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Budget Impact of Drugs for Ultra-Rare Non-Oncological Diseases Projected to Remain Moderate in Europe

INNOVAL HC
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IV

Abstract

Ultra-rare disorders (URDs) have been defined by a prevalence of less than 1 per 50,000 persons. Little is known about the current and future budget impact of ultra-orphan drugs, however. The goal of this study was therefore to conduct a budget impact analysis (BIA) of drugs for ultra-rare non-oncological diseases in Europe. For purposes of this analysis, the BIA had a time horizon of 10 years (from 2012 to 2021) and adopted a European payers' perspective. The estimate was based on prevalence data for URDs for which patented drugs are currently available and for which drugs are in clinical development and hence may be expected to be launched in the foreseeable future. A total of 18 drugs under patent protection or orphan drug designation for non-oncological URDs were identified. Furthermore, 29 ultra-orphan drugs for non-oncological diseases under development that have the potential of reaching the market by 2021 were found. Total budget impact over 10 years was estimated to be €14,112 and €5,449 million for approved and pipeline ultra-orphan drugs, respectively (total: €19,561 million). Relative to total pharmaceutical expenditures in Europe, spending on ultra-orphan drugs is estimated to be at 0.7% at present and expected to increase to 1.6% in 2021. In conclusion, the present analysis does not support concerns regarding an uncontrolled growth in expenditures for drugs for URDs. Continuous monitoring of the budget impact as an input to rational policy making is recommended.

IV

Introduction

In the United States (U.S.), in the European Union (EU), as well as in Japan, Australia and some other jurisdictions, legislation has been adopted to encourage the development of treatments for rare or "orphan" diseases. Under this legislation, developers and manufacturers of so called orphan drugs used to treat orphan diseases benefit from a range of incentives, including reduced or waived licensing fees, extended market exclusivity periods, and in the U.S. and Japan, tax relief on development costs.

In theory, there are no distinct (sub-) categories of rare and ultra-rare disorders and treatments. Increasing rarity of a condition merely represents the end of a continuum, just like increasing severity and increasing comorbidities represent continuous, not discrete phenomena. For policy-makers, it may nevertheless be pragmatic to define different categories of disorders and interventions, irrespective of the (absence of) theoretical merits of such an approach.

"Orphan disorders" have been defined by U.S. and EU legislation. In the U.S., these are disorders with a prevalence of less than 200,000 affected persons, in the EU, prevalence must be less than 5 per 10,000 (or less than 0.05 percent) of the population. Currently, no official definition of "ultra-orphan disorders" has been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons.

Many drugs developed to treat (ultra-)orphan diseases will not meet the cost-effectiveness thresholds stipulated by some official regulatory bodies such as NICE, i.e., not to exceed a cost of £20,000 to £30,000 per quality-adjusted life year (QALY) gained. On the other hand, it is less clear how large cost-effectiveness ratios translate into a budget impact for payers. An analysis by Schey and colleagues (2011) predicted a modest share of orphan drugs as part of total pharmaceutical expenditures in Europe, reaching a maximum of 4.6% in 2016. Recent extensions of the model presented similar country-specific projections for France and Sweden, suggesting that in these countries orphan medications may account for 4.9% and 4.1% of total drug expenditure by 2020, respectively (Hutchings et al., 2014).

An open question is how drugs for URDs as opposed to orphan drugs impact health expenditures in Europe. Given the inverse relationship between disease prevalence and annual per-patient orphan drug costs (Schlander and Beck 2007; Simoens 2011), a lower number of patients affected could be compensated by higher per-patient costs. Therefore, it is a priori unclear whether the budget impact of drugs for URDs is smaller compared to orphan drugs due to the smaller patient population.

The goal of the present study was therefore to conduct a budget impact analysis (BIA) of drugs for ultra-rare non-oncological diseases in Europe. The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system context given inevitable resource constraints (Mauskopf et al. 2007). In contrast to the analysis by Schey et al. (2011), we used actual data on the current drug pipeline, as available. We focused on non-oncological diseases as they are more likely to represent distinct disease entities with typically less off-label

use. Also the approved indications of cancer treatments are more often broadened over time (Kobayashi and DeLap 2001).

Methods

For purposes of this analysis, the BIA had a time horizon of 10 years (2012 to 2021) (since data past 10 years is not readily available or reliable) and adopted a European payers' perspective. The estimate was based on prevalence data for ultra-rare diseases for which drugs under patent protection or orphan drug designation are currently available (based on approval from the European Medicines Agency), or for which drugs are currently in clinical development (based on the Medtrack patent database, Medtrack United States, New York, NY). All input variables are listed in Table 1.

Drugs under patent protection or orphan drug designation

To identify drugs for URDs under patent protection or benefitting from market exclusivity conditions due to an active orphan drug designation by the end of 2012, which were approved by the European Medicines Agency for non-oncological diseases, we applied a cutoff prevalence rate of 1:50,000 (= 0.002%) in the general population. When possible, we used prevalence data gathered by Orphanet (2012, 2013). Alternatively, we relied on international or national data sources (mostly Western Europe and the United States) as listed in Tables 2 and 3. Drugs licensed for both oncological and non-oncological use (e.g., cord blood transplants) were excluded as

well as drugs for URDs without patent protection or an active orphan drug designation at the end of 2012.

***Table 1**: Base-case values and ranges used in the budget impact model and sensitivity analysis*

Variable	Base case (range)	Reference
Market penetration rate	22% (10%-30%)	Schey 2011
Markup for prices in Europe compared to U.S.	20% (0%-30%)	Medical Marketing Economics 2011
Annual growth rate in sales volume	10% (5%-15%)	Adapted from EvaluatePharma (2013)
Savings one year after the first generic entry	20% (0%-50%)	EU Competition Commission
Savings two years after the first generic entry	25% (0%-50%)	EU Competition Commission
Clinical phase durations		Adapted from Tufts Center for the Study of Drug Development (REF)
Phase I trials	2 years (1.5-2.5)	
Phase II trials	1.5 years (1-2)	
Phase III trials	1.5 years (1-2)	
Approval	1.5 years (1-2)	
Transition probabilities		Adapted from Tufts Center for the Study of Drug Development
Phase I → phase II	70.6% (60%)	
Phase II → phase III	45.4% (40%)	
Phase III → NDA	63.6% (50%)	
NDA → approval	93.2% (80%)	
Discount rate	3.5% (0%-5%)	Average of the discount rates recommended in England, Germany, and the Netherlands

NDA: New Drug Application

Information on patent expiration dates was obtained from the Medtrack database. We assumed a period of 10 years for market exclusivity.

European sales data for each ultra-orphan drug was extrapolated from U.S. sales data. To this end, we estimated the proportion of patients treated (penetration rate) in the U.S. from the prevalence rate, the relationship between prevalence and annual drug cost, and the general price difference for ultra-orphan drugs between the U.S. and Europe (Medical Marketing Economics 2011).

We then calculated sales in Europe by adjusting for penetration rate and annual drug costs in Europe. As a reference value for the penetration rate in Europe, we used a 22% estimate by Schey et al. (2011) for orphan drugs. For drugs for URDs, uptake may be even lower due to even fewer patients correctly identified with a particular disease. Therefore, a 10% penetration rate was tested in the sensitivity analysis. In terms of the price difference between the U.S. and Europe, we conservatively[1] assumed that prices in Europe are 20% higher (Medical Marketing Economics 2011), thus potentially overestimating budget impact in Europe.

When estimated budget impact in Europe was above global non-U.S. sales, we used global non-U.S. sales as an estimate for European sales.

In order to estimate budget impact for ultra-orphan drugs without information on U.S. sales data, we described the relationship between annual per-patient drug costs and prevalence based on existing data using a mathematical

[1] In the present context, we use the term "conservative" to characterize all those assumptions potentially leading to a higher sales forecast. Whenever we had a choice between plausible assumptions, we selected the "conservative" one.

function. We then applied the function to ultra-orphan drugs without information on U.S. sales data, by predicting annual per-patient drug costs based on the prevalence data available for the target disease in question.

For URD drugs with an indication for more than one URD (i.e., eculizumab and miglustat), we were not able to separate sales data by indication. Therefore, we assumed that market exclusivity for all indications would last until expiration of market exclusivity for the last indication authorized.

Annual growth rate in sales volume was conservatively assumed to be 10% based on a 7.7% estimate for the growth in global orphan drug sales between 2012 and 2018 (EvaluatePharma 2013). This growth captures a potential increase in the size of the eligible population as mortality may be reduced without curing the condition and disease awareness and diagnostic rates may improve with availability of treatment. Based on a sample of medicines that faced generic entry in the period from 2000-2007 (EU Competition Commission), we assumed average savings (as measured by a weighted price index of originator and generic products) of 20% one year after the first generic entry, and about 25% after two years.

Drugs under development

We identified pipeline drugs for non-oncological URDs from the Medtrack database as well. We also included drugs which are developed for URDs but where the combined prevalence of all URDs under development is larger than 1:50,000 (e.g., "lysosomal storage disorders"). The reason is that ultimately in these cases the drug may be approved for only one of the URDs. Future sales volume for pipeline URD drugs was estimated

based on the relationship between annual per-patient drug costs and prevalence for approved drugs as described above. Given that in markets where competitors already exist prices and penetration rates may be lower, this is again a conservative assumption, thus potentially overestimating budget impact. Annual growth rate in sales volume was assumed to be the same as for approved drugs.

Clinical phase durations as well as transition probabilities between phases of drug development were based on data from the Tufts Center for the Study of Drug Development for all drugs. We assumed durations of 2, 1.5, 1.5, and 1.5 years for phase I trials, phase II trials, and phase III trials, and approval, respectively. While for some ultra-orphan drugs clinical phase durations might be shorter due to accelerated approval, for highly innovative technologies (e.g., antisense and gene therapy), they can be longer due to safety concerns (Tambuyzer 2010; Orfali et al. 2012). For transitions to phase II, phase III, New Drug Application (NDA) submission, and NDA approval we assumed probabilities of 70.6%, 45.4%, 63.6%, and 93.2%, respectively. Transition probabilities for ultra-orphan drugs may in fact be lower than for other drugs, particularly in case of challenging disease targets or particularly difficult methods of delivery (e.g., central nervous disorders and gene therapy). Again, our assumption is conservative. Uncertainty of time and risk of development was again reflected in sensitivity analyses (cf. Table 1).

Discount rate

The annual discount rate of costs (from a payer's perspective) was assumed to be 3.5%, which is the average discount rate recommended by guidelines in England, Germany, and the

Netherlands. The discount rate was applied to the budget impact estimate as well as its reference values, i.e., total pharmaceutical and total health expenditures in Europe, respectively (see below). As the analysis does not hold a commercial perspective, we did not apply the average company cost-of-capital.

Sensitivity analysis

To address uncertainty around the mean budget impact estimate, we conducted univariate sensitivity analyses. We also conducted a worst-case scenario analysis, where we used maximum values for the two most influential variables.

Results

We identified 18 drugs for non-oncological URDs under patent protection or benefitting from market exclusivity conditions due to an active orphan drug designation (Table 2).

Furthermore, we found 29 drugs for non-oncological URDs under development that have the potential of reaching the market by 2021 (Table 3).

***Table 2**: Drugs for URDs under patent protection or benefitting from market exclusivity conditions due to an active orphan drug designation for non-oncological diseases*

Active substance	Indication(s)	Prevalence (per 100,000)	Reference
Alglucosidase alfa	Glycogen storage disease type II	1.5	Orphanet Report Series
Alipogene tiparvovec	Hyperchylomicronaemia	0.1	A.D.A.M. Editorial Board 2013
Amifampridine	Lambert-Eaton myasthenic syndrome	1.0	Orphanet Report Series
Betaine anhydrous	Homocystinuria	0.4	Orphanet Report Series
Budesonide	Graft-versus-host disease	1.7	Jacobsohn 2007
Carglumic acid	Hyperammonaemia	*Only a few cases have been reported worldwide§*	Genetics Home Reference
Deferasirox	Chronic iron overload	0.4	Orphanet Report Series; Lobo 2011
Eculizumab	Paroxysmal nocturnal haemoglobinuria, atypical haemolytic uremic syndrome	1.1*	Orphanet Report Series; Zimmerhackl 2006
Galsulfase	Mucopolysaccharidosis VI	0.2	Orphanet Report Series
Idursulfase	Mucopolysaccharidosis II	0.6	Orphanet Report Series
Ivacaftor	Cystic fibrosis and the G551D-CFTR mutation	0.55	Orphanet Report Series; Cystic Fibrosis Foundation 2011
Lomitapide#	Homozygous familial hypercholesterolemia	0.1	Health Grades
Laronidase	Mucopolysaccharidosis I	1.3	Orphanet Report Series
Miglustat	Type 1 Gaucher disease, Niemann-Pick type C disease	1.8*	Orphanet Report Series
Nitisinone	Hereditary tyrosinemia type 1	0.05	Orphanet Report Series
Rilonacept	Cryopyrin-associated periodic syndromes	0.1	Hoffman 2008
Tafamidis	Transthyretin amyloidosis	0.5	Coelho 2008
Velaglucerase alfa	Type 1 Gaucher disease	0.9	Orphanet Report Series

§As no sales were reported in Europe in 2012, future budget impact was considered negligible.

*Combined prevalence for two conditions.

#Approved by European Medicines Agency in 2013.

***Table 3**: Pipeline drugs for ultra-rare non-oncological diseases. Product names are listed when active substance names were unavailable or unspecific*

Active substance	Indication(s)	Prevalence (per 100,000)	Reference
Alpha glucosidase (recombinant, human)	Glycogen storage disease type II	1.5	Orphanet Report Series
Alpha mannosidase (recombinant)	Alpha mannosidosis	0.095	Meikle 1999
AP1903®	Graft-versus-host disease	1.7	Jacobsohn 2007
APG101®	Graft-versus-host disease	1.7	Jacobsohn 2007
Anthim®	Pulmonary anthrax	0.00047	Centers for Disease Control and Prevention 2009
Asfotase alfa	Hypophosphatasia	1	Fraser 1957
Autologous lymphocytes	Graft-versus-host disease	1.7	Jacobsohn 2007
Begedina®	Graft-versus-host disease	1.7	Jacobsohn 2007
Beta-1,3/1,6 glucan	Neuromyelitis optica	1.5	Orphanet Report Series
Coagulation factor XIII (recombinant, human)	Factor XIII deficiency	0.05	Orphanet Report Series
Cysteamine bitartrate	Juvenile neuronal ceroid lipofuscinosis	0.4	Orphanet Report Series
Ecopipam	Lesch-Nyhan syndrome	0.38	Orphanet Report Series
Eculizumab	Cold agglutinin disease, kidney transplant (delayed graft function and antibody mediated rejection), neuromyelitis optica	3.1*	Berentsen 2006, Organ Procurement and Transplantation Network, United States Renal Data System, World Health Organization
Eliglustat	Gaucher disease type 1	0.94	Orphanet Report Series
Emricasan	Liver transplantation	0.00029	World Health Organization
Imatinib mesylate	Graft-versus-host disease	1.7	Jacobsohn 2007
Inolimomab	Graft-versus-host disease	1.7	Jacobsohn 2007
Mycophenolate mofetil	Lung transplant rejection	0.000043	World Health Organization; Orens 2009
N-sulfoglucosamine sulfohydrolase (recombinant, human)	Mucopolysaccharidosis type IIIA	0.3	Orphanet Report Series

Active substance	Indication(s)	Prevalence (per 100,000)	Reference
Ornithine phenylacetate	Type A hepatic encephalopathy	0.6	Hoofnagle 1995
Pentostatin	Graft-versus-host disease	1.7	Jacobsohn 2007
Raxibacumab	Pulmonary anthrax	0.00047	Centers for Disease Control and Prevention 2009
Recombinant human beta-glucuronidase	Mucopolysaccharidosis VII	0.047	Meikle 1999
Reparixin	Lung transplantation	0.000048	World Health Organization
SAF301®	Mucopolysaccharidosis IIIA	0.3	Orphanet Report Series
SBC103®	Mucopolysaccharidosis IIIB	0.47	Meikle 1999
Sebelipase alfa	Wolman disease	0.28	Orphanet Report Series
Siplizumab	Graft-versus-host disease	1.7	Jacobsohn 2007
Thravixa®	Pulmonary anthrax	0.00047	Centers for Disease Control and Prevention 2009

*Drugs were included when the prevalence of all ultra-orphan diseases in total is larger than 1:50,000 (see "Methods").

To estimate budget impact for URD drugs without information on U.S. sales data, we estimated the relationship between annual per-patient drug costs and prevalence based on existing data. A power function with the following equation provided an excellent fit ($R^2 = 0.92$):

$$C(p) = 16325p^{-0.623}$$

where C is annual per-patient drug costs in Euros and p is the prevalence per 100,000 persons.

Total budget impact over 10 years was estimated to be €14,112 and €5449 million for approved and pipeline URD drugs, respectively (total: €19,561 million). Yearly estimates are shown in Figure 1. The increase in budget impact was 138% over the 10-year period from 2012 to 2021. The annual increase was 9%.

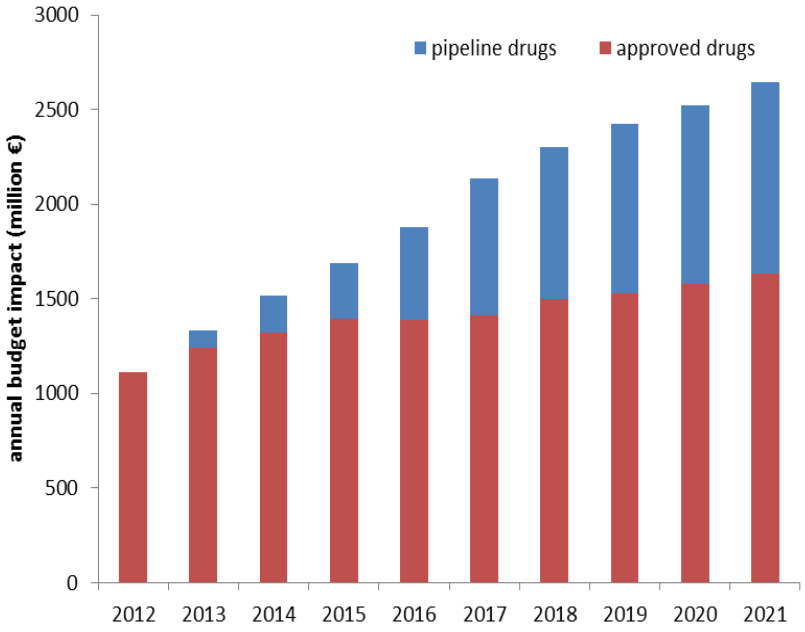

***Figure 1**: Annual budget impact of approved and pipeline drugs for URDs over 10 years (2012 to 2021) from a European payers' perspective.*

To set expenditures for URD drugs in relation to total pharmaceutical expenditures in Europe, we used recent estimates by IMS Health on the pharmaceutical market size in Europe in 2012 (€163 billion) as well as on the expected annual growth rate (1.1%). Results are shown in Figure 2. Also, we set expenditures for ultra-orphan drugs in relation to total health

expenditures in Europe (Figure 2), assuming that the past growth in EU health expenditures (OECD 2012) would continue in the future.

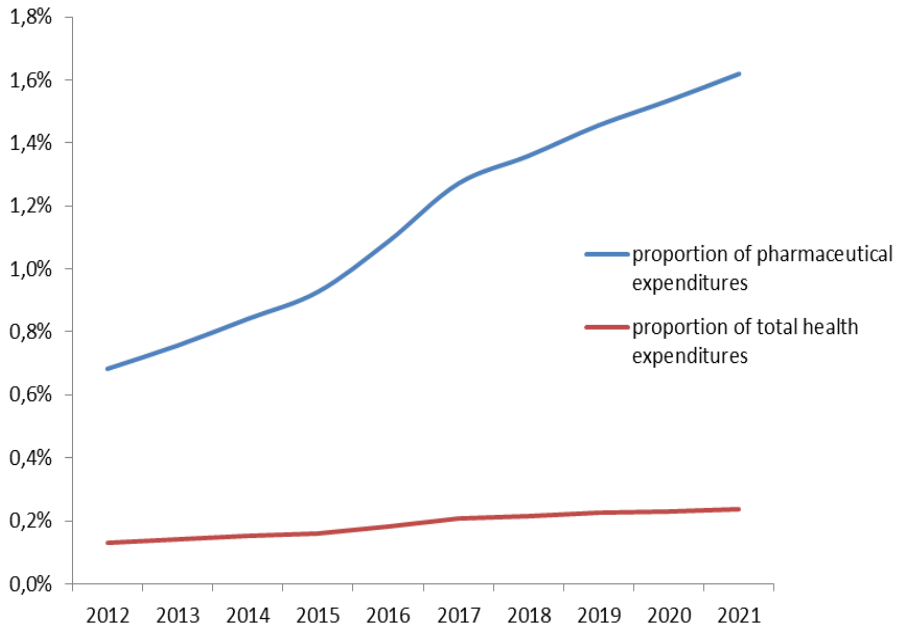

***Figure 2**: Proportion of pharmaceutical and total health expenditures in Europe spent on drugs for URDs.*

Sensitivity analysis

In the univariate sensitivity analysis, the variables with the largest impact on the budget impact were the market penetration rate and the annual growth rate in sales volume (Table 4). The worst-case scenario analysis based on the two variables yielded a budget impact of €27.839 million. The impact of uncertainty around the prevalence rate was estimated

separately based on the above power function. Based on an elasticity of -0.623, a 10% increase in prevalence leads to a 6.23% decrease in price and a 3.1% (110% x 93.77%) increase in sales (budget impact).

***Table 4**: Univariate sensitivity analyses.*

Variable	**Budget impact in million € (percentage of pharmaceutical expenditures)**
Base case	19561 (1.3%)
Market penetration rate	
Lower limit (10%)	12686 (0.9%)
Upper limit (30%)	23260 (1.6%)
Markup for prices in Europe compared to U.S.	
Lower limit (0%)	17788 (1.2%)
Upper limit (30%)	20427 (1.4%)
Annual growth rate in sales volume	
Lower limit (5%)	16758 (1.1%)
Upper limit (15%)	23186 (1.6%)
Savings one year after the first generic entry	
Lower limit (0%)	19839 (1.4%)
Upper limit (50%)	19143 (1.3%)
Savings two years after the first generic entry	
Lower limit (0%)	20831 (1.4%)
Upper limit (50%)	18291 (1.2%)
Clinical phase durations	
Phase I trials	
Lower limit (1.5 years)	19635 (1.3%)
Upper limit (2.5 years)	19529 (1.3%)
Phase II trials	
Lower limit (1 year)	20263 (1.4%)
Upper limit (2 years)	19418 (1.3%)
Phase III trials	
Lower limit (1 year)	20380 (1.4%)
Upper limit (2 years)	19354 (1.3%)

Approval	
Lower limit (1 year)	20018 (1.4%)
Upper limit (2 years)	18765 (1.3%)
Transition probabilities	
Phase I → phase II	
Lower limit (60%)	19522 (1.3%)
Phase II → phase III	
Lower limit (40%)	19243 (1.3%)
Phase III → New Drug Application	
Lower limit (50%)	18789 (1.3%)
New Drug Application → approval	
Lower limit (80%)	18789 (1.3%)
Discount rate	
Lower limit (0%)	21999 (1.5%)
Upper limit (5%)	18643 (1.3%)

Discussion

Our analysis shows that based on patent expiries and a limited number of new market entrants, budget impact of ultra-orphan drugs for non-oncological diseases in Europe may be expected to increase at a modest rate only.

The predicted average annual increase in budget impact is 9%, which translates into a 5% increase above the expected growth in total health expenditures. Growth is expected to level off after 2017.

Relative to total pharmaceutical expenditures in Europe, spending on ultra-orphan drugs is estimated to be 0.7% at present and this share is expected to increase moderately after 2017. In this regard it is important to remember that we assumed an annual growth rate of 10% for ultra-orphan drugs

but of 1.1% only for non-URD pharmaceuticals. Estimates were relatively robust to changes in the sensitivity analysis.

Using the estimate by Schey et al. (2011) as a basis, the predicted budget impact of drugs for ultra-rare non-oncological diseases is 32% of the budget impact of orphan drugs for oncological and non-oncological diseases. We aimed to use conservative assumptions throughout, thus potentially overestimating budget impact. This may explain, in part, the relatively high share of predicted spending for drugs for URDs when judged against the forecast by Schey and colleagues (2011).

There are important differences between our study and that by Schey et al. (2011), however; that is, we did not consider oncological diseases, and we estimated the occurrence of new diseases based on actual data on the current drug pipeline. Still, our model is far from being perfect, but in BIAs this is rarely the case due to limited information availability (Sullivan et al. 2013). First, sales on drugs for URDs may present an overestimation because it cannot be excluded that a portion of sales is attributable to non-ultra-rare diseases. Second, although market exclusivity for orphan drugs is usually granted over a 10 year period, it may be extended to 12 years for pediatric products, or may be reduced to 6 years if, at the end of the 5th year of exclusivity, the drug no longer satisfies the original designation criteria (e.g., there is sufficient evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity) (European Commission 2008). Such reduction has not been applied so far, however. Third, we assumed a fixed growth rate in sales across all products. However, growth rate may depend on the product cycle, with higher growth during earlier stages and lower growth during later stages. Forth, due to a lack of data, the model did not include potential savings from avoided clinical events and reductions in morbidity due to

ultra-orphan drugs as well as potential savings from treatments that are currently prescribed but will be substituted in the future due to drugs for URDs. On the other hand, savings from avoided clinical events and reductions in morbidity are not achieved in the short run due to the presence of fixed costs (Adang 2008).

In conclusion, our analysis does not support concerns about an uncontrolled growth in expenditures for ultra-orphan drugs. The estimated budget thus leaves room for future innovations in this area. We recommend continuously monitoring the budget impact in order to provide an input to rational policy making.

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