

A CASE STUDY ANALYSIS

Challenges in the NICE Evaluation of Multi-indication Medicines for Rare and Ultra-rare Diseases

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Executive Summary

Previous work (Henderson et al., 2020) has shown that medicines for rare and ultra-rare conditions face distinct economic and ethical challenges from medicines for more common conditions, and that appraisal processes designed for medicines for more common conditions may not be appropriate for medicines for rarer conditions. Small patient populations, heterogenous patient pathways, limited clinical experience, and often no accepted standard of care, makes it more difficult to generate the same standard of evidence in rare and ultra-rare conditions as in more common conditions. In addition, small patient populations with rare and ultra-rare conditions typically mean that prices for these medicines must be higher to achieve the same returns on investment as medicines for more common conditions, making it difficult to meet the same cost-effectiveness thresholds.

The National Institute of Health and Care Excellence (NICE) has implicitly acknowledged these challenges by establishing the 'Highly Specialised Technologies' (HST) appraisal pathway, an auxiliary appraisal route that considers only highly-specialised technologies for very rare conditions. Medicines evaluated under this route are assessed against a more pragmatic standard of evidence and uncertainty, and can be judged against a substantially higher cost-effectiveness threshold compared to medicines for more common conditions, depending on the absolute magnitude of health benefit.

However, the current entry criteria for HST are highly restrictive and they effectively exclude submissions for ultra-rare conditions when the medicine has marketing authorisation for another indication. In these cases, the medicines must be appraised under the standard technology appraisal (STA) route, regardless of the rarity of the indication. The STA route was not designed to consider the greater uncertainties and higher prices associated with medicines for rare and ultra-rare conditions and is, therefore, less likely to recommend these medicines. This represents an important barrier to patient access to medicines for rare and ultra-rare conditions.

The objective of this report is to enumerate specific challenges encountered in NICE's appraisal of medicines for rare and ultra-rare medicines and how these challenges were subsequently resolved to highlight positive and less positive practices in appraisals. To this end, we conducted a series of stakeholder interviews to identify key perceived challenges, understand intricacies of the NICE appraisal process and the interplay with NHS England, and inform the selection of specific case studies.

A number of common themes became apparent in the interviews, primarily that:

- Current structures for incorporating patient feedback into NICE recommendations could be improved.
- There needs to be greater recognition of the value of innovation as a *process*, especially for first-in-class medicines.
- There are concerns about **extending the current Cancer Drugs Fund (CDF) to include non-cancer medicines in the form of a new Innovative Medicines Fund**. The main areas of concern were the criteria by which 'innovation' and eligibility for the Fund would be judged and what would happen in circumstances where additional data collection is unlikely to resolve uncertainty.
- **Criteria for consideration under the Highly Specialised Technologies are open to differing interpretations**, which leads to concerns over equality of access to care.

- There is **a need for greater willingness and flexibility by the NHS in adopting innovative pricing schemes**, particularly where a medicine has multiple indications.

The case studies, focusing on a selection of multi-indication or highly specialised medicines, explored some of these same issues in more detail and highlighted the challenge of assessing uncertain evidence in the context of rare and ultra-rare conditions.

- In **the case of everolimus**, uncertainty was resolved through statistical modelling and expert clinical input, representing the use of alternative sources of information to come to a positive resolution.
- Conversely, **the case of ibrutinib** highlights an often unrealistic expectation on the part of NICE that the CDF can resolve any and all uncertainties in the evidence base around medicines for rare and ultra-rare conditions. In this case, the manufacturer declined to participate on the grounds that real-world evidence was unlikely to resolve the uncertainty of concern.
- Similar uncertainty was encountered in **the case of nusinersen**. In this case, a creative managed access agreement was reached to provide coverage with data collection, similar to the CDF but in a non-oncology context. There was a positive resolution ultimately, but the *ad hoc* nature of the managed access agreement in this context highlights potential inequities in access to innovative medicines between oncological and non-oncological medicines.
- **The case of ibrutinib** also highlights the potential for further NHS England restrictive criteria to be applied following a NICE positive recommendation. In the case of ibrutinib, NHSE's decision to add restrictive criteria, citing the level of clinical uncertainty as a justification for their decision, was reversed following clinical expert input and extensive media coverage and debate in the House of Lords.
- Finally, **the case of midostaurin**, for which a NICE Final Appraisal Document (FAD) was recently published, provides a recent example of the challenges associated with the evaluation of multi-indication medicines for rare diseases. The flexibility and pragmatism demonstrated in the appraisals of everolimus and ibrutinib also seem to have been applied to midostaurin. Based on appraisal documents, NICE appears to have recognised the rarity of the indication but declined to consider midostaurin under the HST appraisal route, primarily on the grounds that it is already approved in a non-HST indication.

We highlight as positive examples those appraisals that took a **flexible and pragmatic approach** to addressing uncertainties or evidence gaps inherent to treatments for rare and ultra-rare conditions, including the use of bespoke statistical modelling, expert testimony, and real-world evidence to supplement rigorous clinical evidence. Less positive examples failed to allow for the greater uncertainty inherent in treatments for rare and ultra-rare conditions and hold submissions to the same evidentiary and cost-effectiveness standards as treatments for much more common conditions and we look forward to positive examples of this new approach in future appraisals.

In this context, we note that the recent NICE methodological review (NICE, 2020) has made a point of encouraging greater flexibility and pragmatism in the consideration of uncertainty with treatments for rare diseases. In particular, it notes "qualitative evidence, expert elicitation and surrogate outcomes may be particularly relevant in rare diseases, **so additional clarity and guidance in the methods may be beneficial** [emphasis added]." Explicit recognition of the role of such 'alternative' forms of evidence in all contexts, but especially rare and ultra-rare diseases, represents a substantial step forward in terms of flexibility. Greater clarity in how such evidence should be weighed alongside more conventional evidence is now urgently required.

Likewise, we suggest that greater clarity is required of the role of the CDF and the proposed IMF in general, and in rare and ultra-rare diseases in particular. The use of a medicine under the CDF can accelerate patient access and promote clinical experience with innovative treatment that can later help resolve key uncertainties or gaps in the evidence. Equally, however, the CDF is limited in its ability to generate data in the context of rare or ultra-rare conditions, where there is often no defined standard of care and/or heterogeneous patient experiences. We suggest that greater clarity is required to close the evidence gaps which the CDF and IMF can and should be expected to resolve to improve the consistency and effectiveness of its use across submissions.

Finally, the methodological review notes that there is a case for avoiding “specific provisions for rare diseases as much as possible” to ensure consistency in methods, but where “it is necessary to make specific provision (for example, in considering uncertainty and risk), it will be important to define what is meant by a **rare disease** carefully. As it stands, the distinction between “highly-specialised technologies” eligible for appraisal under the HST route, and other medicines for rare and ultra-rare conditions that are subject to the same evidence and cost-effectiveness standards of much more common conditions, is not clear. How NICE considers this distinction should be made clearer, and eligibility for the HST appraisal route broadened to include more medicines for rare and ultra-rare conditions.

1 Introduction

Rare diseases: General background and common challenges

A rare, or orphan, disease is defined by the European Medicines Agency (EMA) as a health condition that affects a small number of people. Rare diseases are defined as conditions affecting fewer than 5 in 10,000 people (Smith, 2015), and ultra-rare or ultra-orphan diseases are those affecting fewer than 1 in 50,000 people (Pant and Visintini, 2018). In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) has typically applied a more conservative absolute prevalence threshold of fewer than 1,000 cases in an England and Wales population of 59 million people (National Institute for Health and Care Excellence, 2004), or a prevalence rate of less than 0.85 per 50,000.

Although the number of people suffering from any one rare disease is small, there are more than 6,000 rare diseases (Orphanet, 2019), and combined, they affect around 6-8% of the European population, or between 27 and 36 million people (Puiu and Dan, 2010). This is equivalent to 4 to 5 million people in the UK. Each year, more than 250 new rare diseases are described in the literature (Dawkins et al., 2018). Furthermore, rare diseases occur in up to 4% of births and often appear in childhood, affecting an individual's health over their entire – often shortened – life.

Challenges in the development and assessment of orphan medicines

Treatments for many rare and ultra-rare conditions include the use of medicines. These medicines for rare and ultra-rare diseases are also called orphan and ultra-orphan medicines, and new innovative treatments are continually being developed (Detiček et al., 2018). However, given the unique circumstances of these medicines, health system decision-makers are likely to face resulting economic and ethical challenges distinct from those encountered by treatments for more common conditions (Henderson et al., 2020). This is especially true of treatments for ultra-rare conditions, where the challenges of rarity are magnified. NICE has recently published a consultation on proposed changes to its methods, which in turn, may provide a much-needed opportunity to address some of the issues faced by orphan medicines during the evaluation process (NICE, 2020).

A recent OHE report (Henderson et al., 2020) explored the current literature regarding the economic and ethical challenges that emerge when evaluating orphan and ultra-orphan medicines and other issues exacerbated by rarity compared to more conventional medicines. The report identified three key areas of discussion, namely: ethical arguments for and against special priority for ultra-rare conditions, the different appraisal processes for ultra-rare disease medicines, and why a standard appraisal process, designed for medicines for more common conditions, may not be appropriate for medicines for ultra-rare conditions. In 2015, the National Institute for Health and Care Excellence (NICE) introduced an alternative appraisal pathway that exclusively evaluates medicines for ultra-rare conditions, i.e., the Highly Specialised Technology (HST) programme. It is intended to improve patient access to technologies for chronic and severely disabling ultra-rare conditions that would otherwise be unlikely to be approved under NICE's standard appraisal process. Despite the positive motivations of an auxiliary route for medicines for ultra-rare conditions, the authors found that there are concerns that the current HST process fails to fully address the challenges it aims to overcome. For example, the criteria for medicines to be deemed eligible for appraisal via the HST route often put ultra-orphan medicines for multiple indications at a disadvantage; they would not be eligible for this route under the current criteria. Indeed, eligibility for the HST appraisal route is highly restricted and excludes most new medicines for rare and ultra-rare conditions. Only 11 medicines have been evaluated under the HST process since its introduction in 2015. The report concludes that whilst, in principle, NICE's HST programme offers an important route to patient access for ultra-orphan medicines, there is significant potential for improved clarity and consistency regarding the criteria and methods applied.

It is often argued that high prices are an inherent characteristic of orphan medicinal products. The drug-development process and costs are broadly similar regardless of the size of the patient population, and therefore the R&D cost per eligible / indicated patient is much higher for ultra-orphan medicines than a treatment for a more prevalent condition. Whilst there is a long-standing debate around the most appropriate way of estimating R&D cost per product, one of the most widely cited estimates is that of DiMasi (2016). They estimate the R&D cost per product to be \$2,558 million by using retrospective accounting of project-level costs and development phase success rates. As these costs are largely fixed and are spread across a smaller patient population for rare and ultra-rare conditions, prices for orphan and ultra-orphan medicines typically need to be higher than prices for more common medicines to achieve an equivalent rate of return (Szegedi et al., 2018). However, this means it is more difficult for medicines for rare and ultra-rare conditions to meet the same cost-effectiveness standard¹ as medicines for more common conditions (Simoens, 2011). A lower likelihood of approval – and therefore a lower expected return on investments – limits incentives for R&D in medicines for rare and ultra-rare conditions (Solà-Morales, 2019), and it has been suggested that this will slow future innovation around rare diseases (Horgan et al., 2020).

This raises ethical concerns around the affordability and accessibility of orphan medicines and has sparked debate around the need for more transparency in orphan drug price setting (Henderson et al., 2020; Picavet et al., 2014). Under a 'health maximisation' approach, orphan medical products (OMPs) are evaluated against the same criteria as non-orphan drugs, despite the economic challenges described above. This approach is a barrier to access to treatment for patients with rare and ultra-rare conditions. Some have proposed that standard NICE evaluation processes to evaluate OMPs are inefficient and that alternative approaches to evaluation could produce a more efficient outcome (Cowles et al., 2017; Drummond and Towse, 2014). Others have suggested that efforts should be made to ensure that egalitarian principles play a role alongside maximising principles. This means that access to treatment for patients with rare and ultra-rare diseases is guaranteed and equal to patients with more common conditions, regardless of the typically higher cost of these products (Juth et al., 2020).

HST and the CDF: theoretical solutions that are not exempt from challenges

Actions have been taken in practice to partially tackle the problems regarding the disadvantaged position of OMPs compared to other non-orphan medicines. In the UK, the establishment of the HST route and the Cancer Drugs Fund (CDF) by NICE can be perceived as an acknowledgement and an attempt to overcome these problems.

The aforementioned HST route may improve an ultra-orphan medicine's chances of being recommended by NICE, given that it increases the cost-effectiveness threshold range from £20,000-£30,000 up to £100,000-£300,000 per quality-adjusted life year gained (Cowles et al., 2017). As of January 2021, all medicines that have been reviewed under the HST guidelines have ultimately been recommended (in some cases, only if certain conditions are met); however, some stakeholders believe that one of the main weaknesses of the HST pathway is the ambiguous entry criteria. Patient representatives have argued that clarification of the criteria is needed, in particular, that repurposing of medicines should be encouraged by allowing treatment with multiple indications to qualify for multiple HST evaluations (Petchey, 2014). Vague criteria can lead to differing interpretations of eligibility for HST review. Henderson et al. (2020) suggested replacing vague, subjective criteria with more quantitative definitions to improve clarity around eligibility HST review and to clarify the distinction between highly specialised and ultra-orphan technologies. We return to this latter point in the discussion section.

¹ Under the STA process, orphan medicines are often assessed against the baseline cost-effectiveness threshold (CET) of £20,000-30,000. There are exceptions where the CET is extended (e.g £50,000 for some cancer and end of life medicines). Under HST, the common CET is expanded to a baseline of £100,000 per QALY gained, sometimes even enlarged to £300,000 for some drugs, advantaging treatments that offer greater QALY gains (Longson, 2017).

Despite the introduction of the HST pathway, many orphan and ultra-orphan medicines are still not being recommended by NICE in comparison with other European countries. Evidence has shown that in England, fewer than 50% of centrally authorised OMPs are routinely funded by the NHS, with one-third of these recommended by NICE (Zamora et al., 2019). In addition, although NICE has been found to have the highest rate of positive ultra-orphan drug recommendations among eight HTA agencies, only around 5% of ultra-orphan drugs are being evaluated (Kawalec et al., 2016). Furthermore, while NICE appraisal processes include the possibility of conducting subgroups analysis (Charlton, 2020), which is the main reason for the high rate of conditional recommendations, a study has shown that 40% of orphan drugs were conditionally recommended in England, while fewer than 11% were fully recommended (Stawowczyk et al., 2019).

The Cancer Drugs Fund was created by the UK Department of Health to improve patients' access to cancer treatments and was redeveloped into its current format in August 2016 (NHS England Cancer Drugs Fund Team, 2016). Promising oncology medicines are still evaluated under the STA process and as such must normally be cost-effective at the £20,000-30,000 threshold, although this threshold increases to £50,000 if pre-defined end-of-life criteria apply (NHS England Cancer Drugs Fund Team, 2016). Where NICE judges that there are important evidence gaps, but there is plausible potential for a drug to satisfy the criteria for routine commissioning, the CDF allows NICE to recommend a drug for use on a conditional basis in order to collect additional data. When NICE consider there to be plausible potential for a drug to satisfy the criteria for routine commissioning, thereby allowing patient to access potentially beneficial treatments in the meantime. Where possible, the CDF appraisal process aims to begin appraisals much earlier than standard evaluations, with the aim of publishing the draft guidance prior to a drug receiving its marketing authorisation and the final guidance within 90 days of marketing authorisation (NHS England Cancer Drugs Fund Team, 2016).

Despite the positive intentions of CDF, collecting additional evidence for rare and ultra-rare diseases is a challenge in itself. NHS England's new CDF Standard Operating Procedure specifies that drugs should be funded through the CDF for as little time as possible, theoretically two years, allowing for some flexibility depending on the rarity of the cancer and the source of the data to address the uncertainty (NHS England Cancer Drugs Fund Team, 2016). However, this time limit is not consistently adhered to in practice; for this, among other reasons, the CDF has been accused of a lack of transparency (Wood and Hughes, 2020). These concerns may have contributed to the NHS's rationale for conducting a study in 2016, in which they consulted the public regarding proposals for reforming the CDF. More than 60% of the respondents agreed that the CDF should include diseases other than cancer, acknowledging that this is common sense and that it would address inequity (Keogh, 2016). In spite of these findings, the remit of the CDF has not been extended to include non-cancer medicines, meaning that there is currently no scope for additional evidence generation for non-oncology drugs. NHS England has, however, recently announced the introduction of an Innovative Medicines Fund which will allow early access to promising new innovative drugs for any condition, including rare and genetic diseases. This scheme will aim to build upon the success of the CDF and operate in the same way, meaning that along with the existing £340 million Cancer Drugs Fund, an additional £340 million will be ringfenced by the NHS for the Innovation Medicines Fund.

The objective of this report is to explore how the aforementioned challenges impact NICE evaluations of orphan medicines, as well as examining to what extent these issues are amplified by rarity and multiple indications. By considering the appraisals process and outcome of medicines with differing characteristics of interest, it is hoped that a better understanding of the nuances of evaluating orphan and ultra-orphan medicines can be obtained.

The report is organised as follows: Section 2 describes stakeholder interviews exploring the practical challenges encountered in NICE submissions for medicines for rare and ultra-rare conditions. It presents the criteria for selecting case studies to illustrate these challenges. It also includes a high-level review of the common challenges these candidate cases raise. Section 3 presents the outcome of the interviews and the complete case studies. Section 4 discusses the main findings.

2 Key stakeholder interviews and common themes in candidate cases

This section uses a combination of qualitative interviews and a review of NICE submissions to identify main challenges in the assessment of medicines for ultra-rare diseases, particularly those with multiple indications. In this section, we describe the methods and findings of the qualitative interviews, a review of NICE submissions, and a discussion of common themes and challenges among these submissions.

2.1 Key stakeholder interviews

As a first step, OHE conducted five qualitative interviews to understand practical challenges in the assessment of medicines for ultra-rare diseases from the perspective of persons who had been through the process. Through these interviews, we sought to identify the key practical challenges in the NICE appraisal process, from the scoping phase to the publication of final recommendations. These interviews assisted in the identification of case studies described in the next section and allowed us to identify some specific assessment challenges in these cases.

Interviewees were specifically selected from different roles within the UK affiliate of a large pharmaceutical company. We interviewed personnel from two business units: the pharmaceutical (pharma) and oncology businesses. Interviewees included personnel from the Health Economics and Outcomes Research, Market Access, Medical and Commercial functions. All responses are anonymous.

2.1.1 Interview findings

Despite the differing roles of the interviewees, a number of common themes were apparent:

First, several interviewees voiced concerns regarding **the current format for considering patient involvement in the NICE committee meetings**, arguing that it is difficult to know how much weight the Committee gives to patient and carer testimonies. They suggested that current practices should be improved to better facilitate patient involvement, particularly for rare and ultra-rare diseases where the impacts on patients and carers may not be as well-understood by committee members as the impacts of more common conditions.

Second, there was a call for **greater recognition of the value of innovation**. First-in-class medicines embody fundamentally new approaches to treatment and hold the potential for dramatic improvements in outcomes with further research and development. Such 'first steps' must be encouraged by valuing the *process* of innovation beyond its initial outcomes. This was deemed essential for first-in-class therapies and/or those where the current standard of care has zero-cost.

Third, the participants considered **the proposed plan to extend the current Cancer Drugs Fund to include non-cancer medicines in the form of a new Innovative Medicines Fund**. While most interviewees agreed that the idea was useful in principle, they had concerns about the practicalities of such a programme. The two main areas of concern were the criteria by which innovation would be judged and what would happen in circumstances where additional data collection is unlikely to resolve uncertainty. These concerns relate particularly to the inherent limitations of evidence based

on very small patient populations and a frequent lack of any standard-of-care by which to judge relative efficacy.

Fourth, there was a consensus that there is **a need for more willingness by the NHS to adopt innovative pricing schemes, particularly where a medicine has multiple indications**. This related to the current wording of clause 3.36 of the Voluntary Patient Access Scheme, which states that “in cases where uniform pricing would lead to a reduction in total revenue for a medicine overall from the introduction of additional indications, other forms of commercial flexibility may be considered for medicines with a strong value proposition”. The 2019 Voluntary Patient Access Scheme (VPAS) is a commitment by the pharmaceutical industry, the NHS, and the UK Government to support innovation for the benefit of UK patients. Its other primary aims are to help get the most cost-effective medicines to patients as quickly as possible and to ensure predictability on spend for the entire branded medicines bill for the NHS. The implication of the above clause is that manufacturers seeking approval for additional orphan indications are constrained by the price agreed for the initial indication. There was a general sentiment that the burden of gaining approval for different prices was so great that manufacturers often decide against seeking reimbursement approval for new indications, even where there is evidence of substantial patient benefit. If manufacturers do decide to seek a NICE recommendation for additional indications, this clause often affects launch strategies, resulting in avoidable delays in patient access. Some interviewees felt that the combination of the VPAS clause and the costs associated with NICE submissions has an undesirable impact on company launch strategies which could adversely affect patient access.

Collectively, these concerns reflect many of the theoretical and practical issues identified in OHE’s previous report on this topic, particularly with respect to the inherent challenges associated with research in very small patient populations and the greater higher degree of uncertainty around the resulting clinical and economic evidence. Likewise, we note that many of these concerns manifest in the real-world case studies reported in the next section, showing that these are not merely theoretical concerns. We will return to these issues in the concluding section of this report.

2.2 Identification and summary of candidate cases

To identify all potentially relevant assessments for inclusion as case studies, we applied the following criteria to OHE’s proprietary **Medicines Tracker**²:

1. Multiple indications*
2. At least one indication for a rare disease
3. Appraised under one of the two NICE HTA routes (HST or STA) since 2015

Based on these criteria, we identified 23 submissions for 11 unique medicines. However, all 23 submissions, including those for orphan indications, were appraised through NICE’s STA process. To include submissions appraised under the HST process, we relaxed the first criterion to include any submission for an orphan/ultra-orphan designation, regardless of the number of indications. On this basis, we identified an additional 14 submissions for 13 unique drugs with a single orphan/ultra-orphan indication assessed under the HST process. It is worth highlighting that we were not able to identify any oncology drugs evaluated under the HST process, and we will return to the absence of oncology medicines later in the report.

² *The Medicines Tracker is a relational database developed by OHE containing detailed information on: (1) the properties of the Centrally Authorised Products (CAPs) approved by the European Medicines Agency (EMA); (2) the EU marketing authorisation; and (3) the results of assessments by the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) since 1 January 2011. The database includes extensions of indications granted over the same period. The Medicines Tracker also captures the availability of medicinal products in England, including those specially commissioned by NHS England and those availability under the Cancer Drugs Fund (CDF).*

For each candidate submission, we extracted the following information:

- **General information about the medicine and indication** including drug name, appraisal type -HST or STA-, and therapy area -distinguishing oncology and non-oncology medicines-. NICE TA numbers were used to identify indications uniquely. We also extracted estimated cost-effectiveness and special criteria such as end of life considerations or other QALY weighting criteria
- **NICE decision and appraisal guidance information.** We looked at NICE decisions for medicines that had at least one orphan indication. For multiple-indication medicines, medicines may have other orphan and non-orphan indications.
 - NICE decisions can be **full approval** for routine reimbursement, an **optimised recommendation** (i.e., restricted to a patient sub-group or lower line of therapy), or a **not recommended**. For oncology medicines, NICE can also give a conditional recommendation, in which case the medicine is included in the **Cancer Drugs Fund (CDF)** for a fixed period to generate evidence that will reduce specific uncertainty around effectiveness or cost-effectiveness.

The submissions are summarised in Tables 1 (oncology) and 2 (non-oncology) on the following pages.



Candidate drug (molecule name)	Number of indications	Decision outcomes (by indication)			Orphan indication considerations (by indication)		Non-orphan indication considerations (by indication)	
		STA Appraisal Outcome	Uncertainty noted	CDF process	ICER per QALY	Other special considerations: EOL/QALY weighting	ICER per QALY	Other special considerations: EOL/QALY weighting
Brentuximab vedotin	3	(A, A*), A	Yes	TA524: Not for this submission but would be beneficial. TA577: Clinical lead CDF TA478: Available via CDF since 2013	TA524: £40k TA577: < £30k	TA524: Not eligible; TA577: EOL not met	TA478: £(18,324, 24,064)	TA478: EOL not met
Cabozantinib	2	(A), A	Yes	TA516: Yes TA463: Yes	TA516: <£30k	TA516: EOL met	TA463: <50k	TA463: EOL met depending on comparator
Daratumumab	2	(A*), A-CDF*	Yes	TA510 Yes TA573: meets criteria according to NICE guidance	TA510: Not identified	TA510: Not eligible	TA573: > £30k	TA573: EOL not mentioned
Everolimus	2	(A), A	No	TA432: CDF reconsideration of a previous indication TA421: CDF reconsideration of a previous indication	TA432: £51,700	TA432: EOL met	TA421: £68k	TA421: EOL not met
Ibrutinib	3	(A or A-CDF)	Yes	TA429: invited to submit proposal TA491: re-admitted TA502: advice to CDF, as per its previous availability. Currently, meets all criteria	TA429: <50k TA491: £54,100 TA502: > (20k, 30k)	TA429: EOL met TA491: EOL not met TA502: EOL met	-	-
Midostaurin	2	A, A	Yes	TA523: Advice CDF	-	-	TA523: <30k	TA523: EOL not met
Obinutuzumab	2	(A*), A-CDF	Yes	TA513: clinical lead CDF TA629 (replaces TA472): clinical lead CDF	TA513: <30k	TA513: EOL not met	TA629: £(15,587 ;17,322)	TA629: EOL Not mentioned
Olaparib	2	(A-CDF or A)	Yes	TA620 (replaces TA381): Meets CDF criteria TA598: Meets CDF criteria	TA620: > (20K, 30K) TA598: <20k	TA620: EOL met for subgroup TA598: EOL not mentioned	-	-
Ramucirumab	2	(N), N	Yes	TA378: No TA403: Does not meet CDF criteria	TA378: >100k as monotherapy	TA378: EOL not met	TA403: >100k	TA403: EOL met for a subgroup
Venetoclax	2	(A-CDF), A	Yes	TA487: Yes TA561: No	TA487: £(50k, 60k)	TA487: EOL met	TA561: within CE threshold	TA561: EOL not met

TABLE 1: SUMMARY OF CANDIDATE ONCOLOGY MEDICINES

N=11 oncology drugs; i = 23 indications. All drugs have multiple indications, except Lutetium (177 Lu) oxotretotide that is a single-indication drug.

A: Approved without restrictions / **N:** Not Approved / **A*:** Optimised by NICE / **A-CDF:** Recommended – CDF by NICE / **CDF:** Cancer Drugs Fund / **D:** Guidance still in development. / **#:** Lutetium (177 Lu) oxotretotide is the only medicine in the table with a single indication. All other drugs have multiple indications.



Candidate Drug (molecule name)	Number of indications	General Information (by drug)		Decision Outcomes (by indication)				Orphan indication considerations (by indication)	
		Multi-indication drug	Evaluation process	Appraisal Type		Uncertainty noted	CDF process	ICER per QALY	Other special considerations: EOL/QALY Weighting
				STA	HST				
Eculizumab	2	Yes	HST	(D)	(A*)	Yes	HST1: Not eligible	HST1: Not mentioned	HST1: QALY weighting not considered (low incremental QALYs)
Asfotase alfa	1	No	STA	-	(A*)	Yes	HST6: Not eligible	HST6: Not mentioned	HST6: QALY weighting not considered
Ataluren	1	No	STA	-	(A)	Yes	HST3: Not eligible	HST3: Not mentioned	HST3: QALY weighting not considered (low incremental QALYs)
Burusomab	1	No	HST	-	(A**)	Yes	HST8: Not eligible	HST8: £(113k, 150k)	HST8: could meet criteria for applying QALY weighting
Darvadstrocel	1	No	STA	(N)	-	Yes	TA556: Not eligible	TA556: Uncertain, but declared as unlikely to be cost-effective	TA556: EOL Not considered.
Eligustat	1	No	STA	-	(A)	Yes	HST5: Not eligible	HST5: Not mentioned	HST5: QALY weighting not considered (low incremental QALYs)
Inotersen	1	No	HST	-	(A)	Yes	HST9: Not eligible	HST9: £150k	HST9: criteria not met for QALY weighting (low incremental QALYs)
Letermovir	1	No	STA	(A)	-	Yes	TA591: Not eligible	TA591: £24k	TA591: EOL not considered
Migalastat	1	No	STA	-	(A*)	Yes	HST4: Not eligible	HST4: Not mentioned	HST4: QALY weighting not considered (low incremental QALYs)
Nusinersen	1	No	STA	(A)	-	Yes	TA588: Not eligible	TA588: Not disclosed but declared as acceptable in terms of use of NHS resources	TA588: EOL could be met for early onset SMA
Patisiran	1	No	STA	-	(A)	Yes	HST10: Not eligible	HST10: £80k	HST10: Does not meet criteria for applying QALY weighting (low incremental QALYs)
Pirfenidone	1	No	STA	(A*)	-	Yes	TA504: Not eligible	TA504: £58k	TA504: EOL not applicable
Voretigene neparvovec	1	No	HST	-	(A**)	Yes	HST11: Not eligible	HST11: £(114k, 155k)	HST11: Met criteria for QALY weighting.

TABLE 2: SUMMARY OF CANDIDATE NON-ONCOLOGY MEDICINES

N=13 non-oncology drugs; i = 14 indications. No submissions found for non-orphan indications for these medicines.

A: Approved without restrictions / **N:** Not Approved / **A*:** Optimised by NICE / **A-CDF:** Recommended – CDF by NICE / **CDF:** Cancer Drug Fund / **D:** Guidance still in development.

2.3 Common challenges identified in submission summaries

We reviewed the full set of candidate submissions to identify common challenges in the context of a conceptual framework developed by Nicod et al. (2019). This framework identifies three types of challenge in the development of orphan and ultra-orphan medicines: **clinical challenges** associated with the small number of patients, a lack of knowledge about the disease, or a lack of clinical expertise on a disease; **regulatory challenges** associated with a lack of appropriate incentives or processes to overcome the clinical challenges; and **economic challenges** associated with the costs of commercialising orphan and ultra-orphan medicines, and the financial burden on patients, family, carers, and society. For consistency with the previous OHE report (Henderson et al., 2020), we have included **ethical challenges** along with regulatory challenges.

Regarding the **clinical challenges**:

- Uncertainty is mentioned by NICE in the appraisal of many of the candidate medicines in the context of the clinical evidence and the economic model. These references are often related to the small number of patients and the higher-than-average variability in patient outcomes.
- It is rare to observe appraisals explicitly incorporated patient input beyond quality-of-life surveys.

Regarding **regulatory & ethical challenges**:

- There were no recommended orphan non-cancer indications' medicines with multiple indications among the submissions identified. There were only a few **full** recommendations for **any** orphan indications, and these were for single-indication medicines. This seems to suggest a failure of the appraisal process to account appropriately for the challenges of assessing orphan and ultra-orphan medicines, particularly in terms of the lack of an assessment route for medicines for rare conditions to complement the HST pathway for ultra-orphan medicines.
- The average time to decision for ultra-orphan medicines was longer than non-orphan medicines, highlighting further challenges in assessing ultra-orphan medicine evidence.
- A majority of orphan cancer indications were recommended for observation in the CDF and met the eligibility criteria but were not ultimately added. In some cases, as noted in the case studies, this may reflect the reluctance of some companies to participate in the CDF. The reimbursement price in the CDF is based on the most pessimistic interpretation of the available data, typically resulting in a substantial discount relative to the proposed price. The unequal burden imposed by this approach reinforces the idea that the CDF should not be seen as a routine or default solution to resolving uncertainty in the evidence around ultra-orphan medicines, and a more pragmatic approach to assessing OMPs is required.
- Many orphan medicines were recommended for a subgroup of the potential patient population, further complicating the assessment of evidence from small clinical trials and potentially raising equity concerns around access to treatment.

Regarding **economic challenges**:

- A higher proportion of orphan compared to non-orphan medicines fail to be recommended when assessed via the STA route. These rejections are typically based on ICERs for orphan medicines exceeding standard cost-effectiveness thresholds, which suggests a possible failure of the STA process to adapt to recognised economic challenges of orphan and ultra-orphan medicines.

3 Case studies

3.1 Selected cases

From the full set of candidate submissions described in the previous section, the following cases were selected to illustrate a range of issues across different appraisal routes (STA and HST), indications (oncology and non-oncology), orphan status, and final recommendation.

- Everolimus (NICE TA432):** An orphan oncology indication (second-line treatment of metastatic renal cell carcinoma) that has been assessed via STA and has multiple indications. This drug was selected because the initial appraisal showed that it is an orphan cancer medicine recommended under STA, with an estimated ICER close to £50,000 per QALY gained, and similar survival benefits to the comparator, but with significantly lower overall costs.

Burosumab (NICE HST8): An ultra-orphan medicine for a non-oncology indication (X-linked hypophosphataemia in children and young people) was assessed via HST with a single indication. Within the HST framework, the magnitude of QALY gains affects the acceptable threshold (larger absolute gains are assessed against a higher cost per QALY threshold). In this case, the absolute QALY gains were assessed against an acceptable threshold of £150,000 per QALY gained, and despite the Committee noting “considerable amounts of uncertainty”, burosumab was recommended as a cost-effective use of NHS resources.
- Midostaurin (NICE ID1573):** A multi-indication drug, the first indication for acute myeloid leukaemia, was appraised via STA and recommended by NICE (TA523). This case study focuses on a second indication in an orphan disease that has recently been appraised via the STA pathway.
- Nusinersen (NICE TA588):** A single indication orphan medicine for a non-oncology indication (Spinal Muscular Atrophy, SMA) assessed via STA. This case study was specifically selected to contrast with the evaluation of midostaurin as it was considered by the same Committee allocated to the midostaurin for advanced SM appraisal and had a similar prevalence.
- Ibrutinib (NICE TA429):** An orphan oncology indication, assessed via STA, with multiple indications (orphan indication is for treating chronic lymphocytic leukaemia). This drug was selected as an example of less-positive practice of assessment. The medicine arguably met the requirements to be evaluated under the HST appraisal route but was assessed under STA.

The key characteristics of each case are summarised in [Error! Reference source not found.](#) on the next page.

TABLE 1: CASE STUDIES SELECTION CRITERIA AND DIMENSIONS

	Route of evaluation	
	STA	HST
Examples of positive practice	<p>Appraisal: Everolimus (AFINITOR) for the second-line treatment of metastatic renal cell carcinoma (NICE TA432)</p> <p>Description: Orphan cancer indication, evaluated via STA</p> <p>Multiple indications: Yes</p> <p>Outcome: Recommended (if provided according to the patient access scheme)</p>	<p>Appraisal: Burosumab (CRYSVITA) for treating X-linked hypophosphataemia in children and young people (NICE HST8)</p> <p>Description: Ultra-orphan non-cancer indication, evaluated via HST</p> <p>Multiple indications: No</p> <p>Outcome: Recommended (if provided according to patient access scheme)</p>
Examples of less positive practice	<p>Appraisal: Nusinersen (SPINRAZA) for spinal muscular atrophy (NICE TA429)</p> <p>Description: Orphan non-cancer indication, evaluated via STA</p> <p>Multiple indications: No</p> <p>Outcome: Recommended (if provided according to the managed access agreement, which includes further evidence generation requirements)</p>	<p>None fulfilled selection criteria – All published HST appraisals as of July 2021 have been recommended.</p>
	<p>Appraisal: Ibrutinib (IMBRUVICA) for Chronic lymphocytic leukaemia in adults who have had at least one prior therapy or who have a 17p deletion of TP53 mutation and in whom chemo-immunotherapy is unsuitable (NICE TA429)</p> <p>Description: Orphan cancer indication, evaluated via STA</p> <p>Multiple Indications: Yes</p> <p>Outcome: Recommended (if provided according to the patient access scheme)</p>	
	<p>Appraisal: Midostaurin (RYDAPT) for advanced systemic mastocytosis (NICE ID1573)</p> <p>Description: Orphan cancer indication, evaluated via STA</p> <p>Multiple indications: Yes</p> <p>Outcome: Recommended (if provided according to the commercial arrangement with NHSE)</p>	

These cases are discussed in detail in the following section, incorporating information from each medicine’s HTA appraisals and committee reports, as well as input from the key stakeholder interviews.

3.2 Case studies

3.2.1 Everolimus for advanced renal cell carcinoma after previous treatment (TA432)

OVERVIEW

Drug: Everolimus (AFINITOR)

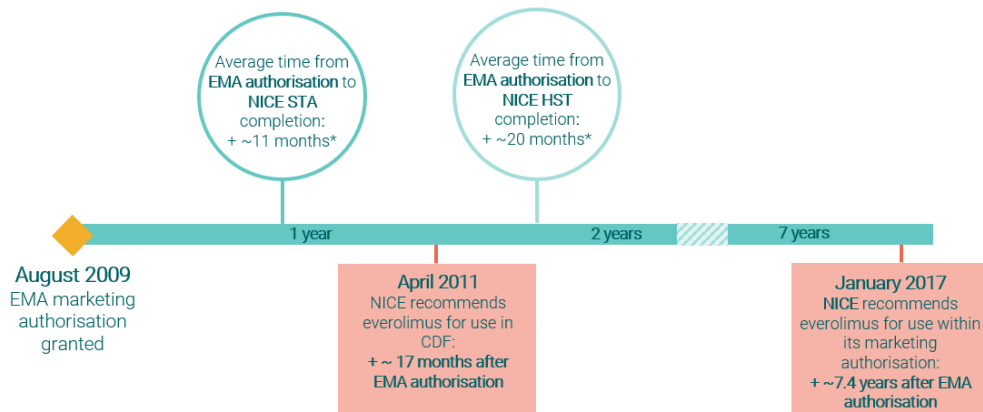
Indication: Second-line treatment of metastatic renal cell carcinoma (RCC)

HTA route: Single Technology Appraisal (STA)

Multiple indications: Yes

NICE recommendation: recommended if the company provides a confidential discount agreed in the patient access scheme.

FIGURE 1: TIMELINE OF EVEROLIMUS APPROVAL FROM EMA AUTHORISATION



* Time from EMA marketing authorisation being granted. Taken from 2015-2019 median review time from Medicines Tracker

BACKGROUND

Renal Cell Carcinoma (RCC) accounts for 2% of global cancer diagnoses and deaths (Padala et al., 2020). The majority of cases are men who have a 70% increased risk of RCC compared to women. The survival rate is highly dependent on the stage of the cancer at diagnosis: 30% of patients with RCC present with advanced disease at diagnosis and a resulting late-stage 5-yr survival of only 12% (Tannir et al., 2018). RCC also has the poorest survival rate of all urological cancers (Padala et al., 2020).

Everolimus has marketing authorisation in the UK for second-line treatment for patients with advanced RCC for whom first-line therapy with tyrosine kinase inhibitors sunitinib and pazopanib have failed. Other second-line treatments include axitinib and cabozantinib, nivolumab, and levanitinib used in combination with everolimus (Tannir et al., 2018). During the time that everolimus was included in the CDF (i.e., between the first and the second everolimus NICE appraisals), axitinib and nivolumab were recommended for second-line treatment of RCC by NICE.

The TA432 appraisal was a CDF reconsideration of a previous technology appraisal of everolimus for second-line treatment of advanced RCC. Following inclusion in the CDF and a discount through the NHS patient access scheme, the NICE appraisal committee judged everolimus compared to the standard of care, axitinib, to be cost-effective at a threshold of £30,000/QALY. The Committee judged

that everolimus met the criteria for a life-extending, end-of-life treatment; however, due to the discount provided through an extension of an existing patient access scheme covering a different indication, everolimus ultimately met the standard £30,000/QALY threshold (NICE, 2017a).

KEY CHALLENGES DURING NICE APPRAISAL

A significant challenge during this appraisal was the substantial uncertainty around the evidence presented in the first appraisal. As a result of this uncertainty, everolimus was funded through an early version of the CDF that did not include an explicit evidence-generation objective. In the re-appraisal, the Committee reviewed evidence of the superiority of everolimus versus placebo, both with best supportive care. Uncertainty in estimating overall survival gain was a key determinant of cost-effectiveness and was discussed in depth by the Committee. The uncertainty stemmed from the fact that in RECORD-1, the pivotal placebo-controlled trial, 81% of the patients on the placebo crossed over to the everolimus arm. For this reason, estimates of overall survival using an intention-to-treat analysis were confounded, and overall survival gain was instead estimated using statistical modelling.

There was further uncertainty in the evidence as the standard of care changed between the first and second everolimus appraisal. During the time that everolimus was reimbursed through the CDF, axitinib was approved by NICE, which replaced best supportive care as the comparator for everolimus. As a result, the evidence for the efficacy of everolimus was compared to axitinib using matched indirect comparison because it was not observed in the original trial population.

RESOLUTION

Two different modelling techniques were used by the manufacturer to estimate overall survival using the data from the RECORD-1 trial. There were significant differences in the estimates used by different modelling techniques and depending on the underlying assumptions. The Expert Review Group's (ERG) analysis differed from the manufacturer's estimates using the same techniques as a result of differences in the assumptions of the model. The Committee concluded that it was likely that survival gain was at least three months.

Importantly, in addition to the quantitative approaches used to cover the evidence gap, the Committee also considered the testimony of clinical experts to add context to the economic modelling. For example, a concern that everolimus would increase treatment costs because of higher observed rates of adverse events associated was assuaged through clinician testimony that adverse events could be managed by cost-neutral 'treatment holidays'. It is likely that this testimony was based in large part on experience with everolimus in clinical practice through its funding under the CDF, highlighting the role of the CDF in generating real-world evidence and broadening clinical experience with innovative treatments, and the importance of informed clinical input to the appraisal process.

DISCUSSION

From a positive perspective, this case highlights how clinical uncertainty around orphan medicines can be managed better by incorporating real-world data collection and informed clinical input. However, there is no clear guidance on the extent to which clinical input informed by real-world practice should be accepted as a substitute for evidence generated as part of a controlled trial or how that acceptance may vary according to appraisal stream or other contextual factors. The NICE guidance on the HTA process states that 'the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases. However, the guidance does not specify how this inherent uncertainty should be considered and does not explicitly address a higher tolerance for clinical uncertainty in evidence around rare and ultra-rare diseases. Each Committee (and each committee member) uses their own discretion in judging the acceptable level of uncertainty and the best approach to address that uncertainty. In the case of everolimus, the Committee allowed the manufacturers to overcome



evidence gaps through the use of bespoke statistical modelling supplemented by expert clinical testimony.

As noted, evidence generation was not a primary objective of early iterations of the CDF, and the incidental data generated in this case did not resolve the gaps in the clinical evidence. However, the use of everolimus within the CDF enabled clinicians to become aware of the treatment and its benefits, allowing expert clinician testimony to resolve the concerns of the Committee in key areas.

Notwithstanding the relative delay in coverage, everolimus can be seen as positive practice. The Committee accepted bespoke statistical modelling to resolve important gaps in the clinical evidence, and referral to the CDF allowed clinicians to develop practical experience with everolimus that contributed to a resolution of Committee concerns.

3.2.2 Burosumab for treating X-linked hypophosphataemia in children and young people (HST8)

OVERVIEW

Drug: Burosumab (CRYSVITA)

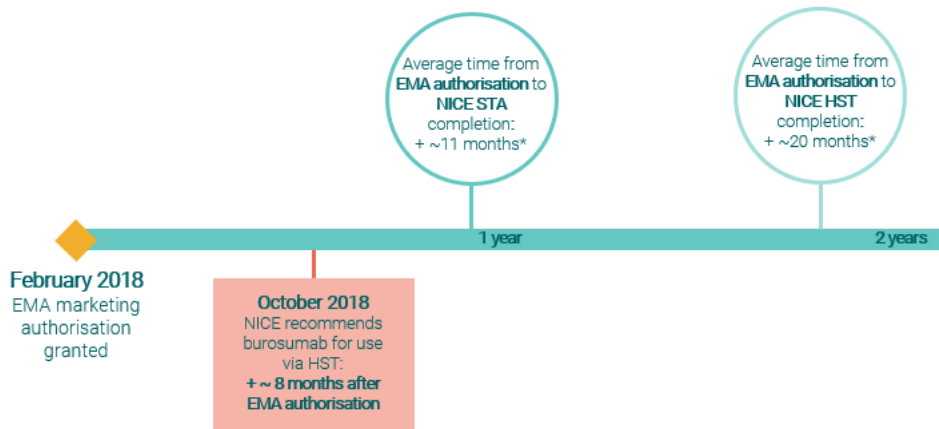
Indication: X-linked hypophosphataemia in children and young people

HTA route: Highly Specialised Technologies (HST)

Multiple indications: No

NICE recommendation: recommended if the company provides it according to the commercial arrangement

FIGURE 2 TIMELINE OF BUROSUMAB APPROVAL FROM EMA AUTHORISATION



* Time from EMA marketing authorisation being granted. Taken from 2015-2019 median review time from Medicines Tracker

BACKGROUND

X-linked hypophosphataemia (XLH) is a rare, genetic, chronically debilitating and deforming condition characterised by low levels of phosphate in the blood. Patients most commonly present in childhood with bowed or bent legs, disproportionately short stature, bone pain, delayed walking, and dental anomalies. Symptoms generally present at 12–15 months of age, but diagnosis can be sooner if there is a family history of XLH. According to the NICE HST final scope for burosumab, it is estimated that there are approximately 250 children and young people with XLH in England and up to 2,500 adults with the condition (NICE, 2017b).

Prior to the introduction of burosumab, there were no treatments that targeted the underlying cause of XLH, and the condition was managed medically with the aim of improving growth, decreasing morbidity, and preventing skeletal deformities (NICE, 2017b).

Burosumab is a monoclonal antibody that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23). By inhibiting FGF23, burosumab blocks its activity, allowing reabsorption of phosphate by the kidneys and, through vitamin D production, improve intestinal absorption of calcium and phosphate. In 2014, burosumab was granted orphan designation by the EMA, and in 2018 it received conditional marketing authorisation whilst the company continued to gather evidence.

KEY CHALLENGES DURING THE NICE APPRAISAL

Burosumab was evaluated via the HST appraisal route. According to the published committee papers, the participating patient organisation and clinical expert estimated that XLH is present in around 1 in 20,000 to 1 in 60,000 of all births in the UK.

As seen in many appraisals of medicines for ultra-orphan conditions, one of the main challenges was around the uncertainty of evidence, and the Committee initially rejected burosumab on the basis of this uncertainty. They noted that the clinical trials suggested burosumab provided short-term clinical benefits in children between 1 and 12 years, but that the evidence was limited and uncertain, and there was no evidence in adolescents. The Committee recognised that there was likely to be some lifetime benefit for people treated with burosumab, as it can prevent irreversible bone damage. However, they concluded that the long-term consequences of the progressive bone disease and ongoing metabolic symptoms of XLH – which would not be affected by burosumab – were uncertain. Furthermore, initial cost-effectiveness estimates for burosumab were much higher than the range NICE normally considers acceptable, even for highly specialised technologies (£100,000-£300,000 per QALY), and thus was not recommended for use in the NHS.

RESOLUTION

Following the consultation period, the manufacturer of burosumab presented additional evidence to the Committee in the form of the results of a phase 3 study comparing burosumab with conventional therapy. This evidence confirmed the long-term disease progression of XLH into adulthood. They also provided an updated economic analysis with a patient access scheme (PAS). In the final evaluation document, the Committee recommended burosumab on the basis of the updated commercial arrangement. The Committee concluded that the updated ICER was in the range of £113,000 to £150,000 per QALY gained; while this is higher than the standard £100,000 per QALY usually applied to HST evaluations, the incremental QALY gains (estimated at around 15 QALYs) meant that the criteria for applying QALY weighting were met.

DISCUSSION

Initial cost-effectiveness estimates for burosumab were beyond the range considered acceptable by NICE, even with additional considerations allowed through the HST appraisal route, and the Committee had concerns around the evidence for the long-term health impact of XLH. However, the manufacturer was able to provide additional evidence regarding long-term health impact, and the higher acceptable cost-effectiveness threshold for HSTs, combined with a revised PAS, allowed NICE to recommend the treatment for routine use.

Many of the challenges associated with appraising ultra-orphan medicines were observed in this case study, including a limited evidence base, particularly in terms of the long-term benefits of the treatment and a relatively high cost per QALY gained. NICE and the manufacturer were able to use the consultation period effectively to generate additional evidence and the higher threshold of the HST process to ensure patients had access to this innovative treatment. However, it should be noted that additional data may not be available during the consultation period in all circumstances and delaying a decision until full evidence is available risks serious health consequences to patients in need whilst access to an innovative treatment is withheld. In these circumstances, we suggest that further evidence should be collected while in use and NICE should exercise flexibility to finetune recommendation based on the real world evidence.

3.2.3 Nusinersen for treating spinal muscular atrophy (TA558)

OVERVIEW

Drug: Nusinersen (SPINRAZA)

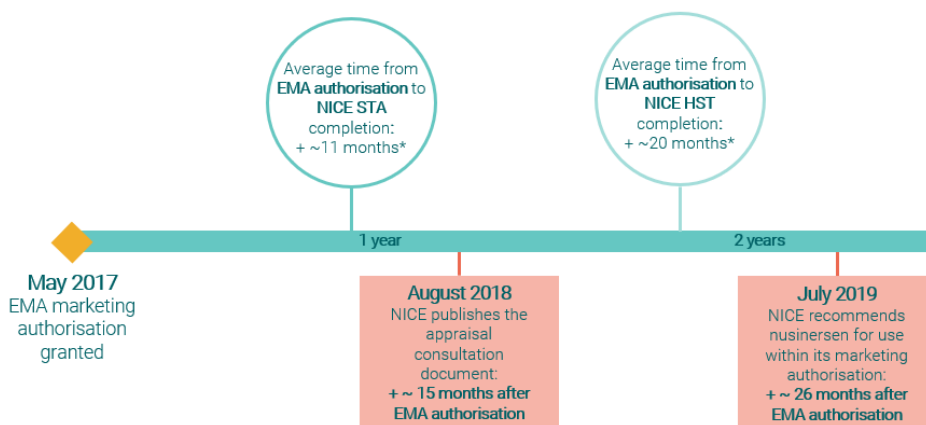
Indication: Spinal muscular atrophy (SMA)

HTA route: Single Technology Appraisal (STA)

Multiple indications: No

NICE recommendation: recommended if the conditions in the managed access arrangement are followed

FIGURE 3 TIMELINE OF NUSINERSEN APPROVAL FROM EMA AUTHORISATION



* Time from EMA marketing authorisation being granted. Taken from 2015-2019 median review time from Medicines Tracker

BACKGROUND

Spinal muscular atrophy, or SMA, is a rare genetic disorder that causes muscle weakness and progressive loss of movement (NICE, 2019a). SMA causes substantial disability and may lead to increased mortality and reduced life expectancy. The most severe forms of SMA typically cause death before the age of 2 years old, although people with later-onset types of SMA usually live into adolescence or adulthood. SMA affects an estimated 1 in 6,000 to 1 in 10,000 births worldwide, and the incidence varies between different types of SMA. It is estimated that about 100 people are born with SMA per year in the UK, and there are currently between 1,200 and 2,500 children and adults in the UK living with SMA.

Nusinersen is a 2'-O-methoxyethyl antisense oligonucleotide that stimulates the survival motor neuron (SMN)-2 gene to increase SMN protein levels. At the time of submission, there were no active treatments for SMA, and the condition was managed through multidisciplinary supportive care. In 2017, nusinersen was granted orphan designation by the EMA via their accelerated access process. This meant that due to its status as a medicine of major interest for public health, the timeframe for review was 150 evaluation days rather than 210.

KEY CHALLENGES DURING THE NICE APPRAISAL

The NICE Committee felt that there was a lack of long-term evidence, and thus the long-term benefits were highly uncertain. This led the Committee to issue a "Not Recommended" decision in the Appraisal Consultation Document. According to the ACD, the most plausible cost-effectiveness

estimates, based on the list price, were between £400,000 and £600,000 per QALY. The ACD noted that nusinersen was the first treatment to address the cause and natural history of motor neurone disease in SMA. Additionally, the Committee recognised that nusinersen is an innovative treatment but stated that it was not presented with any data to show distinct and substantial benefits that had not been captured in the economic analyses.

Section 3.20 of the ACD refers to the manufacturer's view that nusinersen should have been considered for evaluation via the HST appraisal route and to NICE's decision to apply the STA route. NICE judged that "the population covered by the marketing authorisation is larger than that which can be considered in HST evaluations, and SMA is not commissioned through a highly specialised service".

RESOLUTION

Following the consultation period, the Committee overturned their initial decision and issued a positive recommendation for nusinersen as an option for treating 5q SMA. Although NICE chose to assess nusinersen under the STA appraisal route, they noted that "the committee was mindful during its decision-making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease". This decision was accompanied by a managed access agreement to address uncertainties in the way of additional evidence generation; it was proposed that the arrangement should last five years with at least three years of additional data collected for analysis. This decision represented a step forward for patients suffering from spinal muscular atrophy, a disease with considerable unmet need. In the final appraisal document, the Committee acknowledged the difficulty of appraising drugs for very rare conditions, with the title of the concluding section indicating that "It is appropriate to be flexible when considering uncertainty".

DISCUSSION

This case study demonstrates the concerns relating to the HST inclusion criteria; the manufacturer of nusinersen believed that it would be a candidate for evaluation via the HST process given the small patient population. Interestingly, the estimated number of patients suffering from SMA (between 1,200 and 2,500 children and adults) is comparable to those suffering from X-linked hypophosphataemia as seen in the previous case study (around 250 children and up to 2,500 adults). The final appraisal document for nusinersen stated that "although nusinersen has several features that are commonly seen in the highly specialised technologies programme, [...] the population covered by the marketing authorisation is larger than that which can be considered in HST evaluations", this raises questions concerning NICE's definition of the relevant population for rare and ultra-rare conditions. Furthermore, there is no explicit prevalence threshold for consideration under HST, so it is difficult to understand the basis for this objection. The document also argued that SMA is not commissioned through a highly specialised service. However, during our qualitative interviews, it became apparent that the definition of a highly specialised service is unclear and that manufacturers and patient representatives would value further clarification and agreement upon the details of what constitutes a 'highly specialised' service.

Another point for discussion is how the NICE Committee came to the decision to accommodate a positive recommendation with evidence development outside of the Cancer Drugs Fund. Whilst this kind of recommendation is possible for non-cancer drugs, they are extremely infrequent. It is clear that in this case, NICE accepted that coverage with evidence development was a valuable and viable option. This begs the question of whether a bias against non-cancer orphan drugs has arisen because of their ineligibility for the Cancer Drugs Fund. It is hoped that the Innovative Medicines Fund will address this imbalance between cancer and non-cancer medicines.

NICE announced on October 29th, 2020, that it had begun the process to review data collected as part of the Managed Access Agreement for nusinersen.

3.2.4 Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429)

OVERVIEW

Drug: Ibrutinib

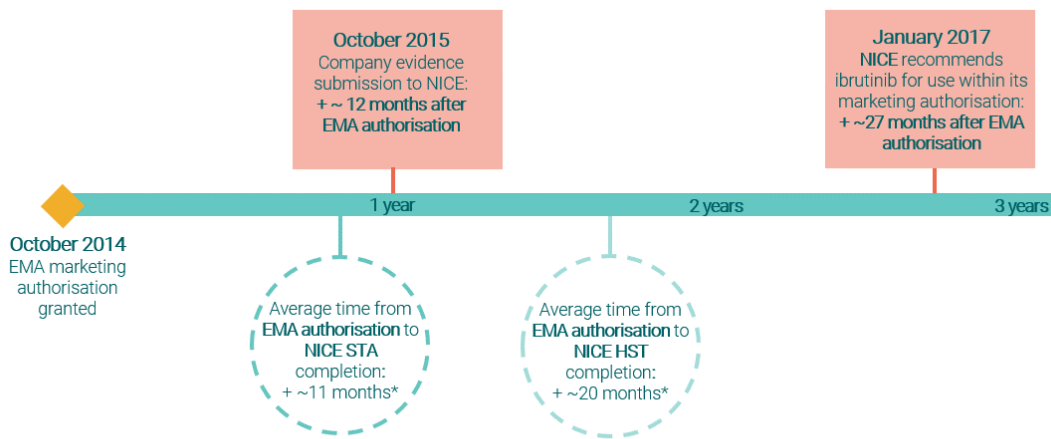
Indication: Chronic lymphocytic leukaemia in adults who have had at least 1 prior therapy or who have a 17p deletion of TP53 mutation and in whom chemo-immunotherapy is unsuitable

HTA route: Single Technology Appraisal (STA)

Multiple indications: Yes

NICE recommendation: Recommended if the company provided a confidential discount agreed in the patient access scheme.

FIGURE 4 TIMELINE OF IBRUTINIB APPROVAL FROM EMA AUTHORISATION



* Average timing from EMA authorisation taken from 2015-2019 median review time from Medicines Tracker

BACKGROUND

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in western countries, accounting for 1.2% and 1% of all new cancer cases in the USA and UK, respectively, with a prevalence of 4.9 cases per 100,000 adults in the US in 2020 (Cancer Research UK, 2015; NIH National Cancer Institute, n.d.; Parmar et al., 2014). It is most prevalent in the elderly, with a median age at diagnosis of 72. The clinical course is variable, with some people experiencing low level disease for decades without requiring treatment while others experience aggressive disease with low rates of survival and few effective treatment options. 5%-10% of people diagnosed with CLL have high-risk disease with characteristic oncogenic mutations (i.e., 17p deletion or a TP53 mutation). High-risk CLL has faster cell growth and increased treatment resistance compared to low-risk CLL.

Ibrutinib was developed as a chemotherapeutic for CLL and received marketing authorisation from the EMA in 2014 for use in people with CLL with a 17p deletion or TP53 mutation who have received at least one prior therapy. There are several treatment options for the patient population covered by the marketing authorisation, including: fludarabine with cyclophosphamide and rituximab; bendamustine; chlorambucil; corticosteroids and; idelalisib with rituximab. In 2012, ibrutinib was granted orphan designation by the EMA for the treatment of chronic lymphocytic leukaemia (European Medicines Agency, 2012). The final scope document was published by NICE in September 2015 to appraise ibrutinib through the STA route following the company evidence submission in October 2015.

There was intense media and political attention following NICE's appraisal and NHS England's decision to restrict ibrutinib's reimbursement to patients who relapse within three years (Smyth, 2018). Arguably, this attention, as well as pressure from patient groups and clinicians, forced NHS England to reverse their decision. They agreed to reimburse the 200 to 300 patients each year who relapse after the three-year cut-off (O'Neill, 2018).

KEY CHALLENGES DURING THE NICE APPRAISAL

NICE decided to appraise ibrutinib through the STA appraisal route. The main challenge in the appraisal was uncertainty in the clinical evidence presented to NICE. This was likely due, in part, to the unusual circumstance in which ibrutinib was put forward for NICE appraisal. NICE approached Janssen to provide evidence on ibrutinib explicitly for consideration within the CDF in April 2016 because of a perceived need in the CLL patient population. The company chose not to apply to the CDF on the grounds that there was already sufficient observational data to support the efficacy of ibrutinib in this indication and that additional evidence generation via the CDF would not resolve any remaining uncertainties, particularly around comparative effectiveness. The Committee ultimately agreed that the uncertainty in the submitted evidence would not be resolved through additional observational evidence given the small population sizes for this indication and the short duration within the CDF. It was for this reason that the evidence package had a greater degree of uncertainty than typical STA submissions. The positive recommendation came in August 2017, well over a year after the Committee approached Jansen about including ibrutinib for use under the CDF.

The uncertainty in the clinical evidence centred on the design of the pivotal trials, which used different patient populations and comparators from those preferred by NICE for this appraisal (NICE, 2017c). For example, the company did not present evidence for untreated patients with a 17p deletion or any evidence in patients with a TP53 mutation. To overcome this, NICE considered the evidence presented from previously treated patients to judge the efficacy in untreated patients. In addition, data on progression-free survival were judged to be 'immature' because the pivotal study was concluded early after an interim analysis revealed a positive treatment effect at a median trial duration of 9.4 months. At 16-months follow-up, the ibrutinib arm still had not reached median progression-free survival; however, data from 30-months follow-up allowed the Committee to conclude that the 'immature' data was indicative of the efficacy of ibrutinib.

The company could not present data on the comparator preferred by NICE: the standard of care in the UK idelalisib plus rituximab. RESONATE, the pivotal trial instead used the comparator of idelalisib plus ofatumumab. Ofatumumab had previously been made available through the CDF but had ultimately not been recommended by NICE as it had not been proven clinically or cost-effective. The company argued, however, that the comparators (idelalisib-rituximab and idelalisib-ofatumumab) were clinically equivalent, and this view was supported by clinical experts. The company also could not present any information comparing ibrutinib with best supportive care for patients who could not take idelalisib. The Committee ultimately concluded that the magnitude of benefit with ibrutinib relative to standard of care suggested that it was also likely to be more effective relative to best supportive care than idelalisib and rituximab.

RESOLUTION

The submission generated concerns over the appropriateness of the pivotal trial comparator, the patient populations represented in the evidence submission, and the substantial uncertainty around estimates of efficacy in terms of progression-free survival. However, the Committee accepted qualitative evidence- in the form of patient and clinician testimony- that ibrutinib was an important innovation in CLL, a disease that has few effective treatment options. NICE drew on clinician testimony to conclude that ibrutinib was an innovative drug as it was first-in-class and offered patients an oral therapy option. Clinician experts stressed the need for new CLL treatments, including second-line treatments such as ibrutinib. The Committee also recognised patient testimony around

the value of different treatment options. Ibrutinib was felt to be particularly valuable to patients as it ameliorates symptoms, including fatigue, that has a significant impact on quality of life.

NICE accepted that these unmet needs justified ibrutinib at an ICER greater than the conventional STA threshold of £20-30k/QALY gained. Ibrutinib was ultimately recommended as a cost-effective treatment for CLL against the end-of-life threshold of £50K/QALY. It was judged that ibrutinib met both the short life-expectancy criteria and the minimum life-extending criteria in order for the end-of-life thresholds to be used. This higher threshold was achieved only by the best-case scenario and following a discount through the patient access scheme (Adkins et al., 2017).

On the basis of the submitted evidence and accepting that additional real-world data collection was unlikely to resolve the uncertainty in the clinical evidence, NICE recommended ibrutinib within its marketing authorisation for treating chronic lymphocytic leukaemia in adults who have had at least one prior therapy or who have a 17p deletion of TP53 mutation and in whom chemo-immunotherapy is unsuitable. The recommendation was made on the condition that the company provided a discount agreed upon within the patient access scheme.

DISCUSSION

In light of the uncertainty in the clinical data, the lack of evidence for key populations, and the use of a comparator that was not standard-of-care in the UK, testimony from patients and clinical experts appears to have been influential in NICE's positive decision. Following patient testimony, the Committee specifically noted that they 'understood the importance of having different treatment options available for treating CLL' and that they 'heard that patients appreciated how well the treatment worked and how easy it was to take'. As CLL is a rare condition, many clinicians who have experience with leukaemia will not have experience with CLL specifically. It is positive that, in the case of this appraisal, NICE consulted with clinicians who were experts in CLL and the treatments, one having been an investigator in the pivotal RESONATE trial in the UK.

In addition to explicitly incorporating patient values and clinician expert input in their decision, NICE also considered end-of-life value criteria, the use of a patient access scheme to address evidence limitations, and the value of innovation as ibrutinib is a first-in-class medicine (Adkins et al., 2017). This reflects a positive and collaborative process by which uncertainty in clinical evidence inherent to orphan indications was resolved through consideration of patient and clinician input.

After initially recommending the CDF to gather additional evidence, NICE accepted that further data collection was unlikely to resolve inherent uncertainties stemming from a relatively small patient population and heterogeneous disease course. Notwithstanding these limitations in the evidence, NICE were ultimately able to recommend ibrutinib, albeit with an undisclosed discount. This suggests that NICE was willing to adapt its evidence requirements to recognise the challenges associated with medicines for ultra-rare conditions. Notably, this case suggests that some recommendations to the CDF may be inappropriate or unnecessary in contexts where evidence generation in clinical practice is unlikely to address key evidence gaps. In this case, a positive outcome was reached through the consideration of wider evidence, including the views of patients and clinician experts.

While the NICE process handled the clinical uncertainty of ibrutinib effectively through the consideration of this wider evidence, NHS England's decision to restrict the eligible patient population post-NICE recommendation is one of a series of post-approval restrictions to approved indications. This case is concerning because NHS England used the level of clinical uncertainty as a justification for their decision. Specifically, they said that the clinical trial used for the NICE appraisal did not include patients who relapsed early (i.e. within three years) and therefore restricted access to these patients despite them being included in NICE's eligible population (Smyth, 2018). If NHS England can override the legal mandate of a NICE positive recommendation, then the HTA process will be undermined and fail to appropriately incentivise the development of high-value medicines. Where



concerns over the representativeness of the data may exist, they are more appropriately addressed in the context of the economic evaluation rather than post hoc restrictions. This is particularly the case for medicines for rare and ultra-rare diseases where the evidence assessment is already complex.

3.2.5 Midostaurin for treating advanced systemic mastocytosis (ID1573)

OVERVIEW

Drug: Midostaurin (RYDAPT)

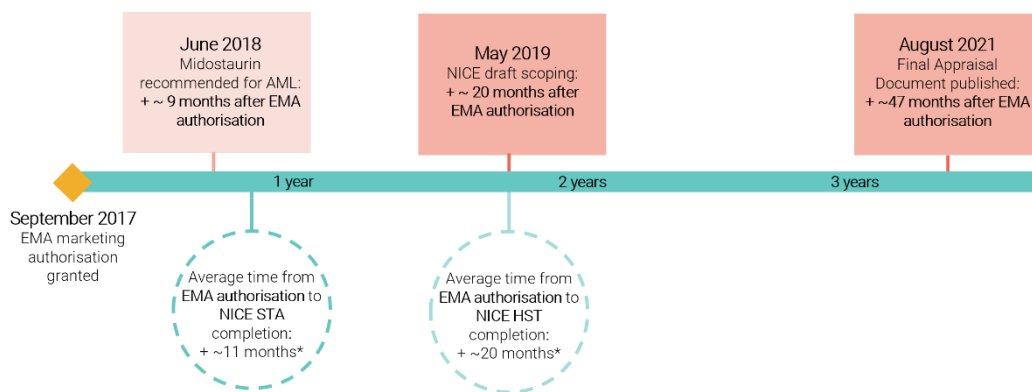
Indication: Advanced systemic mastocytosis

HTA route: Single Technology Appraisal (STA)

Multiple indications: Yes

NICE recommendation: Recommended if provided according to the confidential commercial arrangement with NHSE

FIGURE 5: TIMELINE OF MIDOSTAURIN APPRAISAL FROM EMA AUTHORISATION



* Average timing from EMA authorisation taken from 2015-2019 median review time from Medicines Tracker

Advanced SM was initially excluded from the NICE Topic Selection process in 2015, as NICE deemed midostaurin for treatment of advanced SM to be ‘out of scope’ due to a small patient population and an insufficient evidence base. However, it was subsequently included, following the reform of the Cancer Drugs Fund in July 2016, which included a new CDF mandate requiring that all new cancer medicines are now required to enter the NICE appraisal process before they are licensed. The timelines are therefore not wholly representative of the NICE process.

BACKGROUND

Mastocytosis encompasses a heterogeneous group of rare diseases, characterised by excessive amounts of mast cells gathering in body tissues, such as the skin, organs, and bones. In many cases, mastocytosis is caused by a mutation in the KIT gene. The mast cells release large amounts of histamine and other mediators into the blood, causing symptoms such as skin rash, itchy skin, hot flushes, vomiting, diarrhoea, and anaphylaxis. In systemic mastocytosis, abnormal mast cells infiltrate various tissues and organ systems, such as the bone marrow, the spleen, the liver, lymph nodes, and/or the gastrointestinal tract. This results in a wide range of debilitating symptoms, including fatigue, itching, bone or muscle pain, osteoporosis, fractures, all of these being systemic symptoms related to histamine and leukotriene release and anaphylaxis, which can be severe. The wide spectrum of varied and severe symptoms confer a substantial negative impact on patient health-related quality of life, as well as a considerable burden on carers.

Indolent systemic mastocytosis, a nonprogressive form of systemic mastocytosis, accounts for about 90% of cases of systemic disease (NICE, 2019b), and advanced systemic mastocytosis (Advanced SM) accounts for the remaining 10%. Advanced SM is the most severe form of the

disease and comprises aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL). Given the rare and heterogeneous nature of the disease, midostaurin was granted orphan designation by the EMA for the advanced SM indication in 2010

The exact incidence and prevalence of advanced SM in England are unknown. A study from Denmark (Cohen et al., 2014) estimates the prevalence to be 0.4/100,000. The study also has an estimated incidence for each subtype: 0.31 per 100,000 for SM-AHN, 0.09 per 100,000 for ASM and <0.01 per 100,000 for MCL. Collectively this represents an average incidence of 0.06/100,000 for advanced SM, and as such, it is estimated that approximately 40 new patients are diagnosed with advanced SM in the UK each year (with 34 patients in England). As reflected in the subtype prevalence data, ASM is typically the least severe subtype of the three, followed by SM-AHN, then MCL, which has a life expectancy under a year.

Midostaurin is a multi-targeted kinase inhibitor, which inhibits FLT3, KIT and other receptor tyrosine kinases. Midostaurin has a marketing authorisation for both newly diagnosed FLT3+ acute myeloid leukaemia (AML) and for advanced SM. It received a NICE positive recommendation for the AML indication in June 2018 (NICE, 2018).

At the time of writing, there are no other licensed treatments for advanced SM. Patient and clinical experts advised that the condition has a poor prognosis with current unlicensed treatment options, particularly for SM-AHN and MCL. The NICE appraisal committee agreed that midostaurin met the criteria to be considered as a life-extending treatment at the end of life across all subgroups of advanced SM

Advanced SM was initially excluded from the NICE Topic Selection process in 2015, as NICE deemed midostaurin for treatment of advanced SM to be 'out of scope' due to a small patient population and an insufficient evidence base. However, it was subsequently included following the reform of the Cancer Drugs Fund in July 2016, which included a new CDF mandate requiring that all new cancer medicines must enter the NICE appraisal process before they can be licensed. The marketing authorisation of midostaurin was granted by EMA in 2017.

KEY CHALLENGES DURING THE NICE APPRAISAL

Only a subset of all patients with advanced SM are eligible for treatment with midostaurin, estimated to be roughly 174 people in the first year of midostaurin availability. Based on an English population of 55 million, this implies a functional prevalence of roughly 1 in 300,000. Despite this very small patient population, midostaurin was considered under the STA rather than the HST appraisal route. Treatments for advanced SM fulfil most (but not all) of the criteria for HST appraisal, with the key exception that "the technology is expected to be used *exclusively* [emphasis added] in the context of a highly specialised service". Midostaurin did not meet this criterion as it was already licensed for the treatment of acute myeloid leukaemia (AML) and is therefore not deemed a highly specialised service by NICE.

The clinical experts advised that the treatment pathway for advanced SM is complex, given that treatment is largely individualised based on symptoms and because of the heterogeneity of the disease subtypes and lack of licensed treatments. This makes it difficult to generalise the treatment pathway and to generate robust comparative clinical data.

Although the Committee acknowledged that midostaurin is more effective than current treatments, they deemed that the level of uncertainty was higher than typically accepted under NICE's STA process, primarily because midostaurin was indirectly compared with current treatments, which are all unlicensed rather than in a direct head-to-head trial. However, the Committee also acknowledged

that the evidence was sourced from the largest available trial in the treatment of advanced SM and that higher-quality comparative evidence was unlikely to become available. The overarching challenge in this case, can therefore be seen as the reluctance of the STA appraisal process to accept the uncertainty inherent around medicines for rare and ultra-rare conditions.

RESOLUTION

In the ACD, NICE concluded that while midostaurin can be considered innovative because there are no other licensed or targeted disease-modifying treatment options for people with advanced SM, it could not be recommended for routine use because cost-effectiveness estimates were substantially higher than the £50,000 per QALY gained threshold for survival extending treatments at the end of life. This conclusion was disputed by the manufacturer, who argued that the result was based on an overly conservative estimate of benefit and that more realistic assumptions produced an acceptable ICER relative to STA's £50,000 per QALY gained threshold. Following the consultation period, the manufacturer reached an agreement with NHS England and NICE that allowed midostaurin to be recommended, without needing to go to a second committee meeting. The FAD details the committee's rationale as follows. First, the committee noted that midostaurin could be considered a life-extending treatment at the end of life, which attracted an ICER threshold of £50,000 per QALY. Second, the cost-effectiveness estimates based on the committee's preferred assumptions and the updated commercial arrangements were below £50,000 per QALY. Third, the committee acknowledged that despite the uncertainty resulting from limitations in the clinical and comparative effectiveness evidence, it had seen enough evidence to conclude that the incremental QALY estimates from the model might not capture all the quality of life benefits associated with current treatment options. Taken together, the committee concluded that despite the limitations in the evidence, the cost-effectiveness estimates were within what NICE considers acceptable and therefore, midostaurin could be recommended.

DISCUSSION

HTA processes do not always acknowledge or account for the difficulty of generating robust clinical and economic evidence in rare conditions, notwithstanding the comprehensive literature that supports this assertion (Henderson et al., 2020). In this case, NICE recognised the rarity of advanced SM and midostaurin as an effective, life-extending treatment at the end of life. However, in their draft guidance, they declined to recommend midostaurin for funding on the grounds that it did not meet the £50,000 per QALY gained threshold adopted under the STA appraisal route for end-of-life treatments and because of important uncertainties around comparative clinical benefit. NICE subsequently recommended midostaurin for funding in their Final Recommendation.

Changes proposed by NICE's methods review consultation emphasise greater flexibility and pragmatism in consideration of the evidence for treatments for rare conditions. Flexibility and pragmatism are essential to ensure timely patient access to orphan medicines with small patient populations, a lack of a well-defined standard of care, and often heterogeneous patient populations. It is possible that the Committee would have reached a different conclusion at the first Committee meeting if midostaurin had been evaluated under these proposed changes, implying that the rejection of the submission at the ACD stage may be based on the timing of the submission rather than the fundamental clinical or economic characteristics of midostaurin for advanced SM.

Furthermore, given the very low prevalence of advanced SM, there is an argument that the STA appraisal route was inappropriate for midostaurin for an orphan indication. This appraisal route was based primarily on the fact that midostaurin is already licensed for a non-HST indication. The HST criterion that a treatment must be used *exclusively* in the context of a highly specialised service means that most multi-indication medicines are effectively excluded from the HST appraisal route, regardless of the characteristics of the indication, and must meet the much more restrictive evidence

and cost-effectiveness criteria of the STA appraisal route. This exclusion on the basis of additional indications not under evaluation disadvantages all patients who could benefit from midostaurin or any other multi-indication medicine and will represent a growing inequity as more multi-indication or tumour-agnostic medicines are developed. (Pushpakom et al., 2019) The impact of excluding multi-indication medicines from the HST appraisal route is exacerbated by barriers to more flexible pricing arrangements. A current VPAS clause (3.36) requires manufacturers to demonstrate that provision of a drug is not commercially viable at a uniform price before flexible arrangements will be considered (Department of Health and Social Care, 2018). This inflexibility encourages manufacturers to focus on indications with the greatest commercial value, delaying or discouraging licensing in 'lower value' indications, even where there may be substantial need. There are concerns from patient groups and clinicians that denying access to midostaurin in an extremely small patient group suffering from a severe and life-threatening disease is unethical, given that midostaurin has been approved by NICE for a non-orphan indication acute myeloid leukaemia and is routinely commissioned by the NHS for that indication. UK patients with advanced SM will not have access to the first disease-modifying licensed medicine for the condition and will continue to be treated with unlicensed treatments without demonstrated efficacy.

In the end, the manufacturer reached an agreement with NHS England and NICE that allowed midostaurin to be recommended. Proposed pragmatic changes to NICE methods are on the horizon, and these updates endeavour to overcome challenges in accessing new health technologies. These changes are pivotal to secure rapid and fair access to clinically and cost-effective health technologies, with specific considerations for the appraisals for rare diseases which face unique barriers, as discussed throughout this report. The appraisal of midostaurin for advanced systemic mastocytosis highlights shortcomings of the current process and the need for these upcoming changes.

4 Summary & Discussion

This report builds on a previous OHE report on ethical and economic issues on the appraisal of medicines for ultra-rare conditions (Henderson et al., 2020) by illustrating some of the practical challenges encountered in the course of NICE evaluations of these medicines. It includes qualitative interviews with people who have been part of multiple evaluations, a high-level review of practical challenges commonly encountered in appraisals of rare and ultra-rare medicines, and detailed case studies illustrating specific challenges and how they were resolved.

The key stakeholder interviews identified a number of common themes:

- **Current structures for incorporating patient feedback into NICE recommendations are suboptimal.** Structures and practice should better facilitate patient involvement, particularly for rare and ultra-rare diseases where the impacts on patients and carers may not be as well-understood by committee members as the impacts of more common conditions.
- **There needs to be greater recognition of the value of innovation as a process.** First-in-class medicines embody fundamentally new approaches to treatment and hold the potential for dramatic improvements in outcomes. Such ‘first steps’ must be encouraged by valuing the process of innovation beyond initial outcomes.
- There were some concerns about **extending the current Cancer Drugs Fund to include non-cancer medicines in the form of a new Innovative Medicines Fund.** The main areas of concern were the criteria by which ‘innovation’ and eligibility for the Fund would be judged and what would happen in circumstances where additional data collection is unlikely to resolve uncertainty.
- Interviewees felt that the **criteria for consideration under the Highly Specialised Technologies are too subjective and open to differing interpretations**, which leads to concerns over fairness and equality. Finally, there was a consensus that there is **a need for more willingness by the NHS to adopt innovative pricing schemes, particularly where a medicine has multiple indications.** There was a general sentiment that the burden of gaining approval for different prices was so great that manufacturers often decide against seeking approval for new indications, even where there is evidence of substantial patient benefit in these indications.

These same themes were seen in a high-level review of NICE submission summaries for rare and ultra-rare indications, as well as additional clinical, regulatory, ethical and economic challenges. Some of the additional **clinical challenges** commonly noted in submission summaries included concerns about uncertainty in the evidence base around rare and ultra-rare conditions and a lack of explicit consideration of patient input. **Regulatory and ethical challenges** included longer decision times under the HST appraisal route relative to the STA route, the role of the Cancer Drugs Fund for rare and ultra-rare indications and, in a related point, the frequency with which additional data generation was requested in rare and ultra-rare contexts. A majority of orphan cancer indications were recommended for the CDF rather than full approval, reflecting concerns about uncertainty in the evidence. However, it was not always clear that additional data collection would resolve many of the underlying uncertainties, and there are instances of manufacturers declining to participate in the CDF for this reason. A more systematic approach to considering acceptable levels of uncertainty in orphan medicine submissions is still required. Equally, restricting the eligibility of the CDF to oncology medicines raises equity concerns for patients with non-oncological conditions. Finally, the key **economic challenge** was that a higher proportion of orphan compared to non-orphan medicines failed to be recommended when assessed via the STA appraisal route. These rejections are typically based on ICERs for orphan medicines exceeding standard cost-effectiveness thresholds, highlighting

a failure of the STA process to adapt to well-recognised economic challenges around the development of orphan and ultra-orphan medicines.

The case studies explored some of these same issues in more detail and highlighted the challenge of assessing uncertain evidence in the context of rare and ultra-rare conditions.

- In **the case of everolimus**, uncertainty was resolved through statistical modelling and expert clinical input, representing the use of alternative sources of information to come to a positive resolution. Conversely, **the case of ibrutinib** highlights an often-unrealistic expectation on the part of NICE that the CDF can resolve any and all uncertainties in the evidence base around medicines for rare and ultra-rare conditions. In this case, the manufacturer declined to participate on the grounds that real-world evidence was unlikely to resolve the uncertainty of concern. This 'reflexive' reliance on the CDF arguably highlights a lack of adaptive or pragmatic solutions to addressing the inherent challenge of greater uncertainty around evidence for rare and ultra-rare medicines. Similar concerns around uncertainty were encountered in **the case of nusinersen**. In this case, a creative managed access agreement was reached to provide coverage with data collection, similar to the CDF but in a non-oncology context. This was ultimately a positive resolution, but the *ad hoc* nature of the managed access agreement in this context highlights potential inequities in access to innovative medicines between oncological and non-oncological medicines.
- **The case of ibrutinib** highlights the benefit of clinician and patient input, as this input played an important role in reversing NICE's initial rejection of ibrutinib. As seen in other submissions, the initial rejection was driven by uncertainties in the evidence and concerns over the relevance of the comparator in the pivotal clinical trial. Ultimately the reversal was based on expert clinical input that the magnitude of benefit associated with ibrutinib was likely to be similar relative to NICE's preferred comparator, and patient input that second-line treatments such as ibrutinib were a pressing unmet need. Reversing the decision on the basis of expert testimony without further clinical data collection can be seen as a positive resolution of the submission.
- Finally, **the case of midostaurin** provides a recent example of the challenges associated with appraising multi-indication medicines for rare diseases. In this case, NICE recognised the rarity of the indication but declined to consider midostaurin under the HST appraisal route, primarily on the grounds that it is already approved in a non-HST indication. Notwithstanding this appraisal route, NICE appears to have afforded midostaurin the same flexibility and pragmatism demonstrated in the appraisals of everolimus and eventually ibrutinib. Ultimately, an agreement was reached between the manufacturer, NICE and NHSE, which allowed midostaurin to be recommended.

4.1 Challenges and resolutions in the context of NICE's methodological review

This report highlights a mixed record of flexibility and pragmatism in NICE appraisals. There are examples of creative solutions, including bespoke statistical modelling and expert testimony to resolve Committee concerns over important data gaps. There are also examples, though, of an expectation of gold-standard clinical evidence that is often not realistic in rare and ultra-rare diseases. In this context, we favourably note that NICE's recent methodological review (NICE, 2020) has made a point of encouraging greater flexibility and pragmatism in the consideration of uncertainty around treatments for rare diseases.

Importantly, NICE's review also notes that forms of evidence, including "qualitative evidence, expert elicitation and surrogate outcomes may be particularly relevant in rare diseases, **so additional clarity and guidance in the methods may be beneficial** [emphasis added]." Explicit recognition of the role of such 'alternative' forms of evidence in all contexts, but especially rare and ultra-rare diseases,

represents a substantial step forward in terms of flexibility. Greater clarity in how such evidence should be weighed alongside more conventional evidence is now urgently required.

Likewise, we would argue that greater clarity is required in the role of the CDF and the proposed IMF in general, and in rare and ultra-rare diseases in particular. As noted in the case studies, the CDF was considered almost reflexively whenever there were gaps or uncertainties in the evidence, with limited consideration of whether RWE collected through the CDF would actually resolve these gaps. The use of a medicine under the CDF can accelerate patient access and promote clinical experience with innovative treatment that can later help resolve key uncertainties or gaps in the evidence. Equally, however, the CDF is limited in its ability to generate data in the context of rare or ultra-rare conditions, where there is often no defined standard of care and/or heterogeneous patient experiences. We suggest that greater clarity is required around what evidence gaps the CDF and IMF can and should be expected to resolve in order to improve the consistency and effectiveness of its use across submissions.

The methodological review also highlights the need to clarify what is meant by a rare disease. It notes that there is a case for avoiding “specific provisions for rare diseases as much as possible” to ensure consistency in methods, but where “it is necessary to make specific provision (for example, in considering uncertainty and risk), it will be important to carefully define what is meant by a rare disease. As it stands, the distinction between “highly-specialised technologies” eligible for appraisal under the HST route, and other medicines for rare and ultra-rare conditions that are subject to the same evidence and cost-effectiveness standards of much more common conditions, is not clear. How NICE considers this distinction should be made clearer, and eligibility for the HST appraisal route broadened to include more medicines for rare and ultra-rare conditions.

4.2 Conclusion

This report highlights many of the challenges faced in the evaluation of medicines for rare and ultra-rare conditions and some examples of positive and less positive resolutions of these challenges in specific appraisals. We highlight as positive examples those appraisals that took a flexible and pragmatic approach to addressing uncertainties or evidence gaps inherent to treatments for rare and ultra-rare conditions, including the use of bespoke statistical modelling, expert testimony, and real-world evidence to supplement rigorous clinical evidence. Less positive examples fail to allow for the greater uncertainty inherent in treatments for rare and ultra-rare conditions and hold submissions to the same evidentiary and cost-effectiveness standards as treatments for much more common conditions. The recent NICE methodological review (NICE, 2020) has made a point of encouraging greater flexibility and pragmatism in the consideration of uncertainty around treatments for rare diseases, and we look forward to positive examples of this new approach in future appraisals.

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About us

Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

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Areas of expertise

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics