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Assessment of significant benefit for orphan medicinal products by European regulators may support subsequent relative effectiveness assessments by health technology assessment organizations

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To maintain orphan drug status at the time of market authorization, orphan medicinal products (OMPs) need to be assessed for all criteria, including significant benefit, by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). Subsequently, health technology assessment (HTA) organizations evaluate the same OMPs in their relative effectiveness assessments (REAs). This review investigates the similarities and differences between the two frameworks for six HTA organizations, including the European Network for HTA. We discuss differences between both assessment frameworks within five domains (clinical evidence used, patient population, intervention, comparators, and outcome measures) for all drugs. Five illustrative cases studies were selected for a qualitative review.

Orphan drug regulation

The European Union (EU) Orphan Drug Regulation was implemented in 2000 to stimulate the development of products for rare diseases, so-called OMPs, through distinct benefits for developers [1,2]. These include regulatory fee reductions, encompassing fees for protocol assistance (specific scientific advice for orphan drugs) and marketing authorization applications, and 10 years of market exclusivity [3]. Orphan drug designation can be requested at any time during the development of an OMP and must also be confirmed (maintained) at marketing authorization to receive 10 years of market exclusivity against similar products. The dedicated committee at the EMA that evaluates the eligibility for orphan drug benefits at these time points is the COMP. A negative COMP opinion at marketing authorization will not affect a positive benefit–risk balance as established by the Committee for Human Medicinal Products (CHMP), but results in a marketing authorization without orphan drug status. Since January 2018, orphan maintenance assessment reports (OMAR) have been published on the EMA website together with the European Public Assessment Report (EPAR), summarizing the rationale of the COMP opinion.

Orphan drug designation criteria

Establishment of an orphan drug designation is based on two criteria, according to European regulation [1]. The first criterion can be called the rarity criterion and states that a product must be intended for the diagnosis, prevention, or treatment of a

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life-threatening or chronically debilitating condition, with the required prevalence of not more than 5 in 10 000 or, as an alternative to the required prevalence, if without incentives it is unlikely that sufficient return on investment could be generated to develop the product [4]. The second criterion can be called the significant benefit criterion and states that either there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the European Community (EC) or, if such a method exists, that the medicinal product will be of significant benefit to those affected by that condition [4,5]. Satisfactory methods are authorised medicinal products and other relevant therapeutic modalities where appropriate [6].

A significant benefit can be substantiated in two ways: either through a clinically relevant advantage to patients (CRA) or through a major contribution to patient care (MCPC). The CRA can be defined as either improved efficacy or a better safety or tolerability. The MCPC is a broader criterion and could, for example, be based on ease of (self-)administration or a reduced treatment burden. To base a significant benefit on a MCPC, the product must be at least equivalent in terms of efficacy and safety compared with authorized medicinal products. Significant benefit is assessed during both the initial orphan drug designation and evaluation of the orphan drug status at marketing authorization. At the initial designation stage, significant benefit can be based on a plausible assumption [4].

Accessibility within individual countries

The adoption of the Orphan Drug Regulation (EC 141/2000) in 2000 and the implementation of the incentives has helped to stimulate the development of drugs for the treatment of rare diseases [7–9]. However, if patients are to benefit from authorized orphan drugs, medicines must be made accessible within individual EU member states. Availability and access are within the remit of each member state and in the hands of governments, HTA organizations, and/or national payers. To make decisions on reimbursement levels for orphan drugs, many countries have implemented processes of HTA, which usually include a clinical assessment that relates the benefit of the new drug to comparators already available in the relevant jurisdiction [10–12]. This part of the HTA process has multiple names across the EU, but the common name implemented by the European network for HTA (EUnetHTA) is REA [13]. HTA processes differ between countries and can include the consideration of additional aspects, such as cost-effectiveness, budget impact, or others, but these are outside the scope of this review because they are not comparable to the significant benefit assessment performed by the COMP.

Relative effectiveness assessments

Significant benefit assessments and REAs share common characteristics. Both assess the benefit of a drug compared with already-existing comparators. However, there are also important differences, because the objective of the significant benefit assessment is to ensure that the product meets the criteria for an orphan drug designation, whereas the objective of a REA is to assist decision-making on pricing and reimbursement for all products (not only orphan drugs). Additionally, significant benefit is assessed on a European level, whereas relative effectiveness is established nationally, which can lead to a multitude of differences in applied and preferred practices and methodologies. No studies exist that compare the methodologies of the two frameworks for OMPs. The EMA and EUnetHTA, as part of their joint work plan, have emphasized the importance of an evaluation of similarities and differences between both practices to identify areas for further research and potential cooperation, and to evaluate whether reports of significant benefit assessments can support the production of REAs [14].

Review process

This study reviews the similarities and differences between the methods and practices used in significant benefit assessments by COMP and REAs by HTA organizations across Europe.

The similarities and differences between both frameworks were assessed in two ways. First, we evaluated whether differences existed between significant benefit and REAs for all products assessed by COMP as well as by a majority (at least four) HTA organizations within five predefined domains. Second, five illustrative cases were selected for a comprehensive qualitative analysis.

Inclusion of jurisdictions and drugs

HTA organizations were selected for inclusion based on online availability of full-text HTA reports including information on the considerations about the available evidence and restricted to reports in a language understood by the assessors (Dutch, English, French, German, and Polish). The HTA organizations selected for inclusion were: the Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT, Poland), the Gemeinsamer Bundesausschuss and the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (G-BA and IQWiG, Germany), Haute Autorité de Santé (HAS, France), the National Institute for Health and Care Excellence (NICE, England and Wales), and Zorginstituut Nederland (ZIN, The Netherlands). In addition, the European Network for HTA (EUnetHTA), a European consortium of national and regional HTA organizations based on voluntary cooperation on HTA, was included.

Medicines were included if their market authorization was granted between 2010 and 2017 and the COMP had performed an assessment of significant benefit at the time of marketing authorization. This study focused only on the assessment of significant benefit conducted at the time of initial marketing authorization (not the original orphan drug designation) and on the evaluation of relative effectiveness. Cost-effectiveness and other factors were not considered. When HTA organizations performed reassessments of the same indication, these dossiers were also included. Drugs that were not assessed by at least four of the six HTA organizations before July 2018 were excluded. For medicines with multiple indications, each indication was studied separately.

Data extraction, case selection, and analysis

To identify differences between significant benefit and REAs, five domains were formulated according to a modified PICO structure, a well-established strategy for formulating questions and search strategies [15–17]. The five domains were established based on discussions during EMA-EUnetHTA meetings and related to: the clinical evidence used in the assessment, the patient population,

the intervention, the comparators included, and the outcome measures. The patient population domain covers the evaluation of the appropriateness of the patient population as well as the evaluation of extrapolations between patient populations.

Differences and similarities were assessed based on how the evidence was evaluated. Thus, in contrast to other research comparing HTAs [11,18,19], we compared the considerations on the evidence rather than the outcomes of the assessments. A standardized data extraction form was developed to reproducibly retrieve information on the five domains for all included medicines based on the assessment reports. One person extracted the data for all drugs assessed by four or more HTA organizations. Based on the data extraction, the group decided through discussion whether differences within the established domains existed. Differences must have been established between the significant benefit assessment and a REA of at least one HTA organization for the drug to be eligible for comprehensive analysis.

Summary statistics describing the differences between both frameworks within all five domains were provided for all included medicines. Subsequently, five illustrative cases were selected for full comparative analysis. The rationale for five cases were provided by the selection criteria. We aimed specifically to illustrate differences between the assessments, and selected four case studies with predefined specific assessment features, which were: (i) being assessed on a European level by EUnetHTA through rapid REA; (ii) having a negative significant benefit assessment; (iii) being approved for significant benefit based on a major contribution to patient care; and (iv) having additional clinical data developed between the timing of significant benefit assessment and REA. The fifth case study was selected to illustrate clear differences between the frameworks. If multiple cases qualified for inclusion, the case that showed differences within the most domains was included.

For the five selected cases, the discussions of the clinical evidence provided in the reports of each organization were analyzed. The main issues that were reported relating to all assessed domains were summarized and compared. Additionally, characteristics related to the regulatory and REA processes were retrieved, namely the dates of assessment, the included studies, and the characteristics of those studies. The interpretation and comparison of the considerations on the clinical evidence in the COMP and HTA reports were validated by presenting the evaluation for commentary in written format to each of the included organizations.

Assessed orphan drugs

Sixty-eight orphan drugs were assessed by the COMP for 75 indications within the inclusion period. Twenty-three of those indications (22 drugs) were assessed by at least four of the included HTA organizations (six by five and 17 by four) and, thus, were included for further analysis (Fig. 1).

Differences between significant benefit and REAs

Of these 23, ten drugs (11 indications, 48%) did not show differences within any of the five domains assessed in this study. For the remaining 12 drugs, differences were detected between the significant benefit and REAs (Fig. 2). Of the five domains that were assessed, most differences were seen in the comparator domain (seven drugs, 58%), whereas no differences were evident for the intervention. Only two of the 12 drugs (17%, midostaurin and blinatumomab) showed differences within more than one domain.

Selection of case studies

Two drugs were evaluated by EUnetHTA (midostaurin and ramucirumab) as a joint REA. Midostaurin was chosen for the comprehensive analysis, because it showed differences within more domains. One of the 12 drugs had a negative significant benefit conclusion (lumacaftor/ivacaftor). Two drugs were approved based on a 'major contribution to patient care' (eliglustat and migalastat). Given that both showed an equal number of domains with differences, eliglustat was arbitrarily chosen. For three drugs, additional evidence had been generated between the time of significant benefit assessment and the REA (blinatumomab, bosutinib, and brentuximab). Blinatumomab was chosen based on the number of domains showing differences. The last

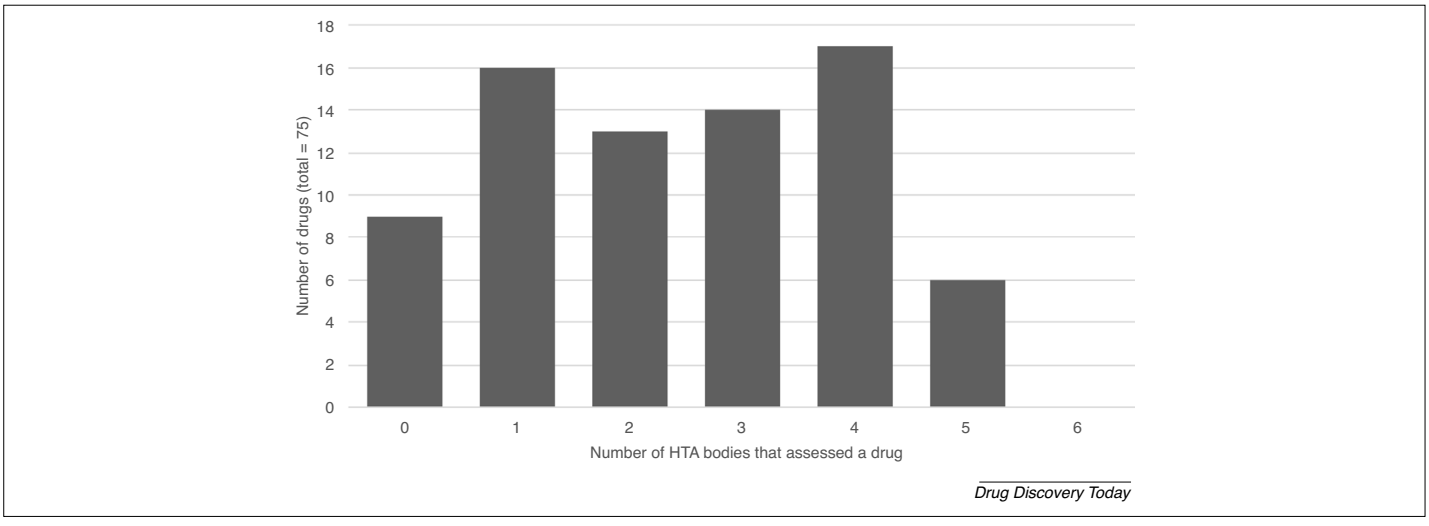

FIGURE 1

Number of drugs assessed by health technology assessment (HTA) organizations out of the orphan products assessed by the Committee for Orphan Medicinal Products (COMP).

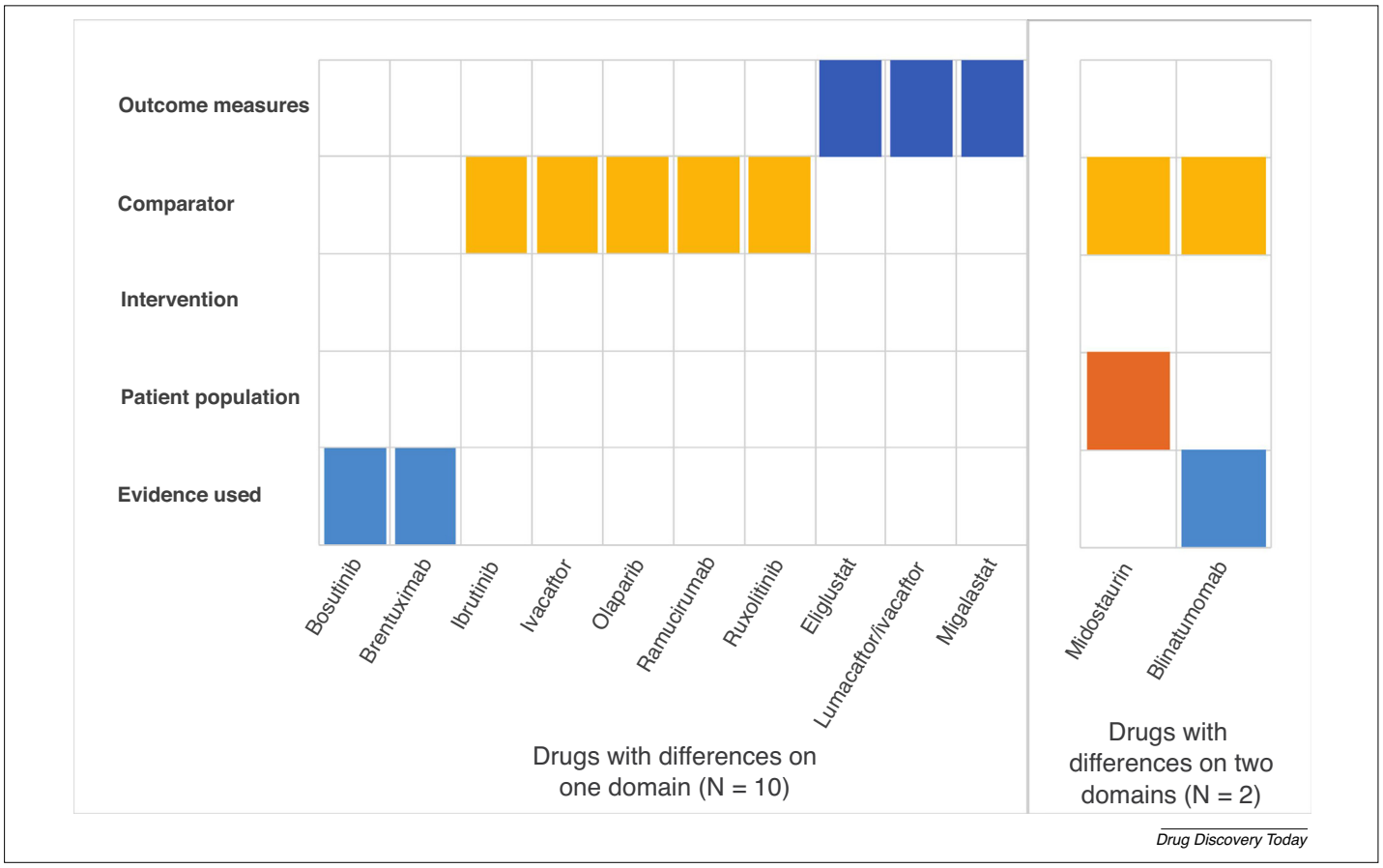

FIGURE 2

Domains that showed differences between significant benefit and at least one relative effectiveness assessment (REA) for all 12 included drugs.

case study that was included (ruxolitinib) was the one that illustrated very clearly the difference in comparators considered.

Qualitative analysis of case studies

Figure 3 shows the timelines of assessment for all drugs in the five case studies. The full discussion of all cases is available through Supplement 1 in the supplemental information online.

Blinatumomab

Blinatumomab was assessed within its indication for acute lymphoblastic leukemia [20–26]. This case study highlighted differences in the clinical evidence used and in comparators considered in the assessments. The difference in clinical evidence was due to results from the pivotal trial not yet being available when blinatumomab received a conditional marketing authorization from the EMA. Significant benefit was concluded based on an indirect comparison with historical data. HTA organizations considered the risk of bias in this indirect comparison to be too high, which led some HTAs to downgrade the relative benefit. NICE performed an assessment after the results of the pivotal trial became available, and some other HTA organizations performed reassessments at that time. COMP considered all comparators included in the historical control data, while HTA organizations differed in opinion about which comparator(s) they found acceptable based on current clinical practice within their own jurisdictions.

Eliglustat

Eliglustat was assessed within its indication for Gaucher disease type 1 [27–31]. Eliglustat was shown to be non-inferior to comparators in trials. Given that no superiority was shown, significant benefit could not be established based on a clinically relevant advantage. A patient preference questionnaire established that 93% of patients preferred the oral administration of eliglustat over intravenous administration of the comparators and the significant benefit was based on a major contribution to patient care. HTA organizations, except NICE, came to different conclusions about the beneficial effects of eliglustat. They found that the benefits resulting from the oral administration on patients' quality of life were not supported by relevant data.

Lumacaftor/ivacaftor

Lumacaftor/ivacaftor was assessed within its indication for cystic fibrosis [32–37]. The significant benefit assessment of COMP considered the primary endpoint of change in percentage of forced expiratory volume in 1 s (FEV_1) as the most relevant outcome, because it is the recommended primary endpoint in the EMA published guideline on clinical development of medicinal products for cystic fibrosis [38]. The most important reason for COMP to give a negative opinion on significant benefit was the lack of improved clinically relevant efficacy (although statistically significant). Therefore, lumacaftor/ivacaftor received a marketing authorization without orphan drug market exclusivity. The HTA organizations emphasized that change in FEV_1 was not considered a relevant clinical outcome, because its

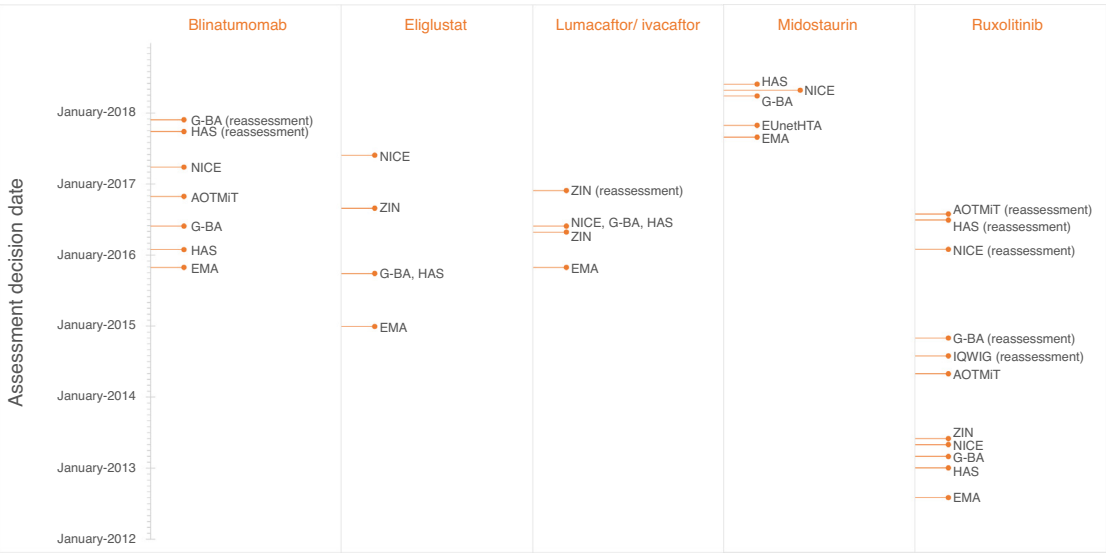

FIGURE 3

Timelines of assessments for the five included case studies. The health technology assessment (HTA) dates represent the dates of overall reimbursement recommendations, not just the relative effectiveness assessment. The decisions of the European Medicines Agency's (EMA) Committee for Human Medicinal Products (CHMP) and Committee for Orphan Medicinal Products (COMP) are provided simultaneously. The delay between EMA approval and reimbursement decisions does not necessarily mean delayed patient access because some countries have open entry for some or all drugs and individual countries can have special procedures that guarantee patient access to novel drugs before a reimbursement decision has been made.

relation to exacerbations or other morbidity or mortality outcomes was unclear. HTA organizations considered the secondary endpoint of pulmonary exacerbations more important. However, they considered the follow-up too short to be able to consider the clinical relevance of the reduction in exacerbations.

Midostaurin

Midostaurin was assessed within its indication for acute myeloid leukaemia (AML) [39–43]. COMP concluded that significant benefit was established based on a clinically relevant advantage, particularly in the FLT3 mutation-positive subgroup. Differences between COMP and the HTA organizations were evident in the patient population and the comparators considered. Related to the patient population, the pivotal trial did not include patients above 60 years of age. This lack of data was extensively discussed by the HTA organizations but not by COMP, because this extrapolation of the patient population is part of the CHMP benefit–risk assessment. Related to the comparators included, COMP assessed whether the control arm in the pivotal trial was representative of standard care in the EU by considering the use of other drugs, and ultimately considered two additional (indirect) comparators (idarubicin and mitoxantrone) next to the comparators included in the pivotal trial. EUnetHTA also included an extra indirect comparator (high-dose daunorubicin induction), different from those considered by the COMP, which was based on Norwegian national treatment guidelines for AML. This additional comparator was not included by the other HTA organizations in their REA.

Ruxolitinib

Ruxolitinib was assessed within its indication for treatment of disease-related splenomegaly or symptoms with primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis [44–53]. This fifth case was included because it was illustrative for the comparator domain, which showed differences most often. For assessment, two pivotal trials were available, each having a different comparator arm (one best supportive care, one best available therapy). In view of the COMP, the broad choice of agents in the best-available therapy arm sufficiently reflected clinical practice as to allow conclusions on a significant benefit over the two authorized products (hydroxyurea and busulfan). However, this did not mean that ruxolitinib was considered to be of significant benefit over each active substance that was used in the best-available therapy arm. The HTA organizations had different preferences for best-available therapy based on national clinical practices. This meant that most of them only considered a subset of patients in the trials relevant for the decision, which complicated the assessments.

Similarities and differences between significant benefit and REAs

The qualitative reviews of the case studies show that there are many similarities in the clinical evidence used by COMP and HTAs to support the significant benefit assessments and REAs, respectively. Where differences exist, they most often related to the choice of comparator(s) to which the OMP under assessment was compared.

Comparators considered

Both for the initial orphan drug designation and at time of marketing authorization, for the assessment of significant benefit, COMP must consider as comparators all satisfactory methods of treatment (approved medicines, other treatments such as surgery)

within the orphan condition [6]. The orphan condition is often broader than the CHMP-approved therapeutic indication. Such comparators include medicinal products that must be authorized centrally or at least in one member state of the EU. By contrast, HTA organizations (excluding Germany) are free to select the comparators that are most suited for their jurisdictions, including off-label drugs for some HTA organizations [54–56]. The case of ruxolitinib illustrates such differences. Our results indicate that these procedural differences are an important factor contributing to differences between both frameworks because the comparator domain was the domain for which differences occurred most often. A consequence of the differences in acceptability of off-label comparators is that an orphan drug regulatory approval can be based on a significant benefit assessment versus an authorized comparator that is not commonly used in some or more member states. Subsequently, HTA organizations would perform REAs versus off-label comparators that might be widely used in clinical practice. This can lead to a different outcome of the benefit of the new therapy. Alignment in such situations would only be feasible if either COMP would be allowed to compare the new drug to off-label treatments (currently prevented by the interpretation of the legislation) or if HTA organizations would be forbidden to compare to off-label treatments.

Patient populations considered

Our results also elucidate reasons for differences related to the population under assessment. COMP can only consider the population included in the approved indication by CHMP as a whole. However, the significant benefit can be driven by a subgroup of patients if the effect on the rest of the population is not detrimental. This is exemplified by the case of midostaurin. By contrast, HTA organizations might consider subpopulations of the approved indication in separate assessments. HTA organizations can split the indication into different subpopulations, each with their own comparator, which can result in different conclusions on the relative benefits in each subpopulation. Thus, whereas the COMP decision will always result in a positive or negative opinion for the full indication, HTA organizations might decide that relative benefits are established for one subpopulation, but not for others. If relative benefits are not established for a subpopulation, the reimbursement rate and price for this subpopulation can be adjusted accordingly. It depends on the HTA organization and the type of drug whether this means nonreimbursement for the subpopulation or that other measures will be applied, such as a lower reimbursement rate or price for the full indication.

Outcomes considered

In line with the orphan drug regulation and the assessment of the benefit–risk balance by CHMP, COMP considers the totality of evidence. The focus is on the clinical relevance of effects observed in the clinical trials on primary and secondary endpoints. In some cases, if a product does not show a significant benefit based on a clinically relevant advantage, significant benefit might still be justified based on a major contribution to patient care (in case efficacy and safety are at least the same as of the comparator), as exemplified by the case of eliglustat. HTA organizations are freer to select the most relevant trials and to consider other endpoints that are deemed clinically relevant, with some HTA organizations specifying relevant endpoints beforehand (e.g., Germany). The case of lumacaftor/ivacaftor exemplifies how HTA organizations focused on an endpoint that they considered relevant, almost entirely disregarding the primary endpoint of the pivotal trial because it was deemed not clinically relevant.

The concept of major contribution to patient care does not exist as a criterion within the included HTA frameworks. Some HTA organizations might consider the effects falling under this criterion to be sufficient to establish a relative benefit (for eliglustat, this was the case for NICE), whereas others might not acknowledge the relevance of such effects unless they have been shown to affect endpoints that are deemed clinically relevant by the HTA organization, such as quality of life. Given that HTA organizations do not have a similar criterion, it is likely that drugs that receive orphan drug designation based on a major contribution to patient care related to the mode of administration will continue to have difficulties in showing incremental effects in REAs when no benefits are established on other outcomes. The case of eliglustat exemplifies how most HTA bodies are reluctant to acknowledge patient convenience as a criterion that would justify a higher relative price.

Availability of evidence, timing, and reassessments

Another clear difference relates to the availability of clinical evidence and the timing of assessments. Significant benefit assessments are always performed by COMP at initial marketing authorization and, since 2017, at the time of major changes to the therapeutic indication approved by CHMP. Reassessments of the same indication are not possible, unless an Article 8.2 referral of the orphan drug regulation is triggered by a member state. This type of reassessment can be requested by member states if they have sufficient evidence suggesting that the criteria of the orphan drug designation are no longer met [57].

HTA organizations generally start their evaluation only after marketing authorization. The five case studies showed that there is usually a lag time between marketing authorization with decision on orphan drug status and HTA decisions. HTA organizations also have more flexibility in the timing of their assessments and most can perform reassessments triggered for example by the availability of new evidence. A consequence of the difference in timing is that COMP must base its decision on the evidence submitted to the EMA by the manufacturer at the time of marketing authorization, whereas the HTA organizations can consider additional evidence not submitted to the EMA or developed later in time. The blinatumomab case demonstrated these aspects. However, in this study, we did not see major differences and, in most cases, both regulators and HTAs looked at the same data.

Differences in scope and processes between the two frameworks

The assessment of orphan drug status at EMA has the specific scope to promote and reward orphan drug development at a European level, whereas the scope of the HTA organizations is to support a decision on the reimbursement of an orphan drug at a national level. In line with their objectives, the two types of assessment have different types of outcome: the outcome of a significant benefit assessment is the binary decision of maintenance or removal of the orphan drug designation and the benefits that

come with it, whereas, for REAs, the outcome can be any of multiple categories, each having a relation to the applied country-specific reimbursement mechanisms.

The approaches for assessing orphan drugs among HTA organizations differ. Some do not have special processes (AOTMiT), but some do offer more general procedures from which OMPs often benefit. Examples of such procedures are the fast-track procedure of HAS, the highly specialized technologies process of NICE, and the exclusion of cost-effectiveness considerations of ZIN based on budget impact [58]. From the included HTA organizations, only Germany has a process specific for orphan drugs, as long as the budget impact threshold is not reached. This process entails that added benefit is considered proven upon marketing authorization of the orphan drug. The comparator(s) included in the pivotal trial (if applicable) must be accepted. The extent of added benefit is still evaluated, defined as nonquantifiable, minor, considerable, or major benefit, to inform subsequent price negotiations [59]. If the orphan drug status is not maintained at regulatory approval, the orphan drug process of Germany no longer applies.

Implications of observed similarities and differences between significant benefit and relative effectiveness frameworks

Clearly there are many procedural and methodological differences between the significant benefit and REAs that could lead to different clinical evidence considerations. However, in our study, such differences were not commonplace. This might be explained in part by the fact that evidence for rare diseases is by nature limited and, therefore, all stakeholders necessarily assess the same evidence [60,61]. Additionally, orphan drugs are often approved based on studies with a limited patient population, thus we hardly saw any population differences [62]. Furthermore, because for rare diseases the treatment options are often scarce, there might be few (if any) treatments available within the indication to compare the new drug to, creating consistency in comparators. Within indications where more treatment options are available, differences in comparators can be more evident, as shown in the case studies. However, comparators were still the same for both frameworks for 16 out of 23 cases. For these reasons, orphan drugs might be particularly suited for closer alignment between regulatory assessments and HTAs. The similarities between the frameworks that were found in this review suggest that closer alignment of the processes of significant benefit evaluation and REA is feasible. Among the potential benefits of closer alignment are shorter timelines between approval and reimbursement decisions and higher predictability of the approval and subsequent reimbursement processes, potentially leading to uncertainties in HTAs being resolved earlier, which would lead to fewer drugs failing to obtain reimbursement.

Nevertheless, because REAs are strongly linked to their national context, the final outcomes might differ between the frameworks even though the considerations of the clinical evidence might have been similar. Thus, significant benefit assessments cannot replace REAs but might provide input for REAs of national HTA organizations. The publication of the orphan maintenance assessment reports (including those for products for which orphan drug designation was not maintained) at marketing authorization could provide relevant added value.

The objective of the orphan drug regulation (i.e., creating more medicines for patients with rare diseases) will not be fulfilled if the approved orphan drugs are not subsequently reimbursed [63–66]. Thus, alignment of both processes is an important health policy topic.

Suggested measures to facilitate alignment

Alignment between significant benefit and REAs for orphan medicinal products could be facilitated by having HTA organizations provide input into the clinical development programs through parallel protocol (scientific) advice (called parallel consultation) with EMA and HTA organizations [67] and through the use of orphan maintenance assessment reports by HTA organizations. Furthermore, with the current activities related to joint REAs within Europe, early interactions between the CHMP, COMP, and EUnetHTA for OMPs further support the efforts to publish EUnetHTA reports as soon as possible after marketing authorization. EUnetHTA and EMA have a joint work plan that includes multiple activities for further alignment, including, but not limited to, initiatives clarifying the principles for wording of the indication and early information sharing between the two organizations [14]. Ultimately, these efforts aim to facilitate appraisal processes at the national level and/or speedier access of products to patients.

Limitations

Given the inclusion criteria aimed at providing illustrative case studies for this analysis, 52 of 75 orphan medicinal products assessed by COMP fell outside of the scope of this analysis. Therefore, it remains unknown to what extent differences within the five included domains were present for these medicines. However, the decision to exclude the 52 products was based on the fact that these were evaluated by fewer HTA organizations and, therefore, any findings on potential differences might not be considered equally valid for general conclusions. Our analysis could be repeated when more REAs are available, but because not all HTA organization assess all drugs, it is unlikely that more than four REAs will be available at any time.

Additionally, the selection of the five cases for further analysis was based on characteristics that the involved stakeholders, EMA and HTA organizations, determined to be of most interest. Different stakeholders with other interests might have ended up with a different selection of five cases out of the 12 drugs that showed differences. However, the descriptive statistics of these 12 cases show that the type of domains covered would be similar to those within the five cases now included.

Another issue might be that the differences between significant benefit and REAs were established by the author group based on an interpretation of the written reports. The written reports serve as a proxy for the internal discussions of each included organization. Given that findings are mostly discussed collectively, it was sometimes hard to interpret each domain separately. Thus, the interpretations of these reports might not always be a true reflection of each consideration. To reduce this risk, we discussed the reports with multiple (five) authors, and we gave each organization the opportunity to check our written comparative analyses of each case study for accuracy. The received feedback was in general agreement with the

interpretations provided by the authors but, in some cases, nuances were added.

Concluding remarks

Although we focused on highlighting explicit differences between the significant benefit assessment and REA frameworks, we found that, for most of the 23 included cases, no major differences between significant benefit assessment and REAs occurred. When differences existed, they were mostly related to the comparators considered. Early interactions between both stakeholders might further diminish these differences in the future. Given that significant benefit and REAs serve different purposes, the ultimate outcome of the evaluations might differ even though the considerations regarding the evidence were similar. Nevertheless, because of the many similarities found in this study, HTA organizations might benefit from reviewing the orphan maintenance assessment reports, as provided on the website of the EMA.

Conflicts of interest

H.G.M.L. reports that he is a past chairman of the Dutch Medicines Evaluation Board and a past member of the EMA CHMP. He is also a member of the Lygature Leadership Team. A.Z. reports that, during this study, she held a position of director of the Transparency & Tariff Councils Office in the Agency for Health Technology Assessment & Tariff System (AOTMiT), Poland.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drudis.2020.04.012.

References

1 Anon (1999) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products. *Off. J. Eur. Union* L018, 0001–0005

2 Anon (2016) *Inventory of Union and Member State incentives to support research into, and the development and availability of orphan medicinal products. State of Play 2015, European Commission.* 2016

3 EMA (2019) *Post-orphan Medicinal Product Designation Procedures. Guidance for Sponsors, EMA.* 2019

4 Fregonese, L. *et al.* (2018) Demonstrating significant benefit of orphan medicines: analysis of 15 years of experience in Europe. *Drug Discov. Today* 23, 90–100

5 Committee for Orphan Medicinal Products and the European Medicines *et al.* (2011) European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat. Rev. Drug Discov.* 10, 341–349

6 Anon (2016) Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03). *Off. J. Eur. Union* 424, 3–9

7 Westermark, K. (2007) The regulation of Orphan Medicines in the EU: objectives reached and main challenges when facing the future. *Pharm. Policy Law* 9, 327–342

8 Melnikova, I. (2012) Rare diseases and orphan drugs. *Nat. Rev. Drug Discov.* 11, 267–268

9 Coté, T. *et al.* (2010) Orphan products: an emerging trend in drug approvals. *Nat. Rev. Drug Discov.* 9, 84

10 Kleijnen, S. *et al.* (2015) Can a joint assessment provide relevant information for national/local relative effectiveness assessments? An In-depth comparison of pazopanib assessments. *Value Health* 18, 663–672

11 Vreman, R.A. *et al.* (2019) Weighing of evidence by health technology assessment bodies: retrospective study of reimbursement recommendations for conditionally approved drugs. *Clin. Pharmacol. Ther.* 105, 684–691

12 Kleijnen, S. *et al.* (2016) Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. *Ann. Oncol.* 27, 1768–1775

13 Kleijnen, S. *et al.* (2014) Piloting international production of rapid relative effectiveness assessments of pharmaceuticals. *Int. J. Technol. Assess. Health Care* 30, 521–529

14 EMA (2017) *EMA-EUnetHTA three-year work plan: 2017–2020, EMA..* 2017

15 Richardson, W.S. *et al.* (1995) The well-built clinical question: a key to evidence-based decisions. *ACP J. Club* 123, A12–A13

16 Higgins, J.P. and Green, S. (2008) *Cochrane Handbook for Systematic Reviews of Interventions.* Wiley

17 Eriksen, M.B. and Frandsen, T.F. (2018) The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. *J. Med. Libr. Assoc.* 106, 420–431

18 Lipska, I. *et al.* (2015) Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? *Clin. Pharmacol. Ther.* 98, 489–491

19 Nicod, E. and Kanavos, P. (2012) Commonalities and differences in HTA outcomes: a comparative analysis of five countries and implications for coverage decisions. *Health Pol.* 108, 167–177

20 EMA (2015) *European Public Assessment Report. Blinatumumab (Blincyto), EMA..* 2015

21 HAS (2016) *Avis sur les Medicaments CT14718. Blincyto (blinatumomab), Anticorps Monoclonal, HAS..* 2016

22 HAS (2017) *Avis sur les Medicaments CT16074. Blincyto (blinatumomab), Anticorps Monoclonal, HAS..* 2017

23 NICE (2017) *Technology Appraisal Guidance. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (TA450), NICE..* 2017

24 G-BA (2017) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Blinatumomab (Neubewertung nach Fristablauf: Akute lymphatische B-Zell-Leukämie), G-BA..* 2017

25 G-BA (2016) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Blinatumomab, G-BA..* 2016

26 AOTMiT (2016) *Assessment Dossier Blinatumumab (Internal Document), AOTMiT..* 2016

27 EMA (2014) *European Public Assessment Report. Eliglustat (Cerdelga), EMA..* 2014

28 NICE (2017) *Highly Specialised Technologies Guidance. Eliglustat for treating type 1 Gaucher disease (HST5), NICE..* 2017

29 ZIN (2016) *GVS-Advies Eliglustat (Cerdelga®) bij Ziekte van Gaucher (type 1) 2016110735, ZIN..* 2016

30 G-BA (2015) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Eliglustat (Sonstige Sphingolipidosen (Gaucher-Krankheit Typ 1)), G-BA..* 2015

31 HAS (2015) *Avis sur les Medicaments CT14208. Cerdelga (Éliglustat), Médicament du Métabolisme, HAS..* 2015

32 EMA (2015) *European Public Assessment Report. Lumacaftor/ivacaftor (Orkambi), EMA..* 2015

33 HAS (2016) *Avis sur les Medicaments CT14927. Orkambi (Lumacaftor/Ivacaftor), Correcteur et Potentialisateur du Gène CFTR, HAS..* 2016

34 ZIN (2016) *GVS-Advies Lumacaftor/Ivacaftor (Orkambi®) bij Cystische Fibrose (CF) Bij Patiënten van 12 Jaar en Ouder die Homozygoot Zijn voor de F508del-Mutatie in het CFTR-Gen (Herbeoordeling) 2016136882, ZIN..* 2016

35 ZIN (2016) *GVS-Advies Lumacaftor/Ivacaftor (Orkambi®) bij Cystische Fibrose (CF) bij Patiënten van 12 Jaar en Ouder die Homozygoot Zijn voor de F508del-Mutatie in het CFTR-Gen 2016055466, ZIN..* 2016

36 G-BA (2016) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Lumacaftor/Ivacaftor (Zystische Fibrose, & 12 Jahre, Homozygot F508del-Mutation), G-BA..* 2016

37 NICE (2016) *Technology Appraisal Guidance. Lumacaftor–Ivacaftor for Treating Cystic Fibrosis Homozygous for the F508del Mutation (TA398), NICE.*. 2016
38 CHMP (2009) *Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis, NICE.*. 2009
39 EMA (2017) *European Public Assessment Report. Midostaurin (Rydapt), EMA.*. 2017
40 HAS (2018) *Avis sur les Medicaments CT17244. Rydapt (Midostaurine), Inhibiteur de Tyrosine Kinase, HAS.*. 2018
41 NICE (2018) *Technology Appraisal Guidance. Midostaurin for Untreated Acute Myeloid Leukaemia (TA523), NICE.* 2018
42 G-BA (2018) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Midostaurin (Akute Myeloische Leukämie; Systemische Mastozytose), G-BA.*. 2018
43 Finnish Medicines Agency and Norwegian Medicines Agency (2017) *Midostaurin with Standard Chemotherapy in FLT3-Positive Acute Myeloid Leukaemia. Rapid Assessment of other Health Technologies Using the HTA Core Model for Rapid Relative Effectiveness Assessment, EUnetHTA.*. 2017
44 EMA (2012) *European Public Assessment Report. Ruxolitinib (Jakavi), EMA.*. 2012
45 HAS (2012) *Avis sur les Medicaments CT12530. Jakavi (Ruxolitinib), Inhibiteur de Tyrosine Kinase, HAS.*. 2012
46 NICE (2013) *Technology Appraisal Guidance. Ruxolitinib for Disease-Related Splenomegaly or Symptoms in Adults with Myelofibrosis (TA289), NICE.*. 2013
47 NICE (2016) *Technology Appraisal Guidance. Ruxolitinib for Treating Disease-Related Splenomegaly or Symptoms in Adults with Myelofibrosis (TA386), NICE.* 2016
48 ZIN (2013) *GVS Beoordeling Ruxolitinib (Jakavi®) ZA/2013058480, ZIN.*. 2013
49 G-BA (2013) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Ruxolitinib, G-BA.*. 2013
50 G-BA (2014) *Nutzenbewertung nach § 35a SGB V. Nutzenbewertungsverfahren zum Wirkstoff Ruxolitinib (Überschreitung 50 Mio € Grenze: Myelofibrose), G-BA.*. 2014
51 IQWiG (2014) *A14-17 Ruxolitinib - Nutzenbewertung gemäb § 35a SGB V, IQWiG.*. 2014
52 AOTMiT (2014) *Assessment Dossier Ruxolitinib (Internal Document), AOTMiT.*. 2014
53 AOTMiT (2016) *Reassessment Dossier Ruxolitinib (Internal Document), AOTMiT.*. 2016
54 Allen, N. *et al.* (2017) Health Technology Assessment (HTA) case studies: factors influencing divergent HTA reimbursement recommendations in Australia, Canada, England, and Scotland. *Value Health* 20, 320–328
55 Mauskopf, J. *et al.* (2011) Differences among formulary submission guidelines: Implications for health technology assessment. *Int. J. Technol. Assess. Health Care* 27, 261–270
56 Spinner, D.S. *et al.* (2013) Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in-depth case series across three jurisdictions. *Clin. Outcomes Res.* 5, 69–85
57 Anon (2008) Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products (2008/C 242/07). *Off. J. Eur. Union* C242, 8–11
58 Nicod, E. *et al.* (2019) HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries. *Health Pol.* 123, 140–151
59 OECD (2018) *Pharmaceutical Reimbursement and Pricing in Germany, OECD.*. 2018
60 Picavet, E. *et al.* (2013) Clinical evidence for orphan medicinal products-a cause for concern? *Orphanet. J. Rare Dis.* 8, 164
61 Onakpoya, I.J. *et al.* (2015) Effectiveness, safety and costs of orphan drugs: an evidence-based review. *BMJ Open* 5, e007199
62 Pontes, C. *et al.* (2018) Evidence supporting regulatory-decision making on orphan medicinal products authorisation in Europe: methodological uncertainties. *Orphanet. J. Rare Dis.* 13, 206
63 Detiček, A. *et al.* (2018) Patient access to medicines for rare diseases in European countries. *Value Health* 21, 553–560
64 Zamora, B. *et al.* (2019) Comparing access to orphan medicinal products in Europe. *Orphanet. J. Rare Dis.* 14, 95
65 Malinowski, K.P. *et al.* (2018) Reimbursement of orphan drugs in Europe in relation to the type of authorization by the European Medicines Agency and the decision making based on Health Technology Assessment. *Front. Pharmacol.* 9, 1263
66 Korchagina, D. *et al.* (2014) Health Technology Assessment, price and reimbursement review for orphan drugs in France. *Value Health* 17, A540
67 EMA (2020) *Parallel Consultation with Regulators and Health Technology Assessment Bodies, EMA.*. 2020