therapy)[46]
    - Bevacizumab (in combination with iIFN-α-2a for first-line treatment of patients with advanced and/or metastatic RCC)[47]and
    - Cytokines

- Clinical trials for indications other than RCC involving pazopanib are ongoing.[48] They address a variety of diseases and combinations of pharmaceuticals.

- Pazopanib treatment should be initiated by a physician experienced in the administration of anti-cancer pharmaceuticals.[44] As pazopanib is administered orally at a fixed dose it can be given in an outpatient setting.

- There is an ongoing head-to-head trial testing the non-inferiority of pazopanib versus sunitinib (VEG108844) and a sub-study (VEG113078) investigating the comparative efficacy of the two first-line agents pazopanib and sunitinib.[18]

3.3.3. Discussion

A number of targeted agents for the treatment of RCC have been approved but there are no direct comparative data available with these agents. It is currently unclear how to choose an appropriate therapy clinically, considering the current information available about the efficacy and safety or pazopanib and other agents.

3.4. Safety

Authors: Marc Van de Casteele, Maria Auxiliadora Castillo, Luisa Muscolo

3.4.1. Methods

Research questions

Element ID	Research question
C0001a	What are the adverse events with pazopanib in renal cell cancer patients and other diseases? What is their type and frequency, seriousness and severity? What are the death rates and discontinuation rates due to adverse events?
C0001b	What adverse events occurred with the approved doses of pazopanib?
C0002	Was there any relationship between the adverse event rate and the daily dose of pazopanib?
C0005	What safety issues can be suspected in elderly patients or other vulnerable groups?
C00062	What precautions need to be taken in sensitive patient populations?
C0007a	What are the known interactions of pazopanib use?
C0007b	Is a Risk Management Plan required for implementing pazopanib?
C0008a	What are the adverse events of pazopanib in renal cancer in comparison with the tyrosine kinase inhibitor sunitinib?
C0008b	What are the adverse events of pazopanib in renal cancer in comparison with bevacizumab (first line)? What are the adverse events of pazopanib in renal cancer in comparison with interferon-alfa or aldesleukin (first line)? What are the adverse events of pazopanib in renal cancer in comparison with the tyrosine kinase inhibitor sorafenib (second line)?

Sources of information

We used the basic search prepared for this pilot. Particular attention was paid to head-to-head comparative safety, but placebo-controlled trials were included, as well as observational studies (especially cohorts and case reports) of pazopanib safety to retrieve rare and long-term adverse drug reactions of pazopanib.
Moreover, we used

- the Risk Management Plan of the European Medicines Agency ,
- latest warnings from the regulatory sources, the European Medicines Agency and the Food and Drug Administration on pazopanib use, and
- information from abstracts presented at congresses and not published as full papers (American Society of Clinical Oncology and European Society for Medical Oncology abstracts).

Additional issue-specific searches were performed for dose relatedness of harms (C0002) and harms for elderly and other vulnerable patients (C0005). We did not seek information from national or other registries of renal cancer patients, or personal communication of patients' experiences, e.g. on internet blogs about pazopanib use in practice, because of suspicion of selection bias for this new molecule.

The following safety information was identified, which added to what was already known from the SPC and EPAR of pazopanib:

- Direct comparison versus placebo in the key randomised controlled trial (RCT; first-line and second-line treatment)
- Direct comparison versus placebo in the Aberdeen subgroup analysis of first-line treatment
- EPAR-pooled study data of three pazopanib trials in renal cancer plus phase I study data
- Indirect comparison by comparing the SPCs of comparators
- Indirect quantification of adverse events of comparators
- Food and Drug Administration self reporting on real life harm

Quality appraisal

We used the methodological guidance presented in the draft Safety Guideline produced by EUnetHTA Joint Action WP5 (Cangini et al; 1 June 2011 version). The quality of safety reporting (grading severity of adverse events) was evaluated by checking what definitions were used to report adverse events in individual RCTs. Both the risks of bias in the studies and the quality of data on adverse events was evaluated using the SIGN checklists, the National Cancer Institute scale for RCTs, and the STROBE checklist for observational studies.

Analysis

In this safety report we focus on the safety profile characterisation of pazopanib as compared with other treatment alternatives. Adverse events are given by organ system categorised by frequency (5 to 10 most frequent adverse events) and seriousness and severity, and reported in a table in accordance with the European Medicines Agency scheme. A more precise description for adverse events is given according to MedDRA Dictionary Terminology.

Characteristics (number of participants, age, sex, country, the study design, follow-up period, dose, mode of administration and duration of pazopanib treatment, outcomes, notes and setting of safety issues) were retrieved from each study. All patients who had been randomly assigned to a study group and had received at least one dose of study medication were included in the analysis. The number of participants with adverse events, absolute risk, relative risk and risk difference (with 95% confidence intervals) are provided. The number needed to harm (NNH) is given when there are statistically significant differences between the treatment groups in any adverse event in the RCTs. Moreover, safety reasons for patients discontinuing are reported. Safety characteristics are summarised in a table following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).

Particular attention is paid to head-to-head safety data. Causality between pazopanib use and adverse events is interpreted cautiously when data is retrieved from indirect comparison. No distinct safety data for first-line use of pazopanib versus second-line use were available. A subgroup of patients treated with first-line pazopanib were separately studied by the Aberdeen HTA Group.[11] The absence of separate safety data in first -line and second-line use of pazopanib hampers indirect comparisons in second-line use.

3.4.2. Summary of main results

Common and typical adverse events of pazopanib in first- and second-line use are gastrointestinal symptoms such as decreased appetite, diarrhoea, vomiting, abdominal pain and nausea, as well as liver function disturbances, proteinuria, hypertension, fatigue and hair depigmentation (C0001a).[7,8] Small numbers needed to harm (NNH) were obtained for diarrhoea (NNH 3), hypertension (NNH 4), liver function disturbances (NNH 4 ALT and 3 AST), neutropenia (NNH 4) and thrombocytopenia (NNH 4) (C0001a).

Severe adverse events occurred in every third patient treated with pazopanib, first- and second-line combined.[8] Grade 3 adverse events were present in 33% of the patients in the pazopanib group and 14% in the placebo group. For Grade 4 adverse events the corresponding figures were 7% and 6%.[9] In the subgroup of first-line treatment only, the percentages of Grade 3 adverse events were 37% for pazopanib and 13% for placebo; for Grade 4 it was 6% in both arms. (C0001a).[29] Diarrhoea and hypertension were the most

frequent reasons to reduce the dose of pazopanib. Hypertension was well managed by antihypertensive medication (C0002).[49]

Serious adverse events occurred in 24% of pazopanib (first- and second-line) treated patients versus 19% in the placebo group.[7,8] In the subpopulation with first-line treatment only the corresponding percentages were 21% and 17%.[29] The most frequent serious adverse events were myocardial ischaemia, gastrointestinal perforation and haemorrhages. Twelve percent of patients on pazopanib had serious pazopanib related adverse events such as brain or myocardial ischaemia and liver failure. The withdrawal rate was 15% for pazopanib and 6% for placebo. The most frequent reasons for discontinuing treatment for safety reasons were diarrhoea and liver function disturbances.[8] Mortality was 4% with pazopanib and 3% with placebo (C0001a).[7,29] Fatal events included gastrointestinal and pulmonary haemorrhage, liver failure, intestinal perforation and ischaemic stroke (C0001a, C0001b).[8,40] "New" causes of treatment-related deaths, such as epilepsy from cerebral metastases have been reported (C0001b).[40]

As grade 3 adverse events occurred more frequently in the pazopanib group compared with placebo, this could suggest a loss of quality of life for patients in whom this occurred. However, there was no statistically significant difference in quality of life during use of pazopanib versus placebo, as measured by questionnaire. In other words, for the overall group of pazopanib-treated patients, quality of life was neither worse, nor better compared with patients treated on placebo (C0001a).[7]

Caution is warranted for numerous patient groups, including those on medications which are Cytochrome P450 3A4 inhibitors (C0007a) as well as patient with previous liver[12] and cardiac dysfunction.[10] Frequent monitoring of liver function tests, thyroid function and other laboratory tests is required to avoid safety problems as far as possible (C0062)[12].

There was no difference in the frequency of adverse events between pazopanib and the comparators in quantitative indirect comparisons (C0008a, C0008b). However, there are some descriptive differences in the adverse event profiles identified in indirect comparisons. For sunitinib (first line) (C0008a)[8,29] and sorafenib (second line) (C0008b)[7,29,31] a high rate of decreased blood cell count, hypothyroidism, stomatitis and palmar-plantar erythrodysesthesia syndrome were reported. Interleukin (first line) showed a high rate of headache, dizziness, confusion, hypotension, erythema, thrombocytopenia, pyrexia and pruritus (C0008b).[7,26] Interferon alpha (first line) and combined therapy with IFN-α plus bevacizumab (first line) showed high rates of nausea and asthenia, and the combined therapy had a discontinuation rate of 1 out of 4 patients because of proteinuria, headache, haemorrhage or dyspnoea (C0008b).[7,26,27]

3.4.3. Discussion

In pazopanib trials patients were in better condition (Eastern Cooperative Oncology Group [ECOG] performance status 0 or 1) compared with patients from registries (ECOG performance status 0 or 4). This raises the question of how comparative or generalisable the results are. For patients with performance status worse than ECOG 1, pazopanib safety data are lacking. So, there is no head-to-head evidence to position pazopanib as better tolerated or less well tolerated compared with each of the alternatives.

More head-to-head RCTs and large observational studies and data are required to confirm the findings of indirect comparisons, and facilitate more robust conclusions. A comparative study of pazopanib versus temsirolimus in poor-risk patients has been announced. An ongoing study comparing pazopanib versus sunitinib (COMPARZ) should clarify in the future which first-line option has the more favourable adverse-event profile. The final data collection for the primary outcome was in December 2011 and the estimated study completion date is May 2013. In addition, an ongoing head-to-head randomised trial

(PISCES) is comparing patients' preferences between pazopanib and sunitinib. For second-line treatment, no head-to-head comparative data are expected in the near future.

3.5. Clinical effectiveness

Authors: Piia Peura, Vesa Kiviniemi, Tuomas Oravilahti, Pertti Happonen, Simona Montilla, Pauline Vitré

3.5.1. Methods

The methods used in this domain are described in three Method cards in the clinical effectiveness section of Appendix 1 plus the tables attached, and in the methods sections of each result card. There are three method cards in Appendix 1:

- Description of evidence base (Method card 1, Appendix 1) ;
- Risk of bias (Method card 2, Appendix 1); and
- Applicability (Method card 3, Appendix 1).

The methods card is a new feature in Core HTA production, proposed by this team, and is, therefore, applied only in this domain.

Research questions

The following research questions were formulated and answered in this domain:

Element ID	Research question
D0001	*Treatment-naïve patients:* In patients with advanced or metastatic renal cell carcinoma, what is the effect of pazopanib on overall survival (OS) compared to sunitinib, bevacizumab plus IFN-α and IFN-α? *Cytokine pre-treated patients:* In patients with advanced or metastatic renal cell carcinoma, what is the effect of pazopanib on overall survival compared to sorafenib?
D0006	*Treatment-naïve patients:* In patients with advanced or metastatic renal cell carcinoma, what is the effect of pazopanib on progression free survival compared to sunitinib, bevacizumab plus IFN-α and IFN-α? *Cytokine pre-treated patients:* In patients with advanced or metastatic renal cell carcinoma, what is the effect of pazopanib on progression free survival compared to sorafenib?
D0005	*Treatment-naïve patients:* In patients with advanced or metastatic renal cell carcinoma, what is the effect of pazopanib on response rates* compared to sunitinib, bevacizumab plus IFN-α and IFN-α? *Cytokine pre-treated patients*: In patients with advanced or metastatic renal cell carcinoma, what is the effect of pazopanib on response rates* compared to sorafenib? * Overall response rate (complete response + partial response), duration of response, time to response
D0012	*Treatment-naïve patients:* In patients with advanced or metastatic renal cell carcinoma, does the use of pazopanib compared to sunitinib, bevacizumab plus IFN-α and IFN-α improve health-related quality of life? *Cytokine pre-treated patients:* In patients with advanced or metastatic renal cell carcinoma, does the use of pazopanib compared to sorafenib improve health-related quality of life?
D0013	*Treatment-naïve patients:* In patients with advanced or metastatic renal cell carcinoma, does the use of pazopanib compared to sunitinib, bevacizumab plus IFN-α and IFN-α improve cancer-specific quality of life?

Element ID	Research question
D0017	*Cytokine pre-treated patients:* In patients with advanced or metastatic renal cell carcinoma, does the use of pazopanib compared to sorafenib improve cancer-specific quality of life? *Treatment-naïve patients:* Do patients with advanced or metastatic renal cell carcinoma prefer using pazopanib instead of sunitinib, bevacizumab plus IFN-α and IFN-α? *Cytokine pre-treated patients:* Do patients with advanced or metastatic renal cell carcinoma prefer using pazopanib instead of sorafenib?

Domain framing

The frame of the clinical effectiveness domain is in line with the general scope of the assessment. As first-line treatment of advanced or metastatic RCC (treatment-naïve patients) the clinical effectiveness of pazopanib is compared with sunitinib, bevacizumab plus IFN-α, IFN-α and best supportive care. As a treatment after prior cytokine therapy (cytokine pre-treated patients) pazopanib is compared with sorafenib. Sunitinib is also indicated for cytokine pre-treated patients; however, based on the recommendations of the European Association of Urology[1], sunitinib was not included as a comparator in the clinical effectiveness domain.

The clinical endpoints included in the assessment are

- overall survival,
- progression free survival,
- response rates (complete response, partial response), duration of response)
- generic and disease-specific health-related quality of life, and
- patient preference

From the decision-maker's point of view overall survival and health-related quality of life are important endpoints. Progression free survival is also considered to be an important intermediate endpoint if it predicts overall survival in metastatic RCC or it is substantiated that health-related quality of life in progression free patients is significantly higher than in patients with progression.

3.5.2. Summary of main results

Pazopanib was not compared with any of the active comparators (sunitinib, bevacizumab plus IFN-α, IFN-α, or sorafenib) in a randomised trial. However, one study (VEG105192) directly comparing pazopanib with best standard care was identified.[8] The VEG105192 enrolled 233 treatment-naïve patients (pazopanib: n = 155, best supportive care: n = 78) and 202 cytokine pre-treated patients (pazopanib: n = 135, best supportive care: n = 67) (D0001).

For the treatment-naïve population in the VEG105192 study, the unadjusted Kaplan-Meier estimate for median (95% CI) overall survival was 22.9 (17.6, 25.4) months in the pazopanib arm, compared with 23.5 (12.0, 34.3) months in the placebo arm.[8] There was no evidence of any differences in overall survival between pazopanib and best supportive care (Table 3) even though crossover between therapies during the study was taken into account (D0001). The estimate for median progression free survival (95% CI) was 11.1 (7.4, 14.8) months in the pazopanib arm, compared with 2.8 (1.9, 5.6) months in the placebo arm (D0006).

The hazard ratio (HR) for overall survival in the cytokine pre-treated population is 0.82 (0.57-1.16) (D0001). For the cytokine pre-treated patients the estimate for median progression free survival was 7.4 months in the pazopanib arm, compared with 4.2 months in the placebo arm; HR (95% CI) = 0.54 (0.35, 0.84) (Table 3) (D0006).

In the treatment-naïve population pazopanib was indirectly compared with IFN-α through one common comparator (best supportive care), and with both sunitinib and bevacizumab plus IFN-α through two common comparators (best supportive care and IFN-α). In the cytokine pre-treated population pazopanib was indirectly compared with sorafenib through one common comparator (best supportive care). Data from five IFN-α studies[20-24], one sunitinib study[25], two bevacizumab plus IFN-α studies[26,27] and one sorafenib study[28] were utilised in the indirect comparisons. Table 3 summarises the main results. The results of the sensitivity analyses were similar to those reported in Table 3.

Table 3. Summary of the main results of the assessment (see ID D0001& D0006).

	Endpoint	HR (95% CI)	Quality of body of evidence (GRADE)[5]
Treatment-naïve patients			
Pazopanib vs. BSC[a]	OS	0.50 (0.14, 2.35)	Low[e]
Pazopanib vs. IFN-α[b]	OS	0.63 (0.17, 2.27)[c]	Very low[e]
Pazopanib vs. sunitinib[b]	OS	0.97 (0.36, 2.61)[c]	Very low[e]
Pazopanib vs. *Bevac* + IFN-α[b]	OS	0.73 (0.20, 2.65)[d]	Very low[e]
Pazopanib vs. BSC[1]	PFS	0.40 (0.27, 0.60)	High[e]
Pazopanib vs. IFN-α[b]	PFS	0.51 (0.33, 0.80)[c]	Low[e]
Pazopanib vs. sunitinib[b]	PFS	0.95 (0.58, 1.57)[c]	Very low[e]
Pazopanib vs. Bevac + IFN-α[b]	PFS	**0.79 (0.50, 1.25)**[d]	Very low[e]
Cytokine pre-treated patients			
Pazopanib vs. BSC	OS	0.82 (0.57-1.16)	-
Pazopanib vs. sorafenib	OS	No data	-
Pazopanib vs. BSC[a]	PFS	0.54 (0.35, 0.84)	High[e]
Pazopanib vs. sorafenib[b]	PFS	1.00 (0.62, 1.60)[d]	Low[e]

Abbreviations: Bevac= bevacuzimab; BSC = best supportive care; PFS = progression free survival; OS = overall survival

[a] The effect estimates (HR, hazard ratio) for pazopanib vs. BSC are based on direct head-to-head comparison within the VEG105192 trial

[b] The effect estimates for these comparisons are based on anchored indirect comparison

[c] The data is from the analysis provided by the manufacturer

[d] The data is from the analysis conducted by the assessors

[e] Quality of body of evidence has been rated using the GRADE approach. Details are presented in Table 68 (OS) and Table 74 (PFS) in the appendix. Quality of evidence reflects the extent of assessors' confidence that the estimates of the effect are correct. **High** = We are very confident that the true effect lies close to that of the estimate of the effect; **Moderate** = We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **Low** = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; **Very low** = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

There was no significant difference in the quality of life of patient treated with pazopanib vs best supportive care. For other comparators no comparative data on quality of life are available (D00012&D0013).

An ongoing randomised controlled trial comparing pazopanib with sunitinib (VEG108844, COMPARZ) in treatment-naïve patients is expected to provide more evidence for decision makers.[18] The results are expected to be reported in 2012.

3.5.3. Discussion

Based on the current evidence, it seems that there is no significant difference in the overall survival between pazopanib and its comparators. However, reliable effects on overall survival effect can be difficult to obtain due to insufficient duration of follow-up. Patients in the control arm may be allowed to crossover to the treatment arm to receive the active agent or they can be treated with similar second or third line agents that may lead to dilution of the overall survival benefit. As early as only 5 or 10 months after randomisation many patients receiving placebo had crossed over to receive pazopanib therapy or another anti-cancer therapy in the VEG105192 study. At the time of the clinical cut-off (15 March 2010) 64% of the treatment-naïve patients in the placebo arm and 34% of those in the pazopanib arm had received further anti-cancer therapies. Crossover between therapies in the VEG105192 study made the interpretations of overall survival data comparing pazopanib and best supportive care challenging since various statistical techniques or other methodological approaches were applied to deal with the crossover. However, irrespective to the approach or technique used, there is no clear evidence that pazopanib would differ from best supportive care in terms of overall survival.

Based on the results of the VEG105192 –trial, pazopanib improves progression free survival when compared with best supportive care in treatment-naïve patients and in cytokine pre-treated patients. In addition, the indirect comparison provided evidence of significant differences in the progression free survival between pazopanib and IFN-α. However, our confidence in this estimate is limited. Progression free survival is commonly used as a surrogate to predict overall survival in cancer. In addition to avoiding the shortcomings of overall survival measurements caused by subsequent treatments or crossovers, it has the benefit of shortening the duration of the trial. Progression free survival is considered to be an important intermediate endpoint if it predicts overall survival in metastatic RCC or it is substantiated that health-related quality of life in progression free patients is significantly higher than in patients with progression. However, a robust comparison of survival and progression free survival is difficult, and there are different opinions regarding the surrogacy of progression free survival for overall survival in the treatment of RCC.

There are no studies directly comparing pazopanib with its comparators. For that reason, methods of indirect comparison were used in the evidence synthesis. The validity of the indirect comparison rests on the assumption of similarity. In other words, if the trials included in the evidence synthesis differ, and the differences are modifiers of relative treatment effect, the results of the indirect comparison are biased. When the quality of evidence is rated using the GRADE approach, indirect comparison always warrants rating down by one level of evidence (e.g. from high to moderate).

The evidence on the effects of pazopanib in patients with advanced and/or metastatic RCC is from RCTs. In the current assessment process, no data from so-called “real life” studies was identified. Therefore judgments about whether the available research evidence reflects the expected results in “real life” practice are based on the results of RCTs. This was done by assessing the applicability of these studies. In the current assessment process, the characteristics that may affect applicability (i.e. effect modifiers) were extracted from individual studies. Because the applicability of the body of evidence might differ in different clinical settings (due to differences in the distribution of the effect modifiers), judgements about major limitations of the applicability of individual studies should be made on a national level. To facilitate this, evidence on current treatment practices should also be assessed and reported at national level.

3.6. Ethical analysis

Authors: Dario Sacchini, Pietro Refolo, Roberta Minacori

3.6.1. Methods

Research questions

Element ID	Research question
F0002	Could the use of pazopanib (and its application/administration) challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?
F0003	What might be the hidden or unintended consequences of the use of pazopanib and its applications for different stakeholders?
F0004	Does the implementation or use of pazopanib challenge patient's autonomy?
F0005	Is pazopanib used for patients/people who are especially vulnerable?
F0006	Could pazopanib (and its application/administration) entail special challenges/risks that the patient/person needs to be informed of?
F0007	Does the implementation of pazopanib challenge or change professional values, ethics or traditional roles?
F0011	Could pazopanib (and its application/administration) benefit or harm any other stakeholders?
F0014	Does the implementation or use of pazopanib affect the realisation of basic human rights?

Information sources

Information was used from the result cards of other domains within this project, published literature, and discussions with the members of WP5. For resource and competence reasons there was no opportunity to elicit primary data (e.g. patients reported outcomes within clinical trials).

Apart from the basic search, a domain-specific literature search was performed for pazopanib and comparators in RCC, and another search for similar technologies and similar conditions, using the search terms: (ethics OR bioethics OR beneficence/nonmaleficence, autonomy, human dignity, human integrity, justice, equity, rights) AND (pazopanib AND renal cell carcinoma) (details in Appendix).

Quality appraisal

Not applicable

Analysis

Narrative

3.6.2. Summary of main results

The use of pazopanib does not appear to alter patients' autonomy (F0004). Even so, patients with advanced RCC need to be considered as "fragile subjects" for several reasons: the clinical condition, eventual co-morbidity, the decline of physical and psychological condition, and treatment-related side effects. Moreover, they may carry a sense of frustration and discomfort that affects their personality (F0005).[12-14] Choosing a pharmaceutical and

balancing the risks and benefits'is primarily the responsibility of the physician, with the patient's freely given consent based on adequate information (F0004-0006).

Implementing pazopanib does not require crucial modifications at the organisational level nor additional special training for healthcare professionals. The current treatment options already require attention to be paid to adverse events management and careful routine pharmacovigilance (F0011).[50-51]

Oral administration is generally perceived as a benefit for the patient, carer and health system, as it may reduce the number of clinic visits or stays. However, there may be negative effects on motivation and compliance via reduced contact with health professionals (F0006).[51,52] Implementing pazopanib might, therefore, require added monitoring of patients' needs and compliance with the therapy, e.g. through a call centre and oncologic tele-consulting for doubts and problems, or a therapeutic diary and pill counts (F0011).[13-15]

Pazopanib is in direct competition with other pharmaceuticals for the treatment of advanced RCC. Manufacturers should, when pricing a product for a condition such as RCC, ensure that the price is set fairly, acknowledging the mix of factors including the extent of disease burden, the extent to which medical need is being met, the extent to which the new technology offers advantages over existing treatments, and the quantity and quality of the evidence supporting those differences. At the same time, competition among the manufacturers of pharmaceuticals for the treatment of the same disease may lead to increased earnings and/or less or missed profits (F0011).[11,51]

3.6.3. Discussion

The following points of debate are highlighted from the ethical point of view:

- No head-to-head trials comparing the efficacy of pazopanib with other active treatment options are currently available (see Clinical Effectiveness and Safety domains). Missing evidence especially on quality of life outcomes inhibits a decisive ethical judgment.

- Some of the recent clinical guidelines include pazopanib as a promising treatment for RCC, while others do not. It is of ethical relevance to reach a shared understanding of the beneficence/non malefience profile of pazopanib in relation to its comparators, in order enhance equality among the patients in need.

- There are doubts about whether standard methods of HTA are suitable for the evaluation of pharmaceuticals for rare diseases because it is difficult to conduct large randomised trials in order to gather adequate evidence on efficacy. Including ethical beneficence/non-maleficence considerations in an HTA of rare diseases can therefore be especially relevant.

3.7. Organisational aspects

Authors: Rossella Di Bidino, Marjetka Jelenc, Matteo Ruggeri

3.7.1. Methods

Research questions

Element ID	Research question
G0001	What kind of work flow, patient flow and other processes are involved in the use of pazopanib?
G0003	What kind of staff, training, other human resources, and special arrangements are required for RCC treatment with pazopanib compared to comparators?
G0005	Are there requirements for level of care or centralisation in the implementation of pazopanib?
GXXY	What kind of monitoring systems need to be organised when introducing pazopanib?

Sources

The Organisational domain used information from:

1. Scientific literature including specific publications focused on organisational aspects;
2. Result cards of other domains in this project (from published data, preferably)

In addition to the basic search performed for the project, a domain-specific search for organisational studies was performed. Search terms used: organisational, management, monitoring system, indicator, training, patient pathway, planning and control system, patient access scheme; referring to pazopanib and/or its comparators and/or RCC. Special attention was given to training implications and monitoring systems.

Additionally, research question specific searches were done for assessment elements G0003 and GXXY.

Quality Appraisal

The main sources of information were guidelines and HTA reports, and no quality assessment of them was conducted. Transferability of data was assessed taking into account how differences among national health systems could impact the information available and provided. Items related exclusively to the characteristics of the technology were considered fully transferable.

Analysis

We identified relevant data through qualitative review of published evidence. Priority was given to studies conducted in real clinical settings and case studies. A descriptive synthesis of available information was performed. Critical points were identified and assessed by HTA experts, some of whom have clinical backgrounds.

3.7.2. Summary of main results

Implementing pazopanib does not require particular changes in the management pathway of RCC compared with the other targeted therapies (G0001&G005).[11] Pazopanib treatment should only be initiated by a physician experienced in the administration of anti-cancer agents. Similar to sunitinib, it can be provided in an outpatient setting, since it is a fixed-dose oral.[11] The introduction of pazopanib should incur no additional hospital visits

compared with the administration of sunitinib (G0003). When the decision to treat a patient with pazopanib is taken, treatment is continued until disease progression or toxicity, patient's decision or death. No additional special training is required for oncologists or urologists with experience in managing patients with renal cancer (G0003).

Routine liver function tests, urinalyses, and cardiological tests are required. Particular monitoring requirements are advised for specific groups of patients (GXXY).[29,53,54]

Adequate attention needs to be given to monitoring and managing pazopanib-specific adverse events, and its real-life effects. Monitoring harms at the macro level will be realised through the common pharmacovigilance activity. Monitoring at an organisational level would benefit from a specific database of clinical monitoring results in order to evaluate the efficacy and effectiveness of pazopanib treatment and assess, as early as possible, the presence of related adverse events. Prescription of pazopanib under strict protocols only could further help to assess effectiveness in real clinical practice (see GXXY). [29,53,54]

3.7.3. Discussion

There were only a few studies that involved pazopanib as the therapeutic option for metastatic renal cell cancer and which described the workflow in detail (e.g. setting, people, steps). Furthermore, evidence about real clinical practice was not available. The currently available information is transferable at the European level.

In the future there is a need to collect evidence on effectiveness and service provision in real clinical settings. National regulatory agencies could define pazopanib-specific risk sharing schemes and link the safety profile to the negotiated price.[59]

3.8. Social Domain

Authors: Payam Abrishami (CVZ); Sinikka Sihvo (Finohta/THL); Wim Goettsch (CVZ)

3.8.1. Methods

The departure point for approaching the social domain is that a rapid REA has a limited scope of time, comparison, and comprehensiveness[56] and is meant to guide clinical/reimbursement decision-making. With this scope and purpose, it is reasonable to take a pragmatic approach and focus on 'standard care' as the reference for comparison. Standard care is the currently accepted standard clinical care, which is most routinely used; the one that the new therapy is intended to replace fully or partially. Among the comparators included in the scoping phase of this pilot REA, sunitinib is thus chosen as the comparator; it is the standard therapy for the first-line treatment of metastatic renal cell carcinoma[11,57] and there are no current standard second-line treatment options[58]. Sorafenib, which is recommended as second-line treatment (after prior cytokine therapy) and defined in the scope of this project, is a tyrosine kinase inhibitor similar to sunitinib. The choice of comparator for examining possible social consequences of the use of pazopanib is, therefore, narrowed down to sunitinib; the standard first-line therapy.

There was only one assessment element in the social domain of rapid REA, which translated into a research question 'Which social areas does the use of pazopanib influence compared with that of sunitinib?'. Unless a safety or efficacy issue is involved, no major differences in social consequences were considered as pazopanib and sunitinib belong to the same therapeutic category. In addition, two patients' forums also revealed no significant patient-related social issues to be considered for this rapid assessment.[59,60] Pazopanib and sunitinib are similar in terms of indication, route of administration, dosing (once-daily), and adverse effects. It was, therefore, concluded that within the scope and the timeframe of rapid pazopanib REA, the single research question of the social domain is not relevant. Consequently, no results (result cards) were developed for this domain.

3.8.2. Summary of results

No results were reported in this domain.

3.8.3. Discussion

Considering the Social Domain 'not relevant' to this project does not mean that the use of pazopanib has no influence on patients' social lives, nor does it mean that the social consequences for patients are unimportant. What it means, however, is that the difference in social consequences is not significant when sunitinib is replaced with pazopanib.

Although the Social Domain is not considered "core" for this rapid REA, a quick evaluation of the issues influencing use from the user's point of view is recommended. In this respect, the following considerations are noteworthy.

- Pazopanib's adverse events compared with sunitinib. When evidence from large-scale head-to-head trial is yet to come, indirect comparison may be considered. In indirect comparisons, the adverse effects of pazopanib and sunitinib are generally comparable (see Safety Domain). An indirect comparison, however, shows that patients experienced adverse effects less frequently with pazopanib than with sunitinib.[11] In a descriptive analysis, the adverse event rates for pazopanib were lower for dyspepsia, mucositis/stomatitis, hand-foot syndrome, skin discolouration, hypophosphataemia, anaemia, and altered taste, and fatigue. But, only the difference in fatigue was statistically significant.

The opinion of patient experts and clinical specialists can also be considered. In the context of NICE's decision-making, the specialists were of the opinion that pazopanib has a more favourable toxicity profile than sunitinib.[11] While pazopanib can be administered for a period of 6 weeks, sunitinib users are often unable to tolerate it after 4 weeks of administration. They require a 2-week rest period and possibly a subsequent dose adjustment to maintain tolerability. This may reduce the benefits gained from sunitinib.[11] In addition, the patient experts highlight that hand-foot syndrome as a result of sunitinib toxicity is frequently an intolerable adverse effect. The reported more favourable toxicity profile of pazopanib might help pazopanib users to have better social functioning.

- Access for patients with physical disability. Sunitinib is recommended for patients with a good performance status, i.e. patients without daily-life disabilities conforming to ECOG performance status score 0 and 1.[57] However, fewer patients with ECOG=0 were recruited to the pazopanib trial that in the sunitinib study. Moreover, in an extension open-label study (VAG107769), patients with ECOG=2 were recruited and permitted to crossover to the pazopanib arm at disease progression.[11] If further evidence confirms that patients with daily-life disabilities (ECOG>1) can benefit from pazopanib, they too may have access to this first-line oral medication.

- Pazopanib's ease of use compared with parenteral alternatives. Pazopanib's oral mode of uptake may have a social advantage due to its ease of use. IFN-α, aldesleukin and bevacizumab are administered intravenously and sometimes subcutaneously. Pazopanib users face no complications of injection and do not have to go regularly to the clinic or hospital for injection or infusion.

Literature on the social consequences of pazopanib (in particular, with a comparative approach) is not available. This is not unexpected given the fact that even for effectiveness and safety more evidence is needed. In fact, the lack of the evidence of the added social value of pharmaceuticals does not mean that it is unimportant for reimbursement or clinical decision-making. The generation of such evidence/methodology is hereby recommended in order to better understand the relative advantages and disadvantages of the use of pharmaceuticals for the patient's social life. Studies of this sort can be carried out concomitantly or in parallel with generating clinical data on effectiveness and safety. This is of particular importance when there are important social issues to consider or an HTA with an extended scope (for instance, a Full Model REA) is intended.

Importance and transferability	How important is this piece of information for decision making? Critical ☐ Important ☒ Optional ☐ How transferable is this piece of information, i.e. can it be used in national decisions as such? Completely ☐ Partly ☒ Not ☐

3.9. Legal Domain

Authors: Sirpa Soini, Paavo Autere

3.9.1. Methods

Scope

Pazopanib has achieved a marketing authorisation at EU level through a centralised procedure, and is entered into the Community Register for Medicinal Products for Human Use under the name *Votrient*.[61]

This domain focuses on the legal framework of the pharmaceutical after centralised market authorisation in the EU. We have considered not only pazopanib but all pharmaceuticals that are subject to the same law because the legal consequences described in the results are the same for all of them.

We shall focus mostly on EU legislation. National systems are relevant for price control and reimbursement, but less significant in other issues, since pharmaceutical law is harmonised in the EU. Hence, member states are obliged to comply with EU legislation. On the other hand, they are not to impose actions that may impede free markets.

In addition, EU Soft law, such as guidelines, declarations, and opinions, may also be relevant. However, due to time constraints we did not examine those for this pilot.

Given the importance of EU legislation in the field of pharmaceuticals since 1965, it is necessary to carefully read the 'scope of application' of each piece of legislation. A basic link to the European Union law (including decisions) is: http://eur-lex.europa.eu/en/index.htm.

Given the limited scope of the legal domain in the pazopanib pilot, we did not perform a systematic search on European Court of Justice (ECJ) praxis as this would require a team of legal experts from various fields, and particularly a legal informatics expert to develop an appropriate search method. The following link leads to the collection of judgements of the ECJ of particular interest for the pharmaceutical sector:
http://ec.europa.eu/health/documents/case-law/index_en.htm.

National price control and reimbursement schemes can affect the use of new pharmaceutical products. We will deal with price control regulation, but national reimbursement systems need to be dealt with nationally in each case as they vary.

Civil liability or drug injury compensation systems are not deemed necessary for HTA decision makers, so we will only comment on this briefly

Research questions

Element ID	Research question
I0003	Which legal rules govern the information that shall be given to the patient on the pharmaceutical?
I0011	Which legal rules govern access to necessary medication?
I0015	What legal consequences does market authorisation through a centralised procedure entail?
I0017	Which legal rules govern the safety of medicinal products?
I0024	Is the pharmaceutical subject to price control?

Sources

We searched in Google Scholar and PubMed and used established legal reference books. For a pragmatic methodological approach it is advisable to consult a reference book in the field, such as Shorthose 2010.[62] For adverse effects, we examined at EU level which rules are relevant to adverse effects (pharmacovigilance).

EU Legislation reference documents in the pharmaceutical sector are available at http://ec.europa.eu/health/documents/eudralex/index_en.htm.

Quality appraisal

Not applicable

Analysis

Narrative

3.9.2. Summary of main results

Law on pharmaceuticals in the European Union is a highly regulated and harmonised field. Member states are obliged to comply with EU legislation, and not to adopt measures that may impede free markets.[63] Non-compliance with EU law, or stricter demands interfering with free markets may result in legal action.

Pazopanib has received a conditional marketing authorisation at the EU level through a *centralised procedure*, and it is entered into the Community Register for Medicinal Products for Human Use under the name Votrient (http://ec.europa.eu/health/documents/community-register/html/h628.htm). The centralised procedure is compulsory for authorising biotechnology-derived and high-technology medicines.[64] The market authorisation holder has stringent responsibilities based on many legislative acts both nationally and at the EU level.

The surveillance of the safety of pazopanib is regulated by EU pharmacovigilance rules that are in place to protect public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the EU market.[64,65] Thus, the marketing authorisation holder has to establish a pharmacovigilance system to ensure the monitoring and supervision of its authorised medicinal products. Specific liability for adverse reactions (drug injuries) is not harmonised in the EU (excluding product liability), and therefore national compensation schemes vary.

The information to be provided to the patient is also regulated. EU law sets requirements for the labelling and package leaflet of the medicinal product.[65] These provisions stipulate in detail the type and content of the information to be given on the package and leaflet. They are required to give accurate and necessary information to the patient in a clearly legible and comprehensible manner. It is not permitted to advertise prescription medications (such as pazopanib) to the general public.

In many member states pharmaceuticals are subject to price control. Member states can organise, manage and finance their health services nationally; including insurance schemes for medication, but these measures should be *transparent*.[66] Price control and reimbursement schemes can limit access to medication in practise; however, an analysis of all the national systems was not performed.

3.9.3. Discussion

We did not consider pazopanib specifically but considered all pharmaceuticals with a centralised EU authorisation status, because the legal consequences described apply to all of them. Thus, the results can be generalised and used for all pharmaceuticals to which market authorisation is granted via a centralised procedure. Further, pharmacovigilance regulation is applied to all medicinal products authorised in the EU.

A centralised procedure allows applicants to obtain a marketing authorisation that is valid throughout the EU. This is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human products containing a new active substance, which was not authorised in the Community before 20 May 2004, and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.

Most of these issues are also related to other domains.

4. Discussion of pilot assessment process: authors' and readers' perceptions

4.1. Introduction

During the pazopanib pilot the feasibility of the new model for rapid assessment of pharmaceutical(s) (Model for Rapid REA) and methodological guidelines of WP5 were tested. At the same time a new collaborative way of working was used. Instead of performing the assessment in the traditional way inside the agency the pilot participants shared tasks with other European HTA organisations and communicated over distances through email messages and e-meetings in English. Moreover, their task was primarily to produce sharable pieces of information for other HTA agencies, and only secondarily a report for decision makers. The content of the pilot report should thus be relevant beyond the national context.

The structure of the Model for Rapid REA, with separate domains for effectiveness and safety assessment, required a separate synthesis balancing the benefits and harms of pazopanib and its comparators. While there is no established methodology for a synthesis of relative effectiveness, the pilot participants had to create this and test it with the topic of pazopanib.

The primary outcome for the pazopanib pilot was:

- Pilot authors' perceptions about the Model for Rapid REA and the methodological guidelines developed in WP5.

The secondary outcomes were:

- Workload and time consumed in the project
- Pilot authors' perceptions on international collaboration
- Report readers' perceptions about the qualities of the pilot report (format of the pilot report, adaptability of information into national purposes, and its readability)

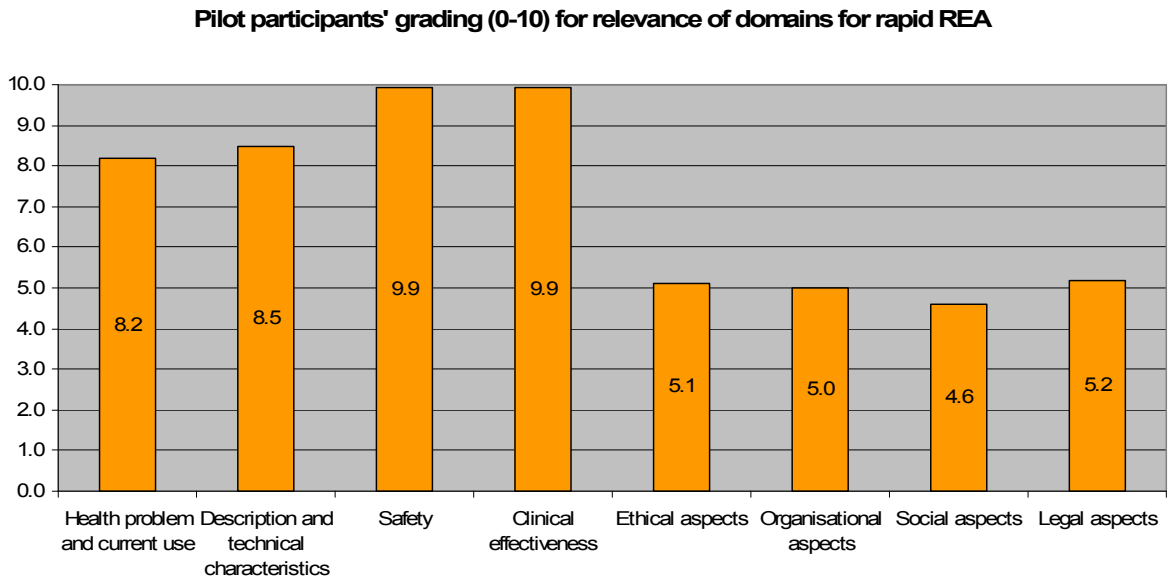
Data for outcomes was collected from pilot participants and partners of WP5 through email queries during the project and a web-based questionnaire after finalising the first draft of the pazopanib report. 76% of the WP5 organisations responded to at least one survey. In addition, the pilot was discussed between WP5 members at a face-to-face meeting in February 2012. Finally, the report was also discussed with the marketing authorisation holder at a face-to-face meeting in March 2012.The results will be described and discussed below.

4.2. Pilot authors' perceptions

4.2.1. Domain structure

There were eight domains included in the first draft version of the Model for Rapid REA. The authors found the four first most relevant, but the last four also gained some support (see Figure 2). Participants mentioned that the relevance of the last four domains depends on the type of pharmaceutical under assessment and can be different on a case by case basis.

Figure 2. Grading of the relevance of the domains by pilot participants (mean value)



Source: Survey of pilot participants (n=16)

The Model for Rapid REA contains generic questions that guide research question formulation. Pilot authors noticed that the generic questions in the model were not always sufficient or clearly formulated. Some important research questions could not be fitted under any of the generic questions, and sometimes the generic question allowed varied interpretations. The pilot authors called for more explicit formulation of the generic questions and clarification with practical examples for the next version of the Model for Rapid REA.

The structure of eight separate domains was perceived as useful for dividing the interests and work across agencies and individuals. The parallel work of the domains was however considered to increase the risk of duplication of work as a natural sequence of assessment; the approach of starting from background information and then moving to safety and effectiveness was missing. We tried to reduce the overlap between domains by having regular e-meetings and within domains by email discussions. It was noted that not all of the apparent duplication is unnecessary; sometimes similar issues need to be considered from slightly different points of view in different domains.

4.2.2. Scoping

The scope was structured into three elements: technology, indication, and comparators. Primary outcomes were not discussed during the scoping phase. This was a deliberate choice while it was planned that the relevant outcomes would be discussed and determined for each domain separately. This approach acknowledges the importance of primary outcomes of all domains, instead of giving priority to efficacy endpoints, which is the usual case. However, it was noticed later during the project that a discussion and agreement about the significance of overall versus progression free survival would have helped the authors. The differing views of countries about using these outcomes in assessment resulted in modifications in the text of several domains so that both outcomes are presented in a neutral and balanced way, so that the results serve as many countries as possible.

There is a trade-off in the inclusion of comparators. In order to achieve European relevance all treatment alternatives to pazopanib should be included as comparators. Moreover,

according to the user policies of The Core HTA the authors should make reasonable efforts to provide information that is useful and applicable beyond their own country setting. Multiple comparators require multiple analyses, however, and the number of analyses may be further increased by multiple indications of the pharmaceutical under assessment. Balancing European relevance and what can be achieved in a rapid assessment within 3 months will probably be reconsidered, case by case, for each assessment.

The relevance of the chosen comparators was discussed in several phases of the pilot. Two comparators (temsirolimus and everolimus) were excluded after a time as it became apparent that their indication was different. Inclusion of interferon and interleukin was questioned as they were considered old medicines, but they were kept in the scope to ensure applicability of the results. Using the guideline that is under development by WP5 'Criteria for the choice of the most appropriate comparator(s)' may assist future scoping exercises. In addition, it was noted that, ideally, a review of current practices, either from the published literature, or by means of a questionnaire to national HTA agencies, clinicians or hospital managers - which is also the subject of one of the research questions of the first domain - should be performed before scoping. Another option would be to re-evaluate and adjust the scope at several time points: first after reading the submission file; second after completing the work of the first domain; and later if required. The possibility of engaging the marketing authorisation holder in the scoping process could also be explored. Although the scope was documented in detail, readers considered that a justification for the choice of comparators and outcomes would have been helpful. For future assessments, the justification should also be reported.

A brief ethical discussion was scheduled for an e-meeting during the scoping phase of the pilot. The aim of that discussion was to test the feasibility and relevance of adding ethical analysis in rapid assessment. A brief introduction included reminders of patient-relevant outcomes, fair and equal patient selection, and the requirement for proper methods. This raised discussion about the appropriateness of the age limit of 65 which has been used in many original studies on pazopanib.

4.2.3. Keeping it comparative

It was stressed at the beginning of the project that all domain teams should follow the scope carefully, and provide information that relates to the differences between pazopanib and the comparators. Several domains had to be reminded to keep this focus. However, there were also good arguments for providing some "absolute" results too: in the absence of head-to-head trials the placebo-controlled studies needed to be presented. The authors of the Social Domain kept strictly focused on relative social consequences of pazopanib and the comparators with the consequence that no relevant data turned out to be available.

4.2.4. The role of ethics in REA

Earlier Core Model pilots had identified that the current domain structure is not optimal for the work of the ethical domain. A separate, stand-alone "ethical assessment" is not possible. Ethics should rather be integrated into all domains in their planning phase and when interpreting the results. It remains a matter of discussion, as to the best format for ethical analysis for full Core HTAs; and also, how to increase the knowledge and understanding of the HTA community about the methods of ethical analysis. For rapid REA projects a more pragmatic solution is needed: e.g. a simple checklist for authors to identify the need to include ethical questions in their assessment, or to use ethical expertise when preparing the summary.

4.2.5. Focusing on HTA doers

It was underlined in several instances during the project that the intended primary user of this document is the HTA researcher. There were discussions during the pilot about the

usability of the report with the repetitive structure of domain reports and result cards. The result cards of the Model for Rapid REA, with their explicit questions, answers and transparency in methods used, is one of the proposed solutions to provide something easily adaptable for national HTA doers. The authors of this pilot project viewed an additional summary, balancing the core findings of various domains and providing insight into the level of uncertainty of the information, as essential, both to the HTA community and to decision makers.

Sometimes the authors struggled with the expressed preference to provide a general answer; to what extent is it possible to provide country-specific results, and how relevant is EU level information for national reports? In the Legal domain it was considered impossible to examine all the regulations on pazopanib from each Member State. In addition, the authors of the Legal Domain chose to present legal information that is generalisable for all pharmaceuticals that are subject to the same market access regulation as pazopanib instead of for pazopanib specifically.

4.2.6. Structured reporting – use of result cards

The question and answer structure, reported in the form of result cards, was generally found functional, although further refinements are needed both in the structure and layout of the cards. Sometimes, as a result of the structure, the authors went into too much detail in their answers. Authors also commented that it was sometimes difficult to identify particular methods for a single question, and it was frustrating and time consuming to repeat the methods and references for each card. On the other hand, some authors noted that result card templates added clarity, and the work became quicker after they had become acquainted with the template. A common complaint was that browsing was cumbersome: it was difficult to get an overall picture of the whole from the separate cards.

4.2.7. Methodological guidelines

The guidelines were used by the relevant domain teams (mainly effectiveness and safety) to some extent. The authors praised the quality of the guidelines, but commented that in some guidelines the target audience was not HTA assessors. They were either too long or too complicated, and did not always offer a solution to the problem described. They lacked recommendations derived from "real life" assessment experience and recommendations on possible consequences of the assessment.

4.3. Duration and workload

The first draft of the pilot assessment was prepared in 3.5 months, from May to August 2011. The time frame was generally considered sufficient, and some of the encountered communication and resourcing problems would have been avoided if the pilot period had not included the summer holiday season. Two months (October and November 2012) were used to finalise the draft report. Collecting data and efforts to standardise and combine all the information from eight domain teams were considered by the coordinators to be the most time consuming and challenging parts of the process. In addition, the various rounds of consultation (December 2011-May 2012: first with WP5 organisations and the marketing authorisation holder, second with the stakeholder advisory group and third with the public) lengthened the process.

There were 52 individuals from 24 HTA organisations in 17 countries who participated in the production of the pazopanib pilot assessment. Of the 52, 27 were authors who did the actual research (Table 4). Each of the 27 authors used a mean of 9 days for the assessment; the amount of input varied between 4 and 30 days. Altogether 250 working days were spent on the assessment. An additional 150 days were used for coordination and editing: this includes the time spent on identifying the topic, and communicating the different phases with various

stakeholders. Substantial coordination input was necessary for this kind of pilot exercise where new tools and methods are introduced.

The work load was perceived by some authors as high. This was interpreted to be a consequence of the new way of working, new templates, and new colleagues from all over Europe. The effectiveness domain reported a heavy work load because of the large number of comparators and the need to separate direct and indirect comparisons. Work load was not evenly distributed amongst the authors in the team, but this was mostly due to how it was agreed within the team, and not because of lack of commitment.

Table 4. Days used for the pilot

Domain	Days	Number of authors	Number of individuals
HPCU	28	3	5
DTC	30	5	7
Safety	48	3	6
Effectiveness	69	5	7
Ethical	23	3	6
Organisational	26	3	5
Social	11	3	5
Legal	16	2	4
SUM/days	251	27	45
Coordination	150		3
Synthesis team	6		4
SUM/days	407	**9 days per author (mean)**	52

4.4. Collaboration

The roles of domain authors and reviewers were mostly considered satisfactory. Author team members had discussions mainly through email and raised discussion items, such as reporting of evidence tables, for e-meetings. The authors were mostly content with the communication in their own domain team but felt that there was too little information exchange across the domains. The guidance and information from coordinators in emails was sometimes difficult to keep track of. Informal ad-hoc discussions did not occur as often as within an office, and this was mentioned as an apparent drawback of collaborating remotely.

Sometimes the views of the pilot participants were completely opposing, e.g. about the usefulness of the literature search performed or the use of risk of bias tables in the assessment. More often the discrepancies were more qualitative in nature, and people found it interesting to learn about the methods and information sources others use. Sometimes the different working practices, approaches or perceptions were considered to be a struggle.

4.5. Report readers' perceptions of the pilot report

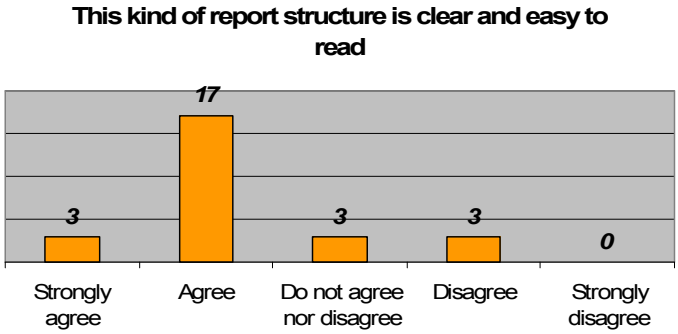
Domain structure and result cards were considered appropriate in 19 of 26 respondents (74%). Most WP5 members who responded to the survey found the report easy to read (see Figure3). This is an encouraging result considering that the current structured format of domain reports and result cards is more suitable for electronic publication and no cross references were available in the draft report.

WP5 members rated the relevance of the domains for REA in a similar way as the pilot doers (Figure 4). The four first domains are always relevant, and the last four domains in some cases only. The English language of the report is not a concern for most of the agencies who responded (20 out of 25 responses).

All respondents considered the results of the first four domains valid, at least partly. Many respondents indicated that it was difficult to assess the validity of the results of the last four domains. Almost half of the respondents thought that the current report structure requires adaptation for use in national report production. Some 87% thought it at least likely that the credibility of the report is increased through broad participation (Figure 5). In addition, 87% of respondents thought performing joint assessments was at least likely to reduce duplication of work in Europe.

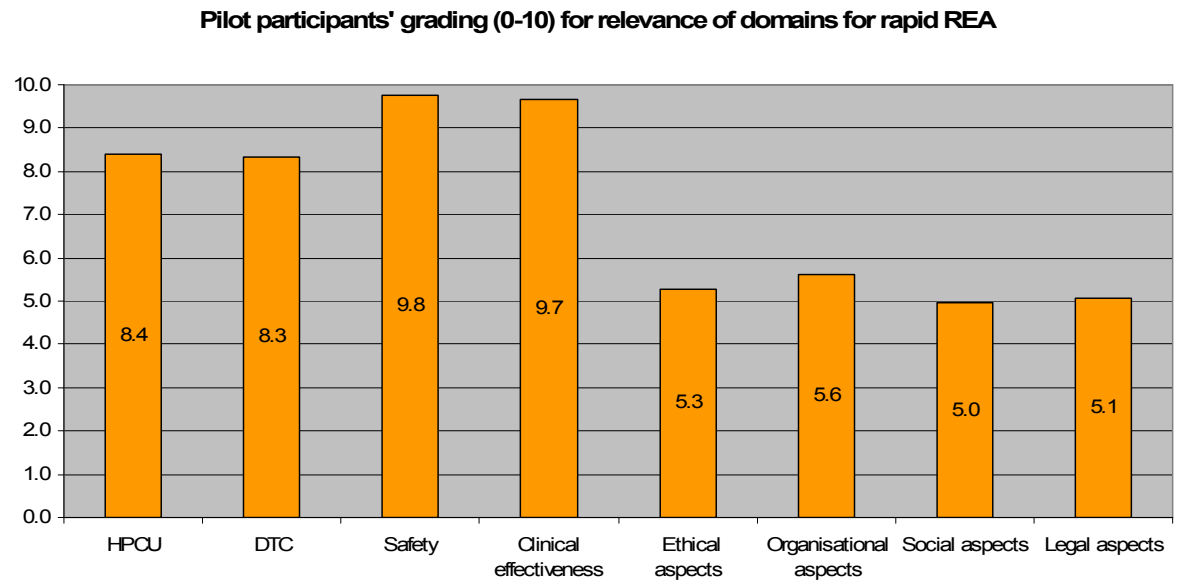
An extensive basic search was performed by the coordinating office. Several organisations who do rapid assessments mentioned that this is not feasible in practice. Most WP5 agencies shared the view that for future assessments the basic document should be the submission file of the marketing authorisation holder with additional searches only if these are required. The marketing authorisation holder mentioned that they felt that the submission file had been only partly used. The reason for this was that the submission file turned out to be not completely fit for purpose for a standalone REA. The submission file provided was based on a submission file prepared for NICE in which the REA is included in the cost-effectiveness assessment.

Figure 3. Readability of report structure (n=26)



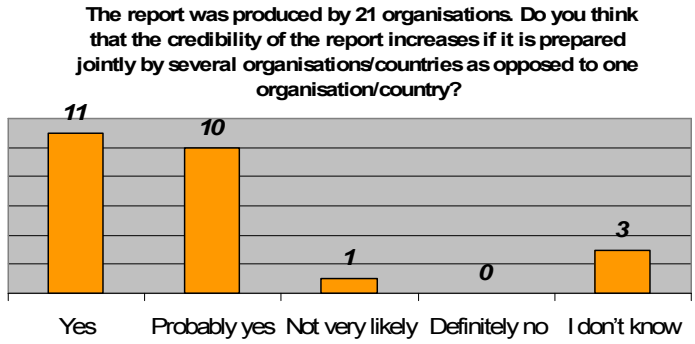
Source: Survey of WP5 organisations

Figure 4. Grading of the relevance of the domains by WP5 members (mean value) (n=26)



Source: Survey of WP5 organisations

Figure 5. Credibility of joint report (n=26)



Source: Survey of WP5 organisations

4.6. Key recommendations for future rapid REA projects

- The number of authoring agencies and individuals needs to be reduced in order to avoid overlapping, increase consistency and improve communications. The benefit of broad participation will be ensured by involving several agencies in an in-depth review.
- The main focus should be on the first four domains. A short checklist can be developed for identifying whether there are relevant ethical, organisational, social, or legal issues to be added.

- The justification for the choice of comparator(s) should be reported.
- The submission file prepared by the marketing authorisation holder should serve as the basic document, and additional literature searches performed if required.
- Reporting guidance for the result cards should be improved.

References

1. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on RCC: the 2010 update. Eur Urol 2010 Sep;58(3):398-406.
2. Karim-Kos HE, de VE, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer 2008 Jul;44(10):1345-89.
3. Bellmunt J, Calvo E, Castellano D et al. Recommendations from the Spanish Oncology Genitourinary Group for the Treatment of metastatic renal cancer. Caner Chemother Pharmacol 2009; 63(suppl 1): S1-S13
4. NCCN. Kidney cancer. 2011. Accessed in May 2011 at: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
5. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic RCC (mRCC): a literature review. Cancer Treat Rev 2008 May;34(3):193-205.
6. Motzer RJ, Russo P. Systemic therapy for RCC. J Urol 2000 Feb;163(2):408-17.
7. CHMP assessment report. Votrient. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001141/WC500094275.pdf
8. Sternberg CN, Davis ID, Mardiak J, Szczylik EL, Lee E, Wagstaff J, et al. Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial. Clin Oncol 2010; 28:1061-1068
9. Escudier B and Kataja V. RCC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v137-v139.
10. Calvo E, Maroto P, del Muro XG, et al. Updated recommendations from the Spanish Oncology Genitourinary Group on the treatment of advanced RCC. Cancer Metastasis Rev 2010; 29 Suppl 1: 1-10.
11. National Institute for Health and Clinical Excellence. Pazopanib for the first-line treatment of advanced renal cell carcinoma. NICE technology appraisal guidance 215. February 2011. In: www.nice.org.uk (Accessed: 10 August 2011).
12. Di Lorenzo G, Porta C, Bellmunt J, et al. Toxicities of targeted therapy and their management in kidney cancer. Eur Urol. 2011;59:526-40.
13. Breitbart W, Heller KS. Reframing hope: meaning-centered care for patients near the end of life. Journal of Palliative Care 2003; 6: 979-88.
14. Carter H. Living with a terminal illness: patients' priorities. Journal of Advanced Nursing 2004; 45: 611-20.
15. Chochinov HM. Understanding the will to live in patients nearing death. Psychosomatics 2005; 46: 7-10.
16. Hutson T.E., Davis I.D., Machiels J.P., et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2010; 20; 28 (3): 475 – 480.
17. Hawkins R, Hong SJ, Ullys A, et al. An open-label extension study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma. Abstract and poster presentation at American Society of Clinical Oncology Annual Meeting 2009. J Clin Oncol 2009; 27 9suppl 15s): Abstract no. 5110.
18. Clinicaltrials.gov. Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARZ) URL: http://clinicaltrials.gov/ct2/show/NCT00720941
19. Clinicaltrials.gov. Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer (PISCES). URL: http://clinicaltrials.gov/ct2/show/NCT01064310?term=PISCES&rank=2
20. Hancock B, Griffin CL, Ritchie A, Gore M, Mead G. Updated results of the MRC randomised controlled trial of alpha interferon vs MPA in patients with metastatic renal carcinoma. Proc Am Soc Clin Oncol 2000;19:Abstract 1336. (Manufacturer's submission)

21. Negrier S. P. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: Results of a randomized controlled trial. Cancer 2007;110:2468-77.
22. Pyrhönen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol 1999;17:2859-67
23. Kriegmair M, Oberneder R, Hofstetter A. Interferon alfa and vinblastine versus medroxyprogesterone acetate in the treatment of metastatic renal cell carcinoma. Urology 1995;45:758-62.
24. Steineck G, Strander H, Carbin BE, Borgstrom E, Wallin L, Achtnich U et al. Recombinant leukocyte interferon alpha-2a and medroxyprogesterone in advanced renal cell carcinoma. A randomized trial. Acta Oncol 1990;29:155-62
25. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27:3584-3590.
26. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26(33):5422-5428.
27. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370(9605):2103-2111.
28. Negrier S, Jager E, Porta C, McDermott D, Moore M, et al. (2009) Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Med Oncol. 2010;27:899-906.
29. Kilonzo M, Hislop J, Elders A, Fraser C, Bissett D, McClinton S, Mowatt G, Vale L. Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma: A Single Technology Appraisal. Aberdeen HTA Group Institute of Applied Health Sciences, University of Aberdeen, 2010.
30. Beck J et al. Final results of the European Advanced Renal Cell Carcinoma Sorafenib expanded-access study: a large open-label study in diverse community settings. Ann Oncol. 2011;22:1812-23.
31. SUMMARY OF PRODUCT CHARACTERISTICS. Proleukin URL: http://db.cbg-meb.nl/mri/spc/nlh-0005-002.pdf
32. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010 Mar;46(4):765-81.
33. Eble JN, Sauter G, Epstein JI, et al (eds). In: Pathology and genetics of tumours of the urinary system and male genital organs. World Health Organization Classification of Tumours. Lyons: IARC Press, 2004: p. 7.
34. Athar U, Gentile TC. Treatment options for metastatic RCC: a review. Can J Urol 2008 Apr;15(2):3954-66.
35. Harding G, Cella D, Robinson D, Jr., Mahadevia PJ, Clark J, Revicki DA. Symptom burden among patients with RCC: content for a symptom index. Health Qual Life Outcomes 2007;5:34
36. Patard JJ, Leray E, Rodriguez A, Rioux-Leclercq N, Guille F, Lobel B. Correlation between symptom graduation, tumour characteristics and survival in RCC. Eur Urol 2003 Aug;44(2):226-32
37. McDougal WS, Garnick MB. Clinical signs and symptoms of RCC. In: Vogelzang NJ, Scardino PT, Shipleyand WU and Coffey DS (Editors). Comprehensive Textbook of Genitourinary Oncology, Williams & Wilkins Co., Baltimore 1995, pp. 154-159.
38. European Association of Urology. Guidelines on RCC. 2010. Accessed in May 2011 at: http://www.uroweb.org/gls/pdf/Renal%20Cell%20Carcinoma%202010.pdf
39. European Medicines Agency. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&murl=&mid=
40. Federal Drug Administration: URL: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm187509.htm

41. Health Canada. URL: http://webprod3.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng
42. Australian Government. Therapeutic Goods Administration. URL: http://www.tga.gov.au/pdf/auspar/auspar-votrient.pdf
43. Medsafe. URL: http://www.medsafe.govt.nz/profs/datasheet/v/votrienttab.pdf
44. SUMMARY OF PRODUCT CHARACTERISTICS. Pazopanib. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001141/WC500094272.pdf
45. SUMMARY OF PRODUCT CHARACTERISTICS. Sunitinib. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000687/WC500057737.pdf
46. SUMMARY OF PRODUCT CHARACTERISTICS. Sorafenib. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000690/WC500027704.pdf
47. SUMMARY OF PRODUCT CHARACTERISTICS Bevacizumab. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf
48. Drabkin HA. Pazopanib and anti-VEGF therapy. Open Access Journal of Urology 2010:2;35-40.
49. Hurwitz H. I., Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009; 15 (12): 4220 – 4227.
50. Colombo GL. Gli studi di costo della malattia in Italia: scenari attuali e prospettive future. Igiene Sanità Pubblica 2002; 8(5): 318-27.
51. Sacchini D. Analisi etica nell'HTA riferita al lapatinib. Italian Journal of Public Health 2009, 6 (1), Suppl. 1: 68-76.
52. La Torre G, De Waure C, Mannocci A, et Al. The application of HTA to the new oral oncologic drugs: the case of lapatinib in metastatic HER2 positive breast cancer. Annals of the Academy of Medicine, Singapore (AAMS), 2009, 38(6), suppl.: S40.
53. Keisner SV, Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. Drugs. 2011 Mar 5;71(4):443-54.
54. Ravaud A. Treatment-associated adverse event management in the advanced renal cell carcinoma patient treated with targeted therapies. Oncologist. 2011;16 Suppl 2:32-44.
55. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. Health Policy. 2010 Aug;96(3):179-90.
56. EUnetHTA Work Package 5 Factsheet (2010) [accessed 2011 August 22]. Available from: http://www.eunethta.eu
57. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. National Institute of Health and Clinical Excellence (NICE); 2009. Technology appraisal guidance 169. [Accessed 2011 September 22]. Available from: http://www.nice.org.uk/nicemedia/live/12143/43556/43556.pdf
58. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. National Institute of Health and Clinical Excellence (NICE); 2009 (reviewed July 2011). Technology appraisal guidance 178. [Accessed 2011 September 22]. URL: http://www.nice.org.uk/nicemedia/pdf/TA178Guidance1.pdf
59. A British patient forum of 'The Kidney Cancer Support Network' [Accessed 2011 September 22]. URL: www.kidneycancersupportnetwork.co.uk/forum
60. A Dutch patient forum for cancer patients 'phpBB Kankerpatient' [Accessed 2011 September 22]. URL: http://www.kankerpatient.net/index.php
61. Community Register for Medicinal Products for Human Use. Votrient. URL: (http://ec.europa.eu/health/documents/community-register/html/h628.htm)

62. Sally Shorthose (Ed.) Guide to EU Pharmaceutical Regulatory Law, Kluwer Law International (2010)
63. Treaty on the Functioning of the European Union ('TFEU') (2008/ C 115/47, consolidated version).
64. Council Regulation 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
65. Directive 2001/83/EC on (as amended last by 2010/84/EU) on the Community code relating to medicinal products for human use.
66. Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems