

HTA Uncovered

Market access consequences of accelerated access pathways

Multiple policy and legislative options have been introduced in recent years designed to accelerate patient access to newly approved therapies, including conditional regulatory approval and adaptive pathways in Europe and breakthrough therapy designation and fast track review in the USA. These initiatives attempt to find the right balance between the need for robust evidence of safety and efficacy and the need for new medicines to address unmet need.

While there has been some criticism of so-called adaptive pathways due to concern about potentially immature data on efficacy and safety, analysis shows that products which succeed in accelerated regulatory pathways also perform relatively well in health technology assessment (HTA).

Consultation with HTA bodies early in the process can be used to improve chances of positive HTA for products with non-traditional regulatory pathways. Ultimately, however, HTA decisions for such products are most likely to be influenced by high unmet needs and a lack of therapeutic options for the patient population in question. Where unmet need is higher, less comprehensive evidence may initially be allowed to enable earlier access to new treatment.

Impact of accelerated regulatory approval on HTA outcomes

Decisions made by HTA bodies for products with conditional marketing authorisation (CMA) by EMA can provide insights on possible outcomes for other accelerated access pathways. An analysis of decisions by national HTA bodies showed the implications on market access for manufacturers choosing to pursue an accelerated access pathway.

EMA has granted 22 drugs conditional marketing authorisation (Table 1). Of these, 15 are indicated for oncology. Furthermore, 10 drugs have an orphan indication. Five drugs (Intelence®, Tyverb®, Vectibix®, Votrient® and Diacomit®) have subsequently gone from conditional to full marketing authorisation.

As of May 2016 most of the drugs (except for Holoclal®, Tagrisso™ and Intelence®) had been evaluated by one or more key agencies (HAS, G-BA, NICE, SMC, TLV, ZIN, CADTH and PBAC) before receiving full market authorisation. These drugs were assessed in 63 HTAs by these key agencies since 2011. Analysis shows that drugs with CMA have a higher probability for a negative recommendation than the average of all HTAs from the same agencies within the same period (Figure 1). However, the

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higher percentage of negative recommendations for drugs with CMA seems to be partly driven by the high number of oncology drugs with CMA; analysis of oncology recommendations by the same agencies shows a similar distribution of positive, restricted and negative recommendations as drugs with CMA. Orphan drugs had the highest percentage of positive recommendations.

Table 1. Products with conditional EMA approval

Therapeutic Area	Drug	Orphan?	#HTAs
Cancer	Adcetris®	✓	6
	Arzerra®	✓	5
	Blinicyto®	✓	2
	Bosulif®	✓	5
	Caprelsa®		4
	Cometriq®	✓	4
	Erivedge®		3
	Pixuvri®		2
	Tagrisso™		0
	Tyverb®		1
	Vectibix®		1
	Votrient®		5
	Votubia®	✓	4
	Xalkori®		5
	Zykadia™		4
Central Nervous System	Diacomit®		0
	Fampyra®		7
Eye	Holoclal®	✓	0
Infectious and Parasitic Diseases	Deltyba®	✓	1
	Intelence®		0
	Sirturo®	✓	1
Musculoskeletal	Translarna™	✓	3
Total	22	10	63

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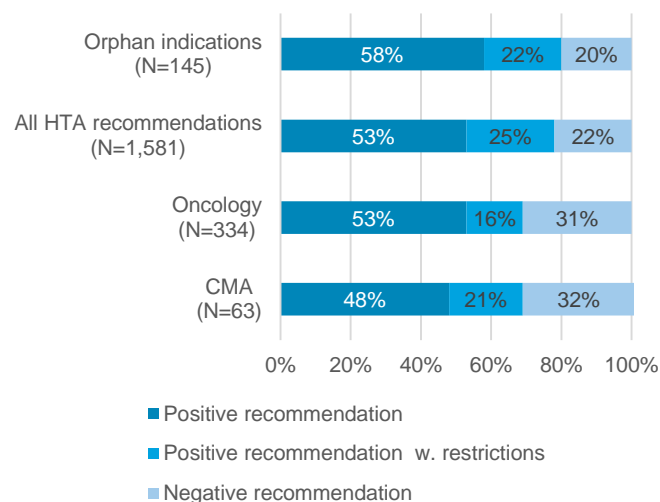


Figure 1. Outcomes of HTAs.

Scope: Single drug assessments, all indications, original submissions, decision date Jan 2011 – May 2016, Countries: France (HAS), Germany (G-BA), UK (NICE, SMC), Sweden (TLV), Netherlands (ZIN), Canada (CADTH) and Australia (PBAC)

Figure 2 shows CMA drugs with an orphan indication have a similar recommendation rate as all orphan drugs. Oncology drugs with CMA also have the same likelihood of positive recommendation as all oncology drugs, but there were slightly more restricted recommendations and slightly fewer negative recommendations for drugs with CMA as compared to all oncology drugs.

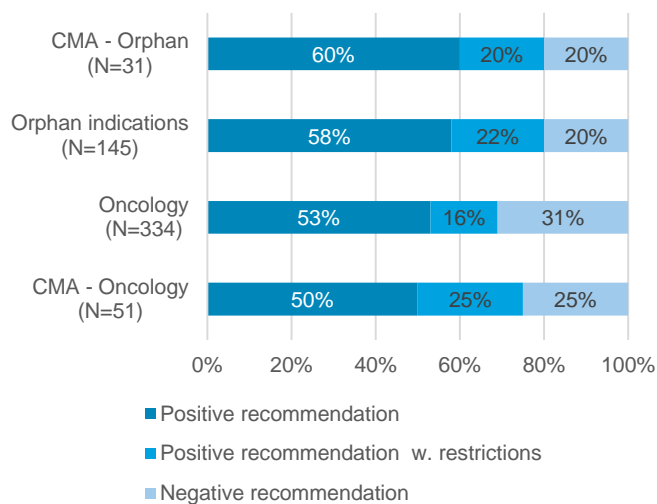


Figure 2. Outcomes of orphan and oncology HTAs

Immature/ insufficient data are potential challenges for products that pursue accelerated access. However, looking at the evidence used for HTAs of drugs with CMA, there does not seem to be a relationship between the type of evidence provided and HTA outcome. While many HTAs of drugs with CMA are based on

single arm trials, use of single arm trials did not seem to have a negative effect on the recommendation (Figure 3). In fact, the majority of HTAs that were based on single arm trials received a positive recommendation. However, this analysis did not take into account conditional recommendations that request further data to re-evaluate a drug at a later time.

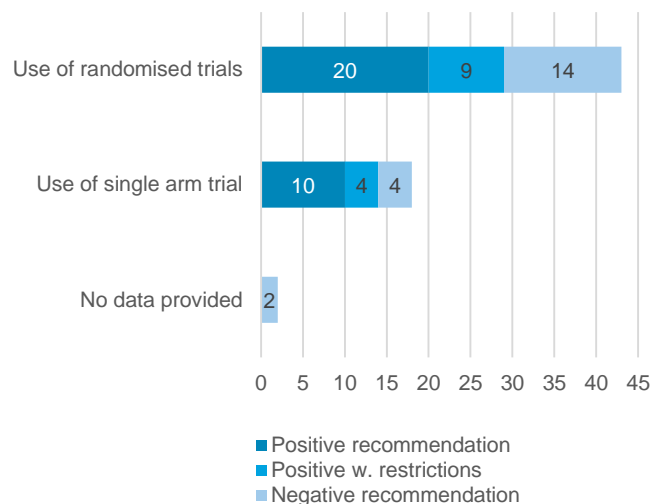


Figure 3. Use of single arm trials in HTAs of CMAs

Positive recommendations of drugs with CMA were mainly driven by clinical benefit and high unmet need (Figure 5, please note that assessments could have multiple decision drivers). For example, HAS said in its assessment of Arzerra®: "At this stage of the disease, there is no alternative drug treatment that has been validated in patients refractory to fludarabine and alemtuzumab. This medicinal product constitutes a salvage treatment."

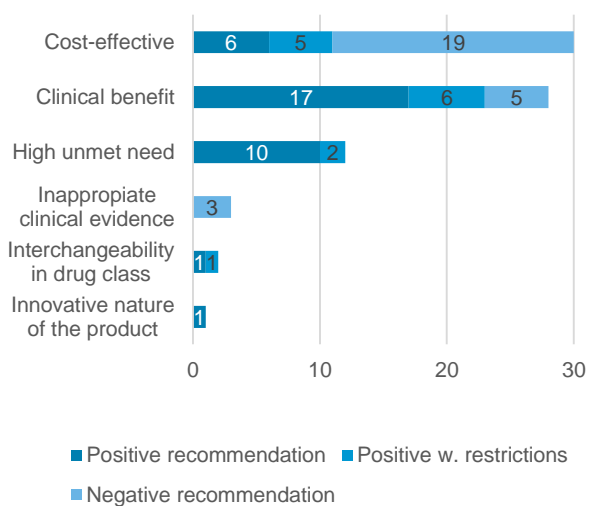


Figure 4. Decision drivers

Although 5 out of 20 negative recommendations mentioned lack of clinical benefit as a contributing factor, most of the rejections were driven by lack of cost-effectiveness.

Figure 5 compares decision criteria for assessments of CMA drugs and all drugs. Assessments are primarily based on clinical benefit. Cost-effectiveness is also important for some agencies, and this was by far the most common criterion contributing to rejection for CMA drugs. The third most influential decision criterion for CMA HTAs was unmet need, which played a relatively smaller role when looking at all drugs. Decisions for all HTAs were also driven by inappropriate clinical evidence (Inappropriate clinical trial design, comparator and/ or patient population), and interchangeability in drug class and safety.

Drugs with CMA also seem to have taken less time from marketing authorisation to a positive HTA recommendation than other HTAs (Figure 6, based on 21 and 315 assessments respectively). While the average time of all HTAs is 438 days, drugs with CMA only took 330 days on average, a difference of three months. As stipulated in German law G-BA assessed all drugs within 1 year, regardless of whether they had an orphan or oncology indication or whether the drugs received CMA. For all other agencies CMA

drugs were approved faster, albeit the number of assessments is low.

Country cases – France and Germany

When looking at ASMR ratings in France, we also see that drugs with CMA generally receive higher ASMR ratings (Figure 7). 79% of assessments for drugs with CMA had an ASMR IV or better ratings in France compared to only 25% of all HAS HTAs in the same timeframe. These higher ASMR ratings for drugs with CMA seem to be driven by clinical benefit and high unmet need. For example, HAS has said of Imbruvica® “Improving the therapeutic management of mantle cell lymphoma is a public health need” and of Erivedge® “There is no alternative drug therapy at this stage of treatment”.

In Germany on the other hand, the ratings for drugs with CMA approval were slightly lower than all G-BA HTA recommendations (Figure 8): 40% of drugs with CMA received a minor or considerable benefit rating, as compared to 47% of all G-BA HTAs. However, relatively more CMA drugs (20% vs. 16%) were rated to have a non-quantifiable benefit; influenced by the higher proportion of orphan drugs, which typically receive at least non-quantifiable benefit.

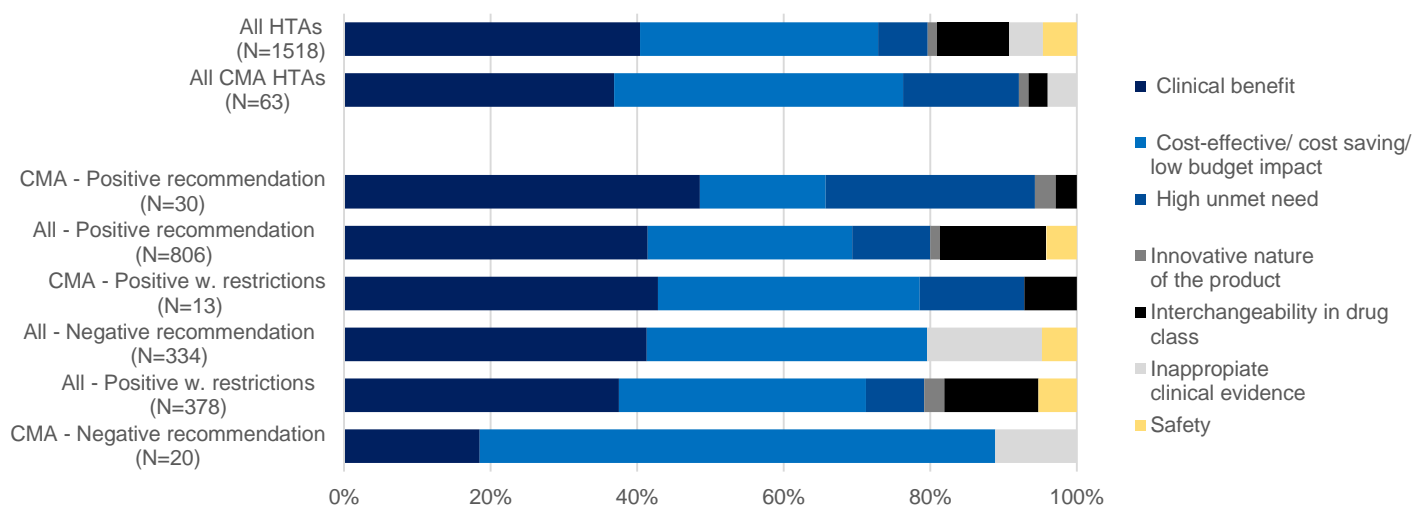


Figure 5. Decision drivers (note: an assessment could have multiple decision drivers)

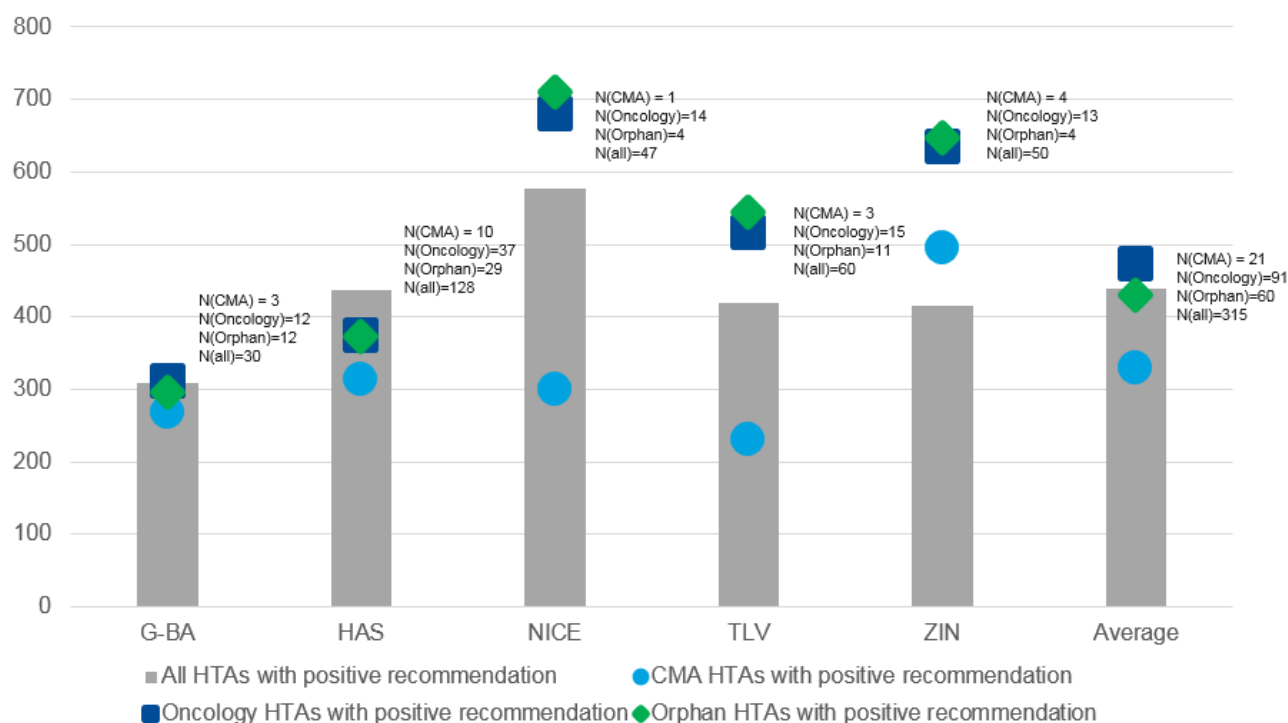


Figure 6. Average time from marketing authorisation to positive HTA recommendation of original, single drug assessments between Jan 2011 and Sep 2015

Improve chances of HTA success through effective consultations with HTA bodies

Chances of a positive HTA can be improved by undertaking effective consultation with HTA bodies in parallel with pursuing regulatory approval. These formal and informal discussions with selected HTA bodies can aid manufacturers in understanding what the HTA challenges are likely to be and how to overcome them. The quality of the advice depends entirely on the quality of the questions asked. The HTA bodies cannot tell manufacturers what to do. They can only respond to specific questions. Furthermore, it is recommended to support the questions with

data and analyses and to be clear on what answers are wanted or expected. So for HTA bodies who use cost-effectiveness analysis, developing an early health economic model allow for highly specific feedback. Parallel scientific advice is one environment where closed questions are more powerful than open questions.

In theory, manufacturers can select up to five agencies for parallel scientific advice. Agencies differ in the likelihood to assess a product, impact and influence and what they base their decision on. However, while several HTA bodies have agreed to join the parallel scientific advice pilot, not all are fully engaged and compelled to take part. For example, smaller agencies are inclined

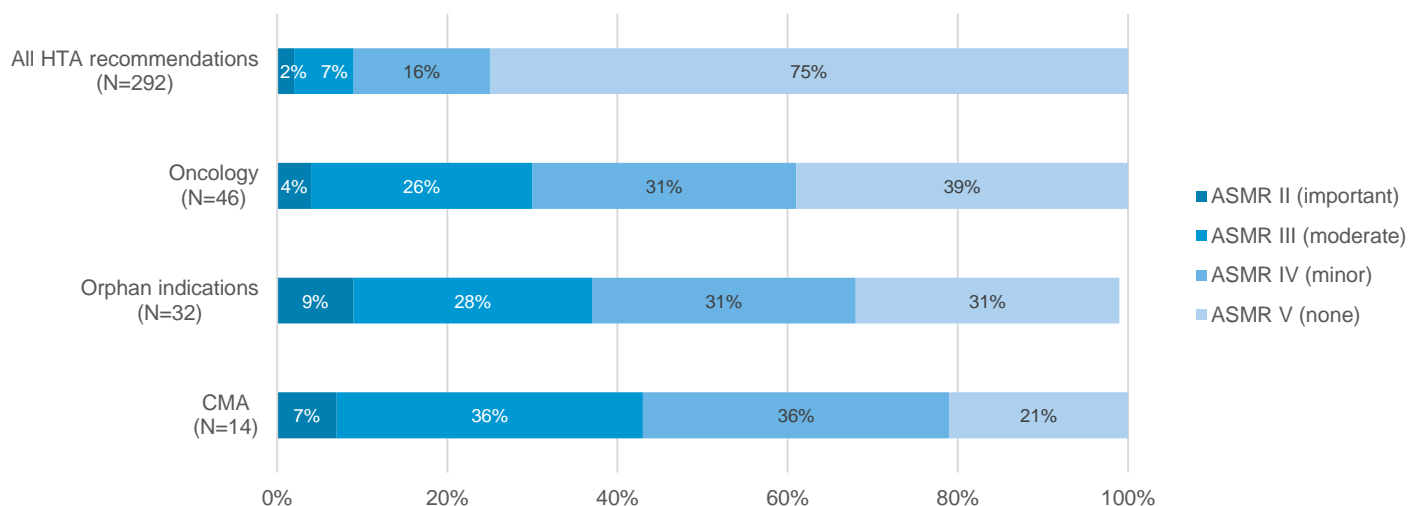


Figure 7. Outcomes of HTAs in France

to be helpful, but do not have the resources to respond to every request.

Conclusion

Drugs with CMA face similar evidence challenges as drugs for oncology or orphan indications, with many HTA decisions based on single arm trials. Although insufficient data did not appear to adversely affect the HTA outcome for CMA drugs, it is advisable to engage with HTA bodies as soon as possible to ensure the most effective and efficient use of the available data. Despite concerns around safety and evidence, CMA drugs do relatively well in HTAs.

Key agencies gave a positive recommendation (with restrictions) to 69% of HTAs for CMA drugs. Among the drugs that received CMA, many are indicated for an oncology and/ or orphan indication. Thus, it is not surprising that CMA assessments share similar decision drivers to oncology and orphan assessments, such as clinical benefit and unmet need.

Ultimately, HTA decisions for such products are most likely to be influenced by high unmet needs and a lack of other therapeutic options. Payers might accept a less comprehensive evidence when the unmet need is higher and thereby enabling earlier access to new treatment.

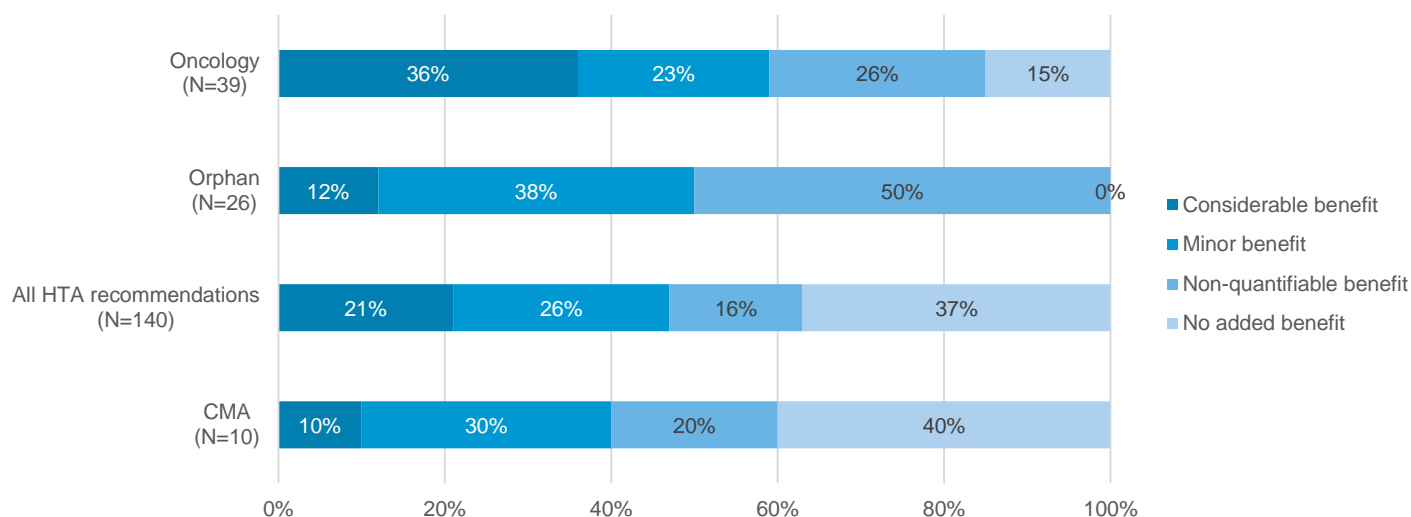


Figure 8. Outcomes of HTAs in Germany

Conditional market authorisation (CMA) by the European Medicines Agency (EMA)

A medicine that addresses unmet medical needs of patients can be granted conditional marketing authorisation (CMA) on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Medicines for human use are eligible if they belong to at least one of these categories:

- aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases;
- intended for use in emergency situations (also less comprehensive pharmaceutical and non-clinical data may be accepted for such products);
- designated as orphan medicines.

CMAs may be granted if the following requirements are met:

- the benefit-risk balance of the product is positive;
- it is likely that the applicant will be able to provide comprehensive data;
- unmet medical needs will be fulfilled;
- the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.

CMAs are valid for one year and will be reviewed annually. The holder will be required to complete specific obligations (ongoing or new studies, or collection of pharmacovigilance data) with a view to providing comprehensive data confirming that the benefit-risk balance is positive. Once comprehensive data on the product have been obtained, the marketing authorisation may be converted into a standard marketing authorisation (not subject to specific obligations).

To enable earlier access to new treatments for areas with high unmet need, payers might accept less comprehensive evidence

The growing influence of USA-based HTA body, ICER and how its findings compare to international agencies

Given the absence of a comprehensive and transparent HTA program in the USA, the Institute of Clinical and Economic Review (ICER) has emerged as an influential source of information for drug decision-making. ICER is an independent non-profit organization founded by Dr Steven D. Pearson in 2007 that seeks to create a reliable and consistent value framework for evaluating innovative treatments, tests and procedures¹. Funded by the Laura and John Arnold Foundation (LJAF), ICER began a new emerging therapy assessment program in July 2015 to apply this framework to new drugs gaining imminent Food and Drug Administration (FDA) approval².

In contrast with some countries, mainly European, which have established requirements for appraising medicines for market access and formulary coverage, the USA has a fragmented approach to HTA with different organisations applying varying requirements and methodologies for evaluation. Historically, health economic and outcomes research (HEOR) evidence has not been considered an essential component in many payer / state-sponsored HTA guidelines, and decision-makers placed varying levels of importance on these outcomes³. With rising drug prices and healthcare expenditures, a focus on value-based decision making has gained increased attention from multiple stakeholders. To fill the void of a transparent method for analysing and judging value, ICER claims that its value framework leverages a combination of trusted methodologies and an innovative approach to affordability⁴. The aim of this analysis was to compare and contrast ICER's value framework and results to HTAs conducted in countries with established HTA processes, and assess the impact of these differences on the pricing and reimbursement decision making process.

ICER vs international HTA methodologies

Focusing specifically on HTA reviews of Entresto™ (sacubitril/valsartan) for the treatment of patients with heart failure and reduced ejection fraction, our analysis compares drivers and decision-making of ICER and renowned HTA agencies (NICE, SMC and CADTH) in evaluating clinical and economic evidence.

Accounting for the national differences, we found that NICE and CADTH restricted the population eligible for treatment with Entresto™ while ICER and SMC issued recommendations for the full label (see Table 1). All four HTA agencies accepted the economic case reporting costs per quality adjusted life year (QALY) gained. The result was at or below the ICER, NICE, and SMC thresholds for cost-effectiveness, whereas CADTH does not apply a threshold. Nevertheless, the final results of ICER's value price benchmark suggested Entresto's™ list price was slightly higher than the calculated USA budget impact threshold for the drug. None of the other agencies negotiated cost reductions through, for example, managed entry agreements. While all four

agencies conduct typical clinical and economic analyses to inform the HTA, ICER's value-based price benchmark process takes its guidance a step further, by recommending a price at which patients in the reviewed population could be treated individually with reasonable long-term value at the individual level, with added short-term costs that would not exceed growth in the national economy.

A closer look at the data sources and clinical and economic evidence critique highlights key differences and similarities between agencies:

Data source: NICE, SMC and CADTH base their assessments on clinical evidence and economic model results submitted by the manufacturer, supplemented by fact checks of the submitted data or additional information provided by expert opinion. In contrast, ICER compiles publicly available information and develops the cost-effectiveness and budget impact model itself, in some cases supplementing the data by requesting unpublished information such as manufacturers' data on file.

Clinical evidence: In their reviews of Entresto™, NICE, SMC and ICER considered the submitted trial, PARADIGM-HF, to be of good quality that demonstrated efficacy in producing significant reductions in cardiovascular (CV) and all-cause mortality and hospitalizations compared to enalapril. CADTH accepted the clinical benefit of Entresto™ but rated the trial as highly selective in patients included, with fewer than 60% of patients screened for the trial entering treatment phase due to low B-type Natriuretic Peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) levels and subsequently, 20% of patients entering the run-in phase excluded due to tolerability issues (limiting its generalisability). Both NICE and CADTH noted that a first-line positioning of Entresto™ was not aligned with the trial's population. Consequently, both agencies restricted Entresto™ to patients that more closely match the inclusion criteria of PARADIGM-HF (e.g., previously treated with statins), while ICER and SMC gave recommendations for the full indication.

Economic evidence: The Markov model developed by ICER was based on PARADIGM-HF and other publicly available data. In addition, ICER received utility data based on PARADIGM-HF EQ-5D measurements from Novartis. The variance in model structures between the four agencies was considerable, ranging from a 5-state cohort model (CADTH), to 2-state models using patient-level data (NICE and SMC) and a 3-state model from ICER.

All international economic models used the angiotensin-converting-enzyme (ACE) inhibitor enalapril as the base case comparator (NICE, SMC and CADTH) but reported secondary analyses using angiotensin II receptor blockers (ARBs). ICER used lisinopril (ACE inhibitor) citing its wider use and lower costs, however, it assumed treatment equivalence to enalapril and only applied lisinopril costs.

The incremental model results showed that ICER's cost effectiveness model yielded comparable QALY gains for

¹ Institute for Clinical and Economic Review (ICER) [website], accessed June 2, 2016. <http://icer-review.org/about/>

² ICER, "ICER Launches New Drug Assessment Program with \$5.2 Million Award from the Laura and John Arnold Foundation" Institute for Clinical and Economic Review (ICER) [website], July 21, 2015. <http://icer-review.org/announcements/icer-ljaf-drug-assessment-announcement/>

³ Michael E. Minshall and John Watkins, "Raising the Bar in the USA: The Impact of Heightened Awareness of the Need for Health-Economic Data in the Absence of a Regulatory Mandate" The Official News & Technical Journal of the International Society for Pharmacoeconomics and Outcomes Research, 2008. <http://www.ispor.org/news/articles/jan08/rb.asp>

Entresto™ over enalapril/lisinopril (0.57 incremental QALYs) versus the models considered most relevant by SMC (0.42 QALY gain) and NICE (ERG base case: 0.33 incr. QALYs). A review of the key model drivers pointed to similar factors across models with relative risk of mortality (all-cause or CV) and duration of treatment effect being the most influential. This was not surprising, as most model base case analyses assumed a continued treatment effect beyond the trial duration.

Overall, ICER's output from traditional analysis of clinical and economic evidence does not appear to vary from international HTA agencies using similar methodologies. After all, Dr Pearson worked as a Senior Fellow at NICE before founding ICER. However, while HTA bodies make decisions directly based on CEA output and ability to achieve commonly cited willingness-to-pay thresholds, ICER's final recommendation is underpinned by the unique approach of assessing a drug's affordability and its value-based price benchmark.

Budget impact

Essential to ICER's value framework is defining the provisional health system value, which integrates long-term care and potential short-term budget impact. Low health system value would be placed on a drug contributing to annual healthcare costs which exceed the annual growth of national GDP + 1%, and garner need for greater stakeholder scrutiny and discussion⁴. The value-based price benchmark further quantifies this value by determining the price at which it would meet acceptable thresholds of \$100-\$150K /QALY and a \$904 million budget impact threshold, if applicable⁴.

Evaluating Entresto™ in this framework resulted in only a 9% discount to the full wholesale acquisition cost (WAC) considered in the analysis, while many of ICER's reviews evaluating other products call for drastic price discounts up to 85%. For example, Praluent® and Repatha®, innovative PCSK9 inhibitors which address the growing burden of CV disease, received a value-based price benchmark of \$2,177 annually compared to the list price of \$14,350. Such extreme differences in price have undoubtedly created noise in the healthcare decision-making discussion and have become the focal point of leveraging ICER's findings.

The manner in which ICER incorporates a 5-year budget impact in its analyses differs from the other HTA agencies (NICE and CADTH do not consider budget impact) and has raised concerns among manufacturers as it often seems to drive ICER's value-based price benchmark. They argue such an approach grossly underestimates the value of products providing patients with a long-term benefit (e.g. vaccine preventing cancer or drug curing a chronic condition), disfavours drugs targeting common conditions, and could perversely penalise innovation (i.e., the budget impact threshold would decrease if the FDA were to approve a higher number of drugs per year)^{5,6}.

Reactions to ICER reports

Despite having no direct impact on reimbursement decisions within the USA, ICER's comprehensive HTAs have encouraged public dialogue between multiple stakeholders on how to maximize health system value. Multiple payers, such as Express Scripts and Harvard Pilgrim Health, have acknowledged the need for an independent, trusted source of information and have alluded to using ICER reports during pricing negotiations^{7,8}. While payers may welcome ICER's contributions, manufacturers have been quick to defend their products against ICER's methodology. Amgen and Regeneron have each criticised the reports for a focus on short-term affordability as opposed to long-term health benefits and its overestimation of drug uptake^{9,10}. Meanwhile some patients fear reduced access to innovative drugs, perceive ICER's value framework and pricing tools to be payer-centric, rather than taking into account patient needs¹¹.

Implications of ICER findings

ICER states that its goal is to create "a common language and mental model of the components of value across life science companies, payers, and other stakeholders,"⁴ though some see its growing influence and recognition as a path to become another NICE or similar centralised HTA body. Given the fragmented nature of decision-making and health coverage in the USA, it is difficult to see how a single institution, ICER or some other agency, could emerge as the sole primary source of information for informing payer decisions. Some may point to Canada, with its 13 separate provincial and territorial health insurance plans and a majority of its population covered by private drug insurers, being similar to the USA and an example of the circumstances under which a centralized HTA body can gain influence. Whilst it is true that CADTH's recommendations are taken into consideration by provincial and some private drug plans, CADTH's recommendations do not carry the same weight or have the same reach as do those of NICE for example. Nevertheless, CADTH's evolution as an independent agency, initially established to respond to manufacturer's demands for a centralised system for reimbursement decisions, and established reputation may serve as a precedent of how ICER's influence can grow within a fragmented system.

During a time when drug pricing faces increased scrutiny in the USA, ICER's value-based price benchmark echoes the public's demands for affordable treatments. Whilst there are differences between the methods of ICER and the other HTA bodies, their similarities appear outweigh their differences. The degree of ICER's direct impact on coverage decisions and pricing negotiations is unknown, it is important to anticipate and address multiple stakeholder interests. Early communication with third party drug investigators, not limited to ICER, may improve the understanding on both the payer and manufacturer side of the drug's value. ICER's assessment process provides manufacturers specific opportunities to engage – through public comment on the

⁴ Dan Ollendorf, "Aligning Drug/Device Prices and Benefits: A Novel Framework for Examining Questions of Comparative Effectiveness, Cost-Effectiveness, and Affordability" ISPOR Boston Chapter presentation, 28 March 2016

⁵ Biotechnology Industry Organization. Feedback to ICER's Value Framework. October 9, 2015

⁶ National Pharmaceutical Council (NPC). Comments on ICER value assessment framework. October 13, 2015

⁷ Dan Mangan, "How Express Scripts plans to cover a \$14,000 drug" CNBC, October 6, 2015. <http://finance.yahoo.com/news/express-scripts-plans-cover-14-210040746.html#>

⁸ Robert Weisman, "Boston watchdog takes aim at rising drug prices" Boston Globe, September 13, 2015. <https://www.bostonglobe.com/business/2015/09/13/drug-price-watchdog-may-new-threat-industry-high-priced-medicines/WmsLum4IV60qcAmeut6RmO/story.html>

⁹ Jill Wechsler, "Drug Pricing Backlash Reaches Fever Pitch" Pharmaceutical Executive, November 4, 2015. <http://www.pharmexec.com/drug-pricing-backlash-reaches-fever-pitch>

¹⁰ Caroline Humer, "Regeneron CEO says drug price critique by independent group unscientific" Reuters, May 12, 2016. <http://finance.yahoo.com/news/regeneron-ceo-says-drug-price-191402168.html>

¹¹ ICER Admits: We serve payers" The Daily Rise [blog] May 13, 2016. <https://patientsrising.org/blog/daily-rise-friday-may-13>

scoping document and on the initial draft review and voting questions¹². To drive informed discussions, promote transparency, and advance stakeholders' perspective on report conclusions, ICER has made process modifications to explicitly incorporate manufacturers in the formal process – and they should take advantage of the opportunity to take part⁴.

As ICER's influence in the drug pricing debate grows, stakeholders should give attention to its role as a voice in the drug evaluation conversation.

Events and publications

Meet us at the following conferences

- PharmAccess Leader Conference: Berlin, 27 – 29 September ([weblink](#))
- SMI conference – workshop “Managing the global to local challenge”; London, 12 October ([weblink](#))
- ISPOR 19th Annual International Meeting, 29 Oct – 2 Nov, 2016, Vienna, Austria ([weblink](#))

Quintiles' 2016 Executive Vision Forum (Boston, MA, USA; October 13)

- The Executive Vision Forum (EVF) is an exclusive hallmark event where industry experts join Quintiles and life science leaders for an intimate conversation about the future of healthcare
- This year's EVF will be held on Thursday, October 13, 2016, 4:00pm – 10:00pm at the Boston Public Library with a program focusing on the topic of [Connecting Insights: Bringing medicines to patients faster](#)

Quintiles Blog ([weblink](#))

- [Show us the evidence](#) – Anke van Engen
- [Going PRO](#) – Jean Paty
- [The Variability of Value](#) – John Doyle, Emily Hawryluk, and Craig White
- [Simplifying PROs](#) – Jean Paty, Emily Hawryluk and Cassie Frickely
- [Overview and Comparison of Frameworks for Oncology](#) – Johan Maervoet
- [Immuno-Oncology Insights: Top 5 Challenges in Today's Immuno-Oncology Trials](#) – Eric Groves
- [On implications of value-based oncology frameworks on clinical trial design](#) – Amar Chawla, John Doyle
- [Evidence at your fingertips](#) – Kenne Mountford

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¹² ICER, “Public Comment Guide” Institute for Clinical and Economic Review (ICER) [website], accessed June 2, 2016. <http://icer-review.org/methodology/stakeholder-engagement/public-comment-guide/>

Table 2: Comparison of Decision Drivers Across Global HTA Agencies

Item	ICER	NICE	SMC	CADTH
Data source	Publicly available sources. Sometimes explicit requests for use of unpublished manufacturer data	Manufacturer submission using (unpublished) trial data supplemented with other sources	Manufacturer submission using (unpublished) trial data supplemented with other sources	Manufacturer submission using (unpublished) trial data supplemented with other sources
Indication under review	Treatment in patients with Class II-IV CHF and reduced ejection fraction	Treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction	Treatment of symptomatic chronic HF with reduced ejection fraction	Treatment of HF with reduced ejection fraction in patients with NYHA II or III
Decision	Clinically effective and yielding appropriate costs per QALY. Value-based price benchmark is \$4,168 (=9% discount from assumed full WAC) for all patients in the reviewed indication	Only in people with NYHA class II to IV symptoms, a left ventricular ejection fraction (LVEF) of <35% and who are already taking a stable dose of ACE inhibitors or ARBs	Accepted for use within NHS Scotland for all patients in the reviewed indication	Only in patients with reduced LVEF, NYHA class II to III symptoms despite four weeks on stable dose of ACE inhibitors or ARBs and certain Plasma B-type natriuretic peptide (BNP) levels
Clinical summary	<ul style="list-style-type: none"> - PARADIGM-HF trial: large, good quality study showing significant reductions for Entresto® in CV and all-cause mortality, HF specific hospitalisation and ED visits in comparison to enalapril - Uncertainties: relative contribution of sacubitril versus valsartan to these results, the expected tolerability of Entresto®, its clinical performance in real-world practice, and its potential for harm in certain patient subgroups 	<ul style="list-style-type: none"> - PARADIGM-HF trial was well conducted and most patients in the trial were taking beta blockers as concomitant therapies, which reflected UK clinical practice - Entresto® statistically significantly more clinically effective than enalapril at reducing hospitalisations and improving both overall mortality and cardiovascular mortality - First-line positioning of Entresto® not supported by trial as majority of patients used ACE inhibitors or ARBs prior 	<ul style="list-style-type: none"> Entresto® was associated with an additional reduction in the risk of cardiovascular death and hospitalisation due to heart failure over the reduction seen with enalapril. Sustained mortality benefit over time unclear (early stopping of the study) Results of NMA, between Entresto and ACE inhibitors, similar to results from PARADIGM-HF study 	<ul style="list-style-type: none"> - Treatment with Entresto® reduced risk of CV mortality or HF hospitalization compared with enalapril - PARADIGM-HF highly selective: most patients excluded due to low BNP or NT-proBNP levels - PARADIGM-HF patients received stable doses of ACEi or ARB, majority had LVEF of 35% or less at baseline and there was limited evidence for patients with LVEF > 35% to 40% or less
CEA summary	<p>Horizon: lifetime</p> <p>Model structure: Markov model with minimum 3 states (NYHA II-IV)</p> <p>Comparator: Lisinopril (ACE)</p> <p>Clinical input: CV mortality and HF hospitalisation</p> <p>Utilities: based on EQ-5D trial data from PARADIGM-HF</p> <p>Assumptions: Lisinopril equivalent to enalapril; baseline probability of CV mortality increased by 3.7% per year to adjust for lifetime horizon and aging</p> <p>ICER: USD 50,915/QALY with 5.56 QALYs for the ACE inhibitor and 6.13 QALYs for Entresto® resulting in a QALY gain of 0.57, while costs were USD 123,578 vs. USD 152,716 for ACE vs. Entresto®, respectively, incr. cost USD 29,138</p> <p>Key model drivers: Duration of treatment effectiveness, monthly cost of Entresto, relative risk of CV mortality</p>	<p>Horizon: lifetime (30 years)</p> <p>Model structure: 2-state Markov model using patient-level data</p> <p>Comparator: enalapril (ACE) and candesartan in secondary analysis (ARB class effect assumed)</p> <p>Clinical input: all-cause mortality and all-cause hospitalization rates</p> <p>Utilities: based on EQ-5D trial data from PARADIGM-HF</p> <p>Assumptions: EQ-5D treatment effect in favour of Entresto®</p> <p>ICER: ERG base case GBP 29,478 (GBP 6,841 and 0.33 incr. QALYs). ERG base case for Entresto® vs. ARBs: GBP 30,140/QALY</p> <p>Key model drivers: all-cause mortality (treatment effect of Entresto on all-cause mortality, baseline risk of all-cause mortality, age), improvements in HRQoL and reductions in hospitalizations</p>	<p>Horizon: lifetime (30 years);</p> <p>Comparator: Enalapril (tx most likely to be replaced in clinical practice) and secondary analysis with ARBs</p> <p>Clinical input: all-cause mortality and all-cause hospitalization (secondary outcome, model results not sensitive to using this data over cardiovascular-related outcomes)</p> <p>Utilities: based on EQ-5D trial data from PARADIGM-HF</p> <p>Assumptions: Tx effect assumed to continue throughout model horizon</p> <p>ICER: Enalapril = GBP 18,348/QALY with 0.42 QALY gain and GBP 7,685 incr. cost; ARBs = GBP 16,621/QALY with 0.57 QALY gain and GBP 9,434 incr. cost</p> <p>Key model drivers: survival estimates, duration of treatment effectiveness (5-year cap on tx duration resulted in ICER of GBP 32k/QALY), time horizon</p>	<p>Horizon: 20 years</p> <p>Model structure: 5-state Markov model</p> <p>Comparator: ACE inhibitor</p> <p>Clinical input: trial data, and a survival model was used to extrapolate cardiovascular mortality values for years 3 to 20</p> <p>Utilities: based on EQ-5D utilities from PARADIGM-HF</p> <p>Assumptions: In years 3 to 20, the distribution of patients among NYHA classes remains constant</p> <p>ICER: Enalapril: CAD 29,999/QALY, CAD 42,787/QALY after reanalyses by CDR (use of 1-year time horizon, different disutility for hospitalization, use of ramipril in place of enalapril, etc.)</p> <p>Key model drivers: not reported</p>
BI summary	<p>1-year BI: USD 1.2 bn for 334,000 pts</p> <p>5-year BI: USD 15bn for up to 1.7m pts</p>	Confidential	<p>1-year BI: GBP 761k for 30,567 pts</p> <p>5-year BI: GBP 14.2m for 31,066 pts</p>	Not provided