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Access to orphan drugs despite poor quality of clinical evidence

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The clinical evidence level of orphan medicines in European market authorization submissions is low: few randomized controlled trials, short treatment follow-up, rarely hard clinical endpoints.
- The success rate at centralized market authorization is lower for orphan drugs (62.9%) than for non-orphan medicines (70.7%).
- The burden of disease of rare diseases is high, affecting the lives of at least 30 million patients in the European Union (EU).

WHAT THIS STUDY ADDS

- As opposed to market authorization, orphan drugs gain reimbursement more easily than non-orphan innovative drugs.
- Lower quality of evidence of clinical efficacy and safety, more uncertainty on cost-effectiveness and higher product prices are accepted for orphan drugs.
- There is a need for collaboration between the European Commission, competent for market authorization, and the EU member states, competent for reimbursement, in assessing the therapeutic risks and benefits of orphan drugs, to reduce the evidence gap post marketing.

AIM

We analysed the Belgian reimbursement decisions of orphan drugs as compared with those of innovative drugs for more common but equally severe diseases, with special emphasis on the quality of clinical evidence.

METHODS

Using the National Health Insurance Agency administrative database, we evaluated all submitted orphan drug files between 2002 and 2007. A quality analysis of the clinical evidence in the orphan reimbursement files was performed. The evaluation reports of the French 'Haute Autorité de Santé', including the five-point scale parameter 'Service Médical Rendu (SMR), were examined to compare disease severity. Chi-squared tests (at $P < 0.05$ significance level) were used to compare the outcome of the reimbursement decisions between orphan and non-orphan innovative medicines.

RESULTS

Twenty-five files of orphan drugs and 117 files of non-orphan drugs were evaluated. Twenty-two of 25 (88%) submissions of orphan drugs were granted reimbursement as opposed to 74 of the 117 (63%) non-orphan innovative medicines ($P = 0.02$). Only 52% of the 25 orphan drug files included a randomized controlled trial as opposed to 84% in a random control sample of 25 non-orphan innovative submissions ($P < 0.01$). The duration of drug exposure was in most cases far too short in relation to the natural history of the disease.

CONCLUSIONS

Orphan drug designation predicts reimbursement despite poor quality of clinical evidence. The evidence gap at market authorization should be reduced by post-marketing programmes, in which the centralized regulatory and the local reimbursement authorities collaborate in an efficient way across the European Union member states.

Introduction

Rare diseases affect small numbers of patients but the number of diseases is very large (about 7000 according to the WHO). The total number of patients affected by rare diseases was estimated to reach 30 million in Europe [1, 2]. Hence, rare diseases are an important health issue and from a societal point of view it is defendable that these patients should equally get access to a safe and effective therapy as do patients who suffer from more common diseases [2].

Following the successful 'Orphan Drug Act' in the USA [3, 4], the European Union (EU) has adopted its 'Regulation on Orphan Medicinal Products' to promote the development of medicines for patients suffering from rare diseases, the 'orphan drugs', in April 2000 [5, 6]. An 'orphan medicinal product' (OMP) designation can be obtained if the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects fewer than five per 10 000 patients, or for which without incentives it is unlikely that expected sales of the medicinal product would cover the investment in its development. Another condition is that no satisfactory method for the diagnosis, prevention or treatment exists, or if it does exist, that the new product will be of significant benefit for those affected by the condition [5].

The (bio)pharmaceutical industry has responded to these incentives as evidenced by the increasing number of OMP designations and of orphan drugs that receive market approval [6]. During the first 6 years of orphan drug legislation in Europe, the European Commission granted 442 OMP designations and approved marketing for 31 orphan drugs [6]. By the end 2008, 569 medicines were granted OMP designation status and 48 orphan drugs were authorized, indicating that the legislation and its incentives were successful in promoting R&D of drugs for rare diseases [6–8]. However, complete success can only be achieved if patients get timely access to therapies that are proven to increase their life expectancy and/or quality of life. Decisions regarding access and reimbursement are taken at a national level [9] and, given the increasing financial pressure in health care and the high acquisition costs of orphan drugs, may vary between different EU countries [10, 11].

We analysed the reimbursement decisions of all orphan drugs submitted for reimbursement in Belgium from 2002 to 2007, with special emphasis on the quality of clinical evidence, as compared with innovative drugs for more common but equally severe diseases.

Methods

The Belgian Commission on Reimbursement of Medicines (CRM), installed in January 2002, uses evidence-based medicine (EBM) principles to evaluate the relative therapeutic value of new medicines and advises the Minister of Social Affairs who takes the reimbursement decisions and who can only deviate from the CRM proposal, which is taken on a two-thirds majority, on either social or budgetary concerns [12, 13]. The reimbursement procedure has been described elsewhere in detail [14].

Innovative products are submitted by the applicant as either products with added therapeutic value (ATV) as compared with existing alternatives for common diseases, or as orphan products in case of rare diseases. The evaluation of the therapeutic value considers five criteria: efficacy, safety, applicability, convenience to patient or health worker and effectiveness. Applications for ATV must be based on superiority trials indicating the submitted product offers better value than the alternatives on any of the five mentioned criteria.

Using the administrative database of the Belgian National Health Insurance Agency, we evaluated all files of orphan drugs submitted to the CRM for reimbursement from 1 January 2002 onwards and for which the procedure ended by 31 December 2007. A chi-squared test ($P < 0.05$ considered statistically significant) was used to compare the outcome of the reimbursement decisions for orphan drugs with those of other 'innovative' ATV medicines for more common disorders submitted during the same period.

An analysis of the evaluation reports of the French 'Haute Autorité de Santé', which systematically uses a five-point scale parameter 'Service Médical Rendu (SMR)' ranging from 'no' (lowest) to 'major' (highest) to describe severity of disease and medical need [15], was done to estimate possible differences (chi-squared test) in disease severity between orphan and non-orphan drugs.

A quality analysis of the clinical evidence in the orphan reimbursement files was performed using the CRM evaluation. The criteria were the presence or absence of randomized controlled trials (RCTs) with or without active control, dose-finding studies, clinical endpoints and/or surrogate endpoints, adequate trial sample size (considering the rarity of disease), presence of long-term safety and efficacy data. A chi-squared test was used to compare the number of orphan drug files including at least one RCT with a random control sample of 25 ATV submissions for non-orphan diseases.

Results

Between 1 January 2002 and 31 December 2007, 25 files (Tables 1–4) of orphan drugs and 117 files of ATV drugs (see appendix) were submitted and evaluated by the CRM. During the first 3 years (2002–2004) orphan drug submissions represented only a small fraction of all submissions of new innovative compounds (6 of 71). During the second 3-year period (2005–2007), however, orphan drug submissions increased to more than a quarter of all submissions of

Table 1

Orphan drugs for inherited metabolic diseases – inborn errors of metabolism

Orphan drug	Indication	Other therapy available	Therapeutic evidence
Fabrazyme agalsidase β	Fabry's disease (*enzyme replacement therapy*)	Yes (agalsidase α Replagal®)	Randomized, double-blind placebo-controlled trial; *n* = 58; 20 weeks; only surrogate endpoints (reduction GL-3).
Wilzin zinc acetate (*not reimbursed*)	Wilson's disease	Yes (zinc sulphate: less expensive)	Only open, uncontrolled study with either zinc acetate or zinc sulphate: series of case reports; *n* = 255 in total; variable doses; variable duration of follow-up; only surrogate endpoints; no data on combination therapy with chelators; no evidence of added therapeutic value as compared with zinc sulphate, already available at a much lower cost.
Orfadin nitisinone	Hereditary tyrosinaemia type I	No	Evaluation not based on trials but only on data from a compassionate use programme during which 207 patients (87 hospitals, 25 countries, between February 1991 and August 1997) received variable doses; historical controls; clinical endpoints; follow-up: up to 4 years.
Carbaglu carbamyl-glutamate/ carglumic acid	Hyperammonaemia because of N-acetylglutamate synthase deficiency	No	Effectiveness 'assumed' based on a retrospective analysis of its effect on a surrogate endpoint (decrease of ammonia concentration) in 12 patients; dose used was 'empirically' chosen.
Aldurazyme laromidase	Mucopolysaccharidosis type I (*enzyme replacement therapy*)	No	One open phase I–II trial (*n* = 10) and one double-blind placebo-controlled RCT (*n* = 45) during 26 weeks, with an open 24-week extension; no dose-finding; two primary non-validated surrogate endpoints: statistically significant improvement of one endpoint (clinical relevance marginal); no significant effect on other endpoint (study considered 'not conclusive').
Zavesca miglustat	Gaucher's disease type 1 (*substrate reduction therapy*)	Yes (*enzyme replacement therapy*)	Two open, uncontrolled trials (*n* = 28), 6 months: reduction in liver–spleen volume, and *n* = 18: no consistent response; one open, randomized active controlled trial (*n* = 36) *vs.* the already available enzyme replacement therapy (aglucerase); surrogate endpoints; 12 months open extension (inferior efficacy of miglustat): questions raised as to whether the new treatment would be sufficient to control the disease in monotherapy.
Myozyme alglucosidase α	Pompe's disease (*enzyme replacement therapy*)	No	Open, dose-ranging study; *n* = 18 (<6 months) in the infantile, progressive form of the disease; 52 weeks comparison with historical control; clinical endpoints: mortality data. Second open label; *n* = 18 (6–36 months); 52 weeks historical control-late onset disease; *n* = 5, open, uncontrolled (optimal dose remains unknown).
Elaprase idursulfase	Mucopolysaccharidosis type 2, A and B (*enzyme replacement therapy*)	No (only symptomatic)	Dose-finding RCT and one adequate randomized, double-blind placebo-controlled trial (*n* = 96), one open-label extension trial; only surrogate endpoints: 6-min walk test (6MWT) and vital capacity (FVC).

RCT, randomized controlled trial.

new innovative medicines claiming ATV (19 of 71). Although most rare diseases are genetic in origin, only eight submissions involved hereditary metabolic diseases. Ten submissions related to haemato-oncological indications. Whereas the orphan drug legislation aims at promoting the development of drugs for rare diseases adequately targeted to patients with unmet medical needs, i.e. for which no therapy is yet available [5], only seven indications were not previously treated with another drug with at least partial efficacy.

The CRM proposed reimbursement in 16 files, but did not reach a two-thirds majority for either a positive or negative proposal in five other files (agalsidase β, alglucosidase α, mitotane, sildenafil, deferasirox). The Minister of Social Affairs decided to reimburse all these orphan drugs. Busulfan, zinc acetate and ibuprofen were submitted for indications for which a treatment was already available at a much lower cost and without any additional therapeutic benefit, and did not obtain reimbursement. Idursulfase was also not accepted by the CRM because of the treatment cost (€350.000 per patient per year), and the absence of clinical evidence in patients younger than 5 years for whom the medical need is most important, but the Minister approved product reimbursement. Hence, the Minister decided to reimburse 22 of 25 (88%) submissions of orphan drugs.

The outcome of the reimbursement decision was clearly more often positive for orphan drugs than for the 117 other medicines claiming ATV, of which only 74 (63%) (chi-squared test $P = 0.02$) obtained reimbursement, often at a lower-price level.

An analysis of the evaluation reports of the French 'Haute Autorité de Santé' showed that 24 of the 25 orphan submissions (96%) *vs.* 86% of all ATV submissions were classified as having a SMR 'important' (chi-squared test $P = 0.20$); 'major' was never granted. Therefore, the greater likelihood of reimbursement for orphan drugs as compared with innovative drugs for more common

Table 2

Orphan drugs for haemato-oncologic disorders

Orphan drug	Indication	Other therapy available	Therapeutic evidence
Xagrid anagrelide	Essential thrombocytosis	Yes (*hydroxyl-carbonide*)	Six open, uncontrolled non-randomized trials (n = 1446 in total); no placebo- or active-controlled trials although in this case the available number of patients certainly could have allowed for this; evidence of reduction in thrombocyte number but no assessment of effect on clinical endpoints (bleeding).
Trisenox arsenic trioxide	Acute promyelocytic leukaemia	Yes (*tretinoin, anthracyclins*)	Only open uncontrolled trials in a limited number of patients (n = 10;12; 40-refractory to other treatment); follow-up: up to 17 months: evidence of better survival, but only open uncontrolled trials
Busilvex busulfan (*not reimbursed*)	Conditioning haematopoietic stem cell transplantation	Yes (*oral busulfan*)	Pharmacokinetic comparison i.v. *vs.* oral busulfan; two open, uncontrolled trials; n = 104; no evidence of clinical benefit *vs.* oral busulfan (historical control) despite a nearly 100-fold higher cost.
Nexavar sorafenib	Advanced renal cell carcinoma	Yes, but second line (*interferon, interleukin*)	Adequately sized randomized double-blind placebo-controlled trial (n = 903) with an adequate clinical endpoint (progression free survival:167 *vs.* 84 days), but only an interim analysis available at the time of the decision to reimburse.
Sutent sunitinib	Gastrointestinal stroma tumour (1) Renal cell carcinoma (2)	Yes, but second line	(1) One adequate placebo-controlled trial; n = 312 patients with relapse post-imatinib treatment; endpoint: time to progression (27.3 *vs.* 6.4 weeks): convincing evidence. (2) Only interim results of an uncontrolled trial (n = 106).
Sprycel dasatinib	Chronic myeloid leukaemia (1) Acute lymphoblastic leukaemia (2)	Yes, but second line (*imatinib*)	(1) Only open, uncontrolled trial; n = 380; only 8 months follow up (only surrogate endpoints: haematologic and cytogenetic response). (2) Only open, uncontrolled trial (n = 367).
Savene dexrazoxane	Anthracyclin extravasation	No	Two open-label uncontrolled trials, n = 80; results compared with historical controls from literature data (considered acceptable in this particular setting).
Lysodren mitotane	Adrenal cortical carcinoma (hormonal hypersecretion)	Surgery in stage III only	Evidence only based on a literature analysis with mainly series of case reports describing effects on mortality, remission and tumour size.
Revlimid lenalidomide	Second line in multiple myeloma	Yes (bortezomib + dexamethasone)	Two adequate randomized, double-blind placebo-controlled trials (n = 353 and 351); primary endpoint = progression-free survival; post-marketing safety data in 4848 patients; no active-controlled trials *vs.* e.g. bortezomib.
Atriance nelarabine	Acute lymphoblastic leukaemia or lymphoma, third line	Trial of various chemotherapeutic regimens based on individual responses	Two uncontrolled trials; primary endpoint = complete responders; survival as secondary endpoint. Overall data on n = 588 patients (172 patients in post-marketing studies); no controlled trials.

diseases cannot be explained by a higher degree of disease severity.

The results of the quality analysis of reimbursement files are represented in Tables 1–4. The clinical data in many files leave many questions regarding long-term effectiveness, safety and optimal dose unanswered. The duration of drug exposure was in most cases far too short in relation to the natural history of the disease. Whereas in a random control sample of 25 ATV submissions, 21 included results of at least one RCT (the other four submissions were last treatment options in oncology), only 13 of the 25 orphan drug files included a RCT (84% *vs.* 52%, chi-squared test $P < 0.01$).

Randomized active-controlled trials were present in three files only, although an active comparator was available in several cases, as only seven indications were not previously treated by another drug with at least partial efficacy. The three products for pulmonary hypertension, for example, could have been compared with epoprostenol which was already available to Belgian patients. The ibuprofen file did not include any head-to-head comparative trial *vs.* indomethacin, whereas in this case such controlled trials were certainly warranted and feasible. Pegvisomant was only compared with placebo in acromegaly, whereas a trial comparing the product with lanreotide or octreotide would have been more appropriate.

Only 12 files (48%) included randomized placebo-controlled trials. The efficacy evidence of dexrazoxane, a treatment of anthracyclin extravasation, although limited to two uncontrolled studies, in which the results were compared with data from historical controls, was considered acceptable in this particular setting. In the case of nitisinone, the comparison with historical control is understandable as this drug proved to be beneficial in terms of survival, but in other cases the clinical data are less convincing. The absence of comparative trials of zinc acetate *vs.* penicillamine in the Wilzin file seems justified, as the two drugs are used in different population groups. However, better evidence would have been obtained if the 255 patients had been included in a well-designed placebo-controlled RCT. Anagrelide was evaluated in over 1400 patients in several uncontrolled trials, but without placebo- or active-control RCT to assess the effect on clinical endpoints. Only the deferasirox file (3000 patients) and some of the oncology files (anagrelide, sorafenib, nelarabine) included sufficient numbers of trial patients. In 10 files, less than 100 and in 16 less than 250 patients were

Table 3

Orphan drugs for pulmonary arterial hypertension and other indications

Orphan drug	Indication	Other therapy available	Therapeutic evidence
Tracleer bosentan	Pulmonary arterial hypertension	Yes (*epoprostenol*)	Two randomized placebo-controlled trials (n = 21; n = 144); surrogate endpoint only: 6-min walking test (6MWT); no dose-finding; no comparative trials.
Revatio sildenafil (=*Viagra*®)	Pulmonary arterial hypertension	Yes (*epoprostenol, bosentan*)	Double-blind, placebo-controlled trial, three doses, 12 weeks, n = 278; 18-week extension; surrogate endpoints only; no comparative trials (no evidence of added therapeutic value *vs.* available therapy at lower cost); limited information on long-term safety.
Thelin sitaxentan	Pulmonary arterial hypertension	Yes (*epoprostenol, bosentan, sildenafil*)	Three randomized, double-blind placebo-controlled trials (n = 178, 247 and 98); one open-label comparison with bosentan; only surrogate endpoints (6MWT and physical capacity); also observational safety data.
Somavert pegvisomant	Acromegaly	Yes (*somatostatin*)	Randomized double-blind placebo-controlled trial; n = 112; three doses; 12 weeks; surrogate endpoint (dose-dependent reduction IGF-1); 12-month open follow-up; no comparative trials *vs.* lanreotide or octreotide.
Pedea ibuprofen (i.v.) (*not reimbursed*)	Patent ductus arteriosus (preterm infants)	Yes (*indomethacin and galenic ibuprofen; both less expensive*)	Several small RCTs (some double-blind and placebo-controlled) using another ibuprofen salt (ibuprofen-lysin) different from Pedea®; n = 131; no direct comparative trials but no evidence of superiority over i.v. indomethacin (only indirect comparison) already available for this indication at a more than 10-fold lower cost; no long-term data; (i.v. ibuprofen is also available as a galenic preparation at much lower cost in Belgium).
Exjade deferasirox (oral)	Iron overload (transfusional haemosiderosis)	Yes (*deferoxamine; deferipron*)	Clinical development programme in 3000 patients; dose-finding studies; one 52-week placebo-controlled trial; a randomized head-to-head comparative trial *vs.* deferoxamine (a product that has to be administered via continuous subcutaneous administration); n = 586: new treatment, although being more convenient to use, was inferior in terms of efficacy.
Duodopa levodopa/carbidopa (intraduodenal)	Advanced Parkinson's disease	Yes [*deep brain stimulation (DBS); oral L-dopa*]	Randomized open comparative trial *vs.* oral treatment (n = 24; 6 weeks), clinical endpoint; no comparative study *vs.* DBS.

RCT, randomized controlled trial.

Table 4

Quality criteria of clinical evidence

Quality criteria	Number (%) of orphan submissions with:	Number (%) of ATV submissions with:
At least one RCT	13 (52)	21 (84)
RCT active control	3 (12)	15 (60)
Dose-finding studies	5 (20)	23 (92)
Use of clinical endpoints	12 (48)	14 (56)
Adequate trial sample size	4 (16)	23 (92)
Adequate duration of exposure	12 (48)	24 (96)

ATV, added therapeutic value; RCT, randomized controlled trial.

included, although for certain extremely rare diseases, e.g. N-acetylglutamate synthase deficiency (carglumic acid), adequate numbers cannot be achieved.

Adequate dose-finding studies were often lacking and, particularly for metabolic diseases, data generated in small children were extrapolated to adults without adjustment for disease severity and onset. Enzyme replacement therapy with aglucosidase α in Pompe's disease appeared to be effective in the infantile form of the disease but evidence in the 'late-onset' form was lacking (uncontrolled data in only five adult patients; optimal dose for adults not known).

In half of the files, both in orphan and ATV submissions, the primary endpoints were surrogate endpoints with very little evidence of a beneficial effect on the clinical outcome. Effects on clinical endpoints were available in eight of the 10 files of orphan drugs for haemato-oncological indications, but only in four of the other 15 files (Tables 1 and 3). It is surprising that the effect of algalsidase β for Fabry's disease was only assessed on surrogate endpoints, whereas clinical endpoints were used to document the efficacy of algalsidase α. Moreover, the fact that these two nearly identical orphan drugs, both reimbursed for the same types of patients, are used at different dose regimens illustrates the problems of the lack of adequate dose finding of these types of products in general.

Discussion

Drug regulatory agencies, such as the European Medicines Agency, traditionally base a decision to grant market approval on the assessment of the quality, safety and efficacy (*vs.* placebo) of drugs. However, third-party payers like the CRM generally base a decision to reimburse predominantly on the health benefits of the new drug relative to existing treatment options [16]. Therefore, reimbursement and access to new medicines, including orphan drugs, depends on the assessment of their relative efficacy. This delays the access to the new medicine by a median of 265 days in Belgium (the duration of the reimbursement procedure until the application of the final decision of the Minister of Social Affairs) but allows for a more accurate estimation of the relative value of the treatment in relation to the cost and, hence, a more optimal use of resources. The introduction of EBM principles in the medicines reimbursement process in Belgium significantly affected the reimbursement decision [12]. Indeed, 90% of all new medicines for common diseases with clinical evidence of ATV, proven by adequate active-controlled RCTs, obtained reimbursement *vs.* only 50% of submissions where evidence of therapeutic superiority was lacking. In some cases the reimbursement decision was negative despite demonstrated ATV because of other factors such as the perception of excessive price, substantial budget impact or lack of cost-effectiveness (e.g. bevacizumab in colorectal cancer, with an incremental cost per life year gained > €80 000).

Although the percentage of orphan medicines obtaining market authorization between 2000 and 2007 (62.9%) was reported to be numerically lower than the percentage of approved non-orphan medicines (70.7%) [17], the present analysis of reimbursement files in Belgium indicates that the percentage of reimbursed orphan medicines (88.0%) is significantly higher than the percentage of reimbursed non-orphan innovative medicines (63.2%). This difference in the percentage of successful market approvals *vs.* reimbursement grants cannot be attributed to differences in the level of evidence in the files, as the percentages of orphan submissions including the results of at least one RCT for market authorization [17] and reimbursement were similar (56.8% and 52.0%, respectively), indicating the same level of evidence in both types of submission. Moreover, the evaluation of the reports of the French 'Haute Autorité de Santé' indicates that the greater likelihood of reimbursement for orphan drugs as compared with innovative drugs for more common diseases can also not be explained by a higher degree of disease severity. It therefore appears that orphan drug status is a strong predictor of reimbursement, and that orphan drugs easily gain market access in Belgium, despite the high cost and the fact that at the time of evaluation they have not the same breadth and quality of clinical evidence as required for new medicines for more common diseases. Only for orphan drugs, the authorization for prescribing and the further clinical follow-up of their use is covered in Belgium by a peer expert group, the so-called 'College of orphan drugs'.

The results of the present quality analysis of reimbursement files of orphan drugs confirm and extend previous observations from a review of the European Public Assessment Reports (EPARs) of 18 orphan drugs that received marketing approval between 2000 and 2004 [18], and a more recent extension of this analysis up to 2007 [17]. Clearly, lower levels of clinical evidence for granting reimbursement and providing access to therapy are accepted than those required for other innovative medicines, where the decision more clearly reflects the amount and quality of the evidence [12]. For orphan drugs, a much higher degree of uncertainty regarding clinical effectiveness and safety is accepted in reimbursement decisions. In Belgium, a pharmaco economic analysis is mandatory to obtain reimbursement at a price premium for ATV medicinal products, but not for orphan drugs. It is obvious that if the same requirements and criteria would be used for orphan drugs, most would not obtain reimbursement taking into account the poor quality of the clinical evidence, the high cost per patient and the huge incremental cost per quality-adjusted life year (QALY) [19]. Orphan drugs are apparently given more priority than other drugs for equally severe but more common conditions.

A balance must be found enabling rapid access to orphan drugs while guaranteeing their quality, efficacy and safety. Assessing the therapeutic value of orphan drugs is more difficult than of other innovative medicines because of the rarity of patients, the disease severity and the heterogeneity and the scarcity of clinical experts [20]. Less rigid criteria are used for the clinical evaluation of the therapeutic value of orphan drugs [18, 19]. Enrolling sufficient trial patients can be difficult in rare diseases and too rigid design requirements (e.g. randomization, clinical endpoints) would prevent many orphan drugs to be accessed by the affected patients at initial submission. Although it is probably unrealistic to use the same standards for reimbursement decisions for orphan drugs as for regular drugs, our analysis indicates that even taking into account the difficulties associated with smaller patient populations and disease heterogeneity, better-designed trials and longer duration of exposure to more patients could have been achieved in many cases. For diseases considered orphan based on prevalence criteria because of short survival despite a relatively common incidence, classical types of RCTs with clinical endpoints are feasible [21].

Regulators carry responsibility in assuring that patients are not denied vital therapy, but also in protecting public health by ensuring that medicines made available are effective and safe. Therefore, there is a need for more quality clinical data to help regulators and payers in assessing the risks and benefits of orphan drugs. In many cases these data are missing, although at least in some cases more robust evidence could have been provided. Some argue that the budgetary impact is limited given the small number of patients [20]. However, although very rare conditions individually equate to small patient numbers, there are cumulatively a large number of patients with these diseases [1, 2]. The increasing fraction of the available health care resources devoted to orphan diseases implies that fewer resources will be available for more common diseases and for larger groups of patients. It is arguable that payers require guarantees that the resources they allocate to orphan diseases are well spent. One can question whether the healthcare system should pay for a treatment if the estimate of the value for health care it produces is unknown, even if it is an orphan drug. Some authors propose that cost-effectiveness should not be a determinant of access to orphan drugs and that a QALY weighted for disease rarity could be used [20, 22, 23], but others argue that rarity by itself is not a good argument for a special status and incompatible with equity principles [24, 25]. It indeed remains to be shown that society really places a higher value on health gains achieved in patients with rare diseases compared with more common but equally serious disorders.

Orphan drugs made available to patients despite uncertainty on their effectiveness and the detection of safety issues is further complicated by the limited experience in practical use because of the low prevalence of the diseases they are used for [26]. They should therefore be part of a prospectively designed structured programme of post-marketing surveillance, with the aim of reducing the evidence gap at the initial submission: access to treatment should be stopped if clinical evidence cannot be demonstrated in such programmes because this would result in exposing patients to therapies with unproven benefit. As also proposed in the 'Final Conclusions and Recommendations of the Pharmaceutical Forum' [27], early dialogue between stakeholders, conditional pricing and reimbursement linked to the creation of registries of all patients receiving the treatment, and well coordinated within and between the EU member states, could be a way to increase efficiency, and to reconcile the need of access to treatment of patients with rare diseases with the necessity to ensure that these treatments are effective and safe, and that the resources are well allocated.

The access to orphan medicines across the west European member states is actually greatest in France and the Netherlands, probably similar to Belgium and Italy, and probably less in the UK [28]. The uncertainty on the real value of the submitted evidence is probably one of the factors leading to this heterogeneity. Because the level of evidence at initial submission is similar for market authorization and reimbursement, there is a need for better collaboration between the competent authorities at market authorization (European Commission) and at reimbursement (EU member states) in the scientific assessment of the (added) therapeutic value. This could also help to avoid that conflicting information is provided by regulators of market authorization and by reimbursement authorities on the expected benefit of orphan drugs to both the patient and the treating physician. Indeed, in at least one of five submissions [29], clear discrepancies (the market authorization suggesting significant benefit over already available treatments, but the reimbursement committee concluding that significant benefit is lacking) appear to exist, leaving the patient to deal with this uncertainty.

In conclusion, lower quality of clinical evidence, a higher level on uncertainty on the clinical effectiveness, safety and incremental cost-effectiveness, and a higher budgetary impact are accepted for orphan drugs at initial submission for reimbursement. This suggests that Health Authorities value the benefits of orphan treatment more highly compared with benefits of treatments of equally severe more common diseases. Further research should be done to examine whether a societal preference for such an 'orphan' premium really exists. In addition, the initial evidence gap should be reduced by post-marketing programmes, jointly performed across the EU member states.

Competing Interests

There are no competing interests to declare.

No financial or other support has been received by any of the authors.

Appendix: Overview table of 117 ATV reimbursement submissions

Product name	Generic name
Abilify	Aripiprazole
Aclasta	Zoledronic acid
Acomplia	Rimonabant
Actiq	Fentanyl citrate
Alimta	Pemextrexed
Angiox	Bivalirudine
Aptivus	Tipranavir
Arixtra	Fondaparinux
Avastin	Bevacizumab
Avelox	Moxifloxacin
Avodart	Dutasteride
Baraclude	Entecavir
Beromun	Tasonermine
Bridion	Sugammadex
Byetta	Exenatide
Caelyx	Doxorubicin
Caspofungin	Caspofungin acetate
Ceprotin	Human C protein
Champix	Varenicline
Concerta	Methylphenidate
Crestor	Rosuvastatin
Datscan	Loflupane
DepoCyte	Cytarabine
Detrusitol Retard	Tolterodine-L-tartrate
Dipeptiven	N(2)-L-alanyl-L-glutamine
Dovobet	Calcipotriol + betamethasone
Duodopa	Levodopa/carbidopa
Dynastat	Parecoxib
Ebixa	Memantine
Efient	Prasugrel
Elidel cream	Pimecrolimus
Emend	Aprepitant
Erbitux	Cetuximab
Etopophos	Etoposide
Exanta	Melagatran
Exubera	Insulin human for inhalation
Ezetrol 10 mg	Ezetimibe
Factane	Coagulation factor VIII
Faslodex	Fulvestrant
Fenquel	Fentanyl
Ferriprox	Diferipron

Appendix: Continued

Product name	Generic name
Flolan	Epoprostenol
Forsteo	Teriparatide
Foscan	Temoporfin
Fuzeon	Enfuvirtide
Gardasil	Human papilloma virus vaccine type 6*-11*-16*-18*
Grazax	Standardized allergen extract of specific pollen
Hepsera	Adefovir
Hexvix	Hexaminolevulinate
InductOs	Dibotermine alpha
Inomax	Nitric monoxide
Inspra	Eplerenone
Invega	Paliperidone
Isentress	Raltegravir
Ivegam-IgM	CMV immunoglobulin
Kepivance	Palifermin
Kineret	Anakinra
Lantus	Insulin glargine
Levemir	Insulin detemir
Lodoz	Bisoprolol/hydrochlorothiazide
Lucentis	Ranibizumab
Lyrica	Pregabalin
Mab campath	Alemtuzumab
Macugen	Pegaptanib
Metvix	Methyl aminolevulinate
Mimpara	Cinacalcet
Muphoran	Fotemustin
Navelbine	Vinorelbine
Novomix	Insulin mix soluble 30%/crystals 70%
Octreoscan	Vial A: Indium, vial B: pentetreotide
Orencia	Abatacept
Osteogeen Proteine (Osigraft)	Recombinant human osteogen protein
Oxycontin	Oxycodone
Pegasys	Peginterferon alpha-2a
Penicillin	Benzylpenicillin
Perfusalgan i.v.	Paracetamol
Photofrin	Porfimer
Pradaxa	Dabigatran etexilate
Prevenar	Pneumococcic vaccine
Prezista	Darunavir
Procoralan	Ivabradine
Prograft	Tacrolimus
Protelos	Strontium ranelate
Protopic ointment	Tacrolimus
Pulmolast	Human alpha1-protease inhibitor
Raptiva	Efalizumab
Relifex (Gambaran)	Nabumetone
Relistor	Methylnaltrexone
Remodulin	Treprostinil
Reyataz	atazanavir
Rhophylac	Human anti-D immunoglobulin
Risperdal Consta	Risperidone
Rotarix	Rotavirus
Sifrol	Pramipexole
Sipralexa	Escitalopram
Spiriva	Tiotropium
Stelara	Ustekinumab
Steovit D3 500 mg/400 IE	Calcium carbonate + cholecalciferol
Strattera	Atomoxetine
Synagis	Palivizumab
Targinact	Oxycodone + naloxone

Appendix: Continued

Product name	Generic name
Targretin	Bexarotene
Tobi	Tobramycin
Toctino	Alitretinoïn
Tygacil	Tigecycline
Tysabri	Natalizumab
Valcyte	Valganciclovir
Valdoxan	Agomelatine
Velcade	Bortezomib
Vfend	Voriconazole
Vimpat	Lacosamide
Wilfactin 1000 I.U. 10 ml^{-1}	Human von Willebrand factor
Xarelto	Rivaroxaban
Xenical	Orlistat
Xigris	Drotrecogine alpha (activated)
Xolair	Omalizumab
Zevalin radiopharmaceutical preparation	Ibritumomab tiuxetan

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