Nuijten et al. Int J Rare Dis Disord 2018, 1:005
Volume 1 | Issue 1
Open Access

International Journal of
Rare Diseases & Disorders

RESEARCH ARTICLE

Evaluation and Valuation of the Price of Expensive Medicinal Products: Application of the Discounted Cash Flow to Orphan Drugs

Mark Nuijten[1*], Hans Joerg Fugel[2] and Jan Vis[3]

[1]*A2M, Amsterdam, The Netherlands*

[2]*Biopharma Consultant, Switzerland*

[3]*Nyenrode Business Universiteit, The Netherlands*

***Corresponding author:** *Mark Nuijten, MD, PhD, MBA, 1 A2M, Dorpsstraat 75, 1546 LG, Amsterdam, The Netherlands, Tel: 31-204-27-827*

Abstract

Background: The current policy for price negotiations on high prices of orphan drugs in Europe is neither a transparent nor a structural solution for reimbursement decisions for orphan drugs. In a previous paper, we proposed the Discounted Cash Flow model as an alternative assessment methodology for the price of innovative drugs including the investor's perspective.

Objective: The objective of this current paper was to apply this concept to orphan drugs in The Netherlands, where pharmaceutical companies were recently challenged by the health authorities because of the perception of high prices.

Methods: We selected the orphan drugs with a positive clinical assessment and an incremental cost-effectiveness ratio exceeding €80,000 per Quality Adjusted Life Year QALY in The Netherlands. We applied the discounted cash flow method, which was adopted to assess the price of a new drug from an investor's perspective.

Results: The actual prices of the drugs in this analysis are in 56% lower than the minimum break-even price based on the Discounted Cash Flow Model. If we build in a margin of 30%, which means that actual price is up to 30% higher than the break-even price, nearly 78% of the drug prices in this analysis may be reasonable from the investor's perspective.

Conclusion: The application of the Discounted Cash Flow to orphan drugs shows that it may be a future useful tool for health authorities and pharmaceutical companies to assess the price of orphan drugs.

Background

Many pharmaceutical companies are now commercialising innovative so-called expensive medicinal products with incremental cost-effectiveness ratios (ICERs), which often exceed the threshold values commonly regarded as acceptable for reimbursement [1]. The ICER, defined as the cost per QALY gained, has become critical in coverage decisions for new innovative medicinal products in many countries, besides other criteria such as clinical criteria (efficacy, safety) and the impact on the new drug on the health care budget, especially the dug budget. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has adopted an incremental cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained, which means that the English society is willing to pay up to £30,000 per QALY gained for a new, innovative, medicinal product [2]. Cost-effectiveness in terms of cost per QALY can also be considered more relevant in Europe than in the United States, but budget impact and effectiveness are also important criteria for payers in the United States [3]. Mostly, the NHS in England can manage additional financial budget impact from new innovative drugs. But when the impact on the budgets is very high, it makes sense for special arrangements (e.g. access schemes) to be put in place. One important step is through price negotiations with the company to help reduce the budget impact of a new treatment [4]. For example, pharmaceutical companies are being forced to cut the price of

Citation: Nuijten M, Fugel HJ, Vis J (2018) Evaluation and Valuation of the Price of Expensive Medicinal Products: Application of the Discounted Cash Flow to Orphan Drugs. Int J Rare Dis Disord 1:005

Accepted: December 17, 2018 ; **Published:** December 19, 2018

high cost cancer drugs for the first time as a result of a new approach by NICE/NHS. In Germany price negotiations between manufacturer and National Association of Statutory Health Insurance Funds take place on the basis of the GBA resolutions (period of 6 months after G-BA resolution) [5]. Finally, also in France, price negotiations are becoming important and are is carried out before any reimbursement schemes are devised. In most cases this is before the drug is launched in the market [6]. Summarizing, central reimbursement procedures are increasingly followed by price negotiations in many EU markets. In this paper, we introduce a new concept for the assessment of a reasonable price, which is particularly relevant for most European countries. For purpose of illustration we apply the concept to The Netherlands, because of public available information on price negotiations and the weight of cost-effectiveness data.

Until recently, the reimbursement process in The Netherlands was the final step before market launch, which usually resulted in a positive or negative reimbursement decision. For expensive drugs, including orphan drugs, there has been a policy to provide conditional reimbursement for a period of 4 years [7]. Since 2015, the Dutch Minister of Health issues price negotiation results for expensive drugs with an ICER far beyond the threshold (i.e., higher than €100,000 euro per QALY). In this context, a drug is considered "expensive" when the annual budget impact exceeds €40 million or the annual costs per patient exceed €50,000. Unlike the reimbursement process, which is formal and transparent, including legal procedures and guidelines, the price negotiations are secret and lack formal rules on process, content, and criteria.

A better understanding of the process can be provided using an example. The Dutch Ministry of Health and the pharmaceutical company Vertex finally agreed on the price for Orkambi (lumacaftor/ivacaftor combination therapy), a new drug for the treatment of cystic fibrosis, in October 2017, after more than 6 months of price negotiations. The Ministry was initially only willing to reimburse Orkambi if Vertex lowered the annual drug price of €170,000 by 80% to £ € 34,000. Their argument was that this price reduction was needed to make Orkambi "cost-effective", which meant that the ICER then would be €80,000 per QALY, which is the upper cost-effectiveness threshold in The Netherlands. The threshold varies between €10,000 and €80,000 per QALY, which depends on the severity of the disease.

The market for orphan drugs is limited because of the low number of potential patients. However, the total costs for the development of orphan drugs are not much different than the R&D costs for non-orphan drugs, approximately US$700 million [7]. As a consequence, the prices for orphan drugs should be much higher than for other drugs, because the costs for development can only be recouped on fewer patients; while a pharmaceutical company can recoup the costs of development for a antihypertensive drug on a billion patients, there are less than 50,000 patients worldwide for Orkambi.

The Dutch Minister argued in the Orkambi case that "the price that the manufacturer is requesting is unacceptably high" and therefore said that it would not be reimbursed. But there is no supporting evidence for this decision. Why is €170,000 per year unacceptably high for Orkambi? After all, only a small number of patients will use this drug. Therefore, the expenses for Orkambi do not represent a major threat to the total budget. The current ad hoc policy in The Netherlands is neither a transparent nor a structural solution for reimbursement decisions for orphan drugs.

The ICER is a measure from a society perspective and reflects what society is willing to pay of one QALY. If the ICER is higher than the threshold, e.g. €80,000 per QALY, than the drug may not be reimbursed. However, innovation depends on the financial markets. Therefore, we take the investors perspective, who demand a sufficient return on investment, because they who donate part of their assets for a short or long time, where the factors of uncertainty and/or risk are important determinants.

In a recent paper, this alternative assessment methodology was proposed for the price of innovative drugs from another perspective that bridges concepts from health economics and business economic valuation [1]. The approach allows the calculation of a minimum drug price, which the investor needs for commitment to the project. This approach may justify a drug price, especially when the drug's ICER exceeds the cost-effectiveness threshold.

The objective of this paper is to apply this concept to orphan drugs in The Netherlands, since health authorities have often challenged the reimbursement of these drugs because of unacceptably high prices. This approach may be particularly relevant to orphan drugs, given their characteristically high ICERs. Although there is no formal legal framework for this concept, it may already be useful in informal price negotiations between health authorities and pharmaceutical companies.

Methods

Concept

The general concept of the assessment methodology for pricing innovative drugs is briefly described here, which is provided in more detail in a previous publication [1]. The initial assumption is that in a pure market economy the price of the new innovative drug would be determined by demand and supply mechanisms. If health authorities leave the responsibility for medical innovation to the market, medical innovation will rely

Table 1: SMA drug: year 1: € 240,000 and NOT € 249,000.

Disease	Drugs	Price*
		Annual
Paroxysmal nocturnal hemoglobinuria (PNH)	Eculizumab	€358,000
Hunter	Idursulfase	€600,000
Cystic fibrosis (CF)	Lumacaftor/Ivacaftor	€169,386
Cystic fibrosis (CF)	Ataluren	€270,000
Primary biliary cholangitis (PBC)	Obeticholic acid	€38,021
Spinal Muscular Atrophy (SMA)	Nusinersen	Year 1: €240,000 > year 1: €249,000
Neuronal ceroid lipofuscinosis, late infantile type 2 (CLN2)	Cerliponase alpha	€595,971
Metabolic disease - alpha-mannosidosis lysosomal disease	Velmanase alpha	€ 500.000
Congenital or acquired lipodystrophy	Metreleptin	€480,000

*Prices were based on horizon scan by health authorities.

on the market mechanisms in the financial markets, which especially include the incentives of investors, who demand a sufficient return on investment. Therefore, the justification of the orphan drug price can be based on the Discounted Cash Flow method, which uses the expected free cash flows and the required cost of capital and can be used to validate the price of the new drug from an investor's perspective.

The discounted cash flow is derived from the present value equation to calculate the time value of money and compounding returns.

$$NPV = CF_1/(1 + r)^1 + CF_2/(1 + r)^2 + \text{----} + CF_n/(1 + r)^n \quad \text{(Eq 1)}$$

Where

NPV = Net Present Value

CF = (Free) Cash Flow

n = The time in years before the future cash flow occurs

r = Cost of Capital

The current analysis starts at T = 0, which is the year of patent registration. We assume that approval by FDA and European Commission occurs at year 8 and that reimbursement dossiers are subsequently submitted in the countries [1]. We assume that there is a reimbursement decision within 1 year after registration, leaving 11 years for sales before the patent expires. Any development and other related costs incurred before obtaining the patent in year 1 are not included in this analysis and are considered sunk costs.

Cash flows from operations represent the sales from the pharmaceuticals, and expenditures necessary for capital expenditures represents the costs for R&D, production costs and marketing. The R&D costs of unsuccessful clinical programs should be allocated to the successful drug. The probability of failure during the development (phase I, II and III) phases is derived from the literature [8].

The hurdle rate, which is the minimum rate that a company expects to earn when investing in a project, is based on the average cost of capital in the pharmaceutical market for pharmaceutical (9%) and biotechnology companies (12%) [9].

The Discounted Cash Flow method can be applied to compare the break-even price for the innovative drug, where the net present value is zero, with the actual drug price in order to assess if the applied drug price is justified based on business valuation theory. When the break-even price is higher, the actual price may not attract investors, but if the break-even price is lower, the actual drug price may not be justified using valuation theory.

In this paper we focus on orphan drugs for the purpose of illustration, but the concepts can also be applied to non-orphan biologicals.

Application

We applied the Discounted Cash Flow method to the projections of forthcoming expensive drugs in The Netherlands, based on information from the Dutch National Health Care Institute (Zorginstituut Nederland - Zin) (Table 1) [10]. We focus only on innovative orphans that are first-in-class drugs. In addition, future "me-too" drugs are not relevant in the context of orphan drugs in EU, as the EC cannot authorise a new orphan drug for the same therapeutic indication that is considered similar [11]. We examined the technology appraisal reports by Zin [10]. Each report consists of three sections: clinical value, cost-effectiveness and the budget impact (BIA). We selected the orphan drugs with a positive clinical assessment and an expected ICER exceeding €80,000 per QALY gained (Table 1). We considered only drugs for orphan diseases and therefore excluded oncology drugs with orphan drug status.

Assumptions

The hurdle rate is 12% in the base case analysis as we can consider that all companies are biotechnology companies. A scenario analysis was performed using 9% cost of capital for pharmaceutical companies and 18% to reflect a higher risk for biotechnology companies in orphan drugs. A premium for small firm risk and a higher risk for drugs in orphan disease area is included in another scenario analysis with 25% hurdle

rate. However, the higher risk of delay, the risk of no reimbursement, and price negotiations may have increased the cost of capital over the last years, when drug costs for Pompe disease and Fabry disease were challenged in 2012 in The Netherlands.

There is a 100% probability of reimbursement, which may be a realistic assessment at T = 0 for the drugs in our study. Since some believe that there is also a risk of reimbursement failure, we included this in a scenario analysis (80% probability of reimbursement).

The probabilities of failure during the development (phase I, II and III) phases are: phase I-II 30%; phase II-III 61%; phase III-approval 31% (Table 2), which are not specific for orphan drug clinical programs [8]. Because of lack of other data, we assume that these probabilities also apply to orphan drugs. A scenario analysis was performed in which higher probability of failures were assumed, because of the specific clinical and epidemiologic constraints in performing randomized clinical trials (RCTs) in orphan diseases. That is, the low number of patients and other factors like heterogeneity in the patient population complicate the execution of classic RCTs and the ability to generate statistically significant and clinically relevant evidence.

The costs of the various phases of development are reported in Table 2 [1]. The sum of production and marketing costs is based on 40% of revenues, which was estimated based on the analysis of financial reports of biopharmaceutical companies. Also, we assume that these costs also apply to orphan drugs, because no specific costs were available for trials of orphan drugs. However, there are different reasons why R&D costs may be different for low prevalence orphan drugs [12]. It can be debated whether R&D costs are actually similar for orphan drugs, because trials require smaller numbers of patients, trials have to meet lower evidence requirements, patients are concentrated in a small number of treatment centers and much pre-clinical development is already done in-hospital. On the other hand, costs might be different because of difficulties finding patients and long follow-up periods required to find effects. Other factors could decrease these costs; for example, orphan drugs acts in the US and Europe may allow smaller or shorter trials for orphan drugs.

The production and marketing costs for orphan drugs may also be different than for other drugs. The production costs may be higher for orphan drugs, which are usually innovative drugs requiring high-tech manufacturing processes. The marketing costs may be lower because there are usually a limited number of centres in a country. For example, in The Netherlands, all Pompe patients are treated at the academic hospital in Rotterdam (Erasmus MC). On the other, for both orphan and non-orphan drugs, there has been a change in the marketing paradigm from the classic sales rep to account management. Scenario analyses were performed in order to assess this uncertainty.

Table 2: The input parameters for the discounted cash flow model.

Model parameter	Value
Cost of development (US$ million)	US$701 million
Cost pre-clinical	US$217 million
Phase I	US$84 million
Phase II	US$142 million
Phase III	US$190 million
Phase IV	US$68 million
Years of development & approval	8 years
Population	Western markets: 872.5 million
	Global markets: 1,670 million
Period of reimbursement	1 year
Net patent period after registration	12 years
Uptake	80% from year 1
Cost of revenue	40%
Hurdle rate	12%
Probability	
- Phase I to II	70% (failure - 30%)
- Phase II to III	39% (failure - 61%)
- Phase III to FDA approval*	69% (failure - 31%)

*Assumption: Same probability for EMA.

The potential number of patients is based on the global potential number of patients. The base case analysis is based on the Western markets, which are the real viable market for pharmaceuticals (Table 2). In a scenario analysis we extended the global market by including non-Western countries (Table 2).

The calculation of the global number of patients is based on extrapolation of the number of eligible patients in The Netherlands by proportion of Dutch population size relative to the global population. This analysis assumes similar prevalence and incidence in all countries; while this assumption is not always true for non-Western countries, these countries are not the main markets for pharmaceutical companies. The BIA sections from the technology appraisal reports by Zin provide the number of patients in The Netherlands as well as the annual cost for each drug. In fact, we do not use the actual drug price in our calculation, as we calculate the break-even price, which we compare with the actual drug price. In a scenario analysis we assume that prices in the US are 30% higher than in Europe.

The base case analysis assumes that there is a reimbursement decision within 1 year after registration. This may be a realistic assessment at T = 0 for the current drugs under investigation. However, since price negotiations may lead to an additional 6 to 12 months delay, which may have been anticipated at T = 0, a scenario analysis includes an additional delay of 12 months.

In the financial analysis, diffusion generally increases

Table 3: The results from the base case analysis.

Disease	Drugs	Price	Break-even price	Mark-up*	
		Annual	Annual	Absolute	%
Paroxysmal nocturnal hemoglobinuria (PNH)	Eculizumab	€358,000	€458,870	-€100,870	-22%
Hunter syndrome	Idursulfase	€600,000	€1,076,579	-€476,579	-44%
Cystic fibrosis (CF)	Lumacaftor/ivacaftor	€169,386	€65,861	€103,525	157%
Cystic fibrosis (CF)	Ataluren	€270,000	€254,464	€15,536	6%
Primary biliary cholangitis (PBC)	Obeticholic acid	€38,021	€46,652	-€8,631	-19%
Spinal Muscular Atrophy (SMA)	Nusinersen	€240,000	€95,860	€144,140	150%
Neuronal ceroid lipofuscinosis, late infantile type 2 (CLN2)	Cerliponase alpha	€595,971	€799,744	-€203,773	-25%
Metabolic disease - alpha-mannosidosis lysosomal disease	Velmanase alpha	€800,000	€799,744	€256	0.1%
Congenital or acquired lipodystrophy	Metreleptin	€480,000	€509,623	-€29,623	-6%

*A positive difference indicates that actual prices are higher than break-even prices and a negative difference indicates that actual prices are lower than break-even prices.

from time of launch over the follow-up period [13]. Therefore, not all eligible patients are treated as soon as the drug is available or even later. The commercial time to reach peak sales (80% of the market) is normally 6 years [14]. However, we assume that the peak uptake will be 80% and will be achieved after year 1 instead of 6 years, because for the uptake is higher in severe diseases without appropriate alternative treatments. A scenario analysis used a peak of 80% uptake after 3 years.

Results

Table 3 shows the base case results, while Table 4 shows the results of the sensitivity and scenario analyses. The actual prices of the drugs in this analysis are in 56% lower than the minimum break-even prices based on the Discounted Cash Flow Model. If we build in a margin of 30%, which means that the actual price is up to 30% higher than the break-even price, 78% of the drug prices in this analysis may be reasonable from the investor's perspective.

The break-even price should not be considered a final cut-off point for several reasons. The base case analysis of the current Discounted Cash Flow model is based on a number of assumptions, each of which may be challenged. Therefore, we performed extensive sensitivity and scenario analyses, which are described in the next section, in order to assess the uncertainty of the results using the current model. Although the break-even price for alpha-mannosidosis lysosomal disease is close to the upper price estimate by Zin, no official price is available yet and therefore our finding should be interpreted with caution.

Whenever the epidemiology data from The Netherlands was similar to international epidemiology data, we used the estimates by Zin. However, since the epidemiology differed for certain diseases, we used international data for these diseases, which were as follows.

Hunter syndrome: The estimated prevalence in the United States is 500 [15]. When adjusted to The Netherland this leads to 26 patients, which may be considered too low.

Neuronal ceroid lipofuscinosis: The estimated prevalence is 2 per million, leading to 35 patients in The Netherlands [16]. The estimate by Zin varied between 10 and 20 patients, which is also quite different from international data.

Congenital or acquired lipodystrophy: The estimate by Zin was 20 patients, which was quite different from what would be expected based on international data (i.e., 3.07 cases per million), which would lead to 64 patients [17].

Table 4 shows the results of the sensitivity and scenario analyses. The hurdle rate, market size, and risk of failure of clinical trials are the most critical parameters in the model. Delay due to the reimbursement procedure and probability of reimbursement failure are also substantial parameters, which may have a substantial impact on the results. Since the other parameters also have a substantial impact on the break-even price, they also need further exploration.

Discussion

In the current health care environment, where the policy is that innovation relies mainly on business entrepreneurship, health authorities have to accept the market mechanisms in all resource markets including the finance market. They should especially accept an adequate return on investment for investors in order to benefit from the societal value of medical innovation [18]. The bottom line is that if health authorities want to establish market mechanisms, they should also consider the rules of free market in investors' market in pharma and biotech and not simply consider a willingness to pay (ICER) from a public perspective.

The objective of this paper was to apply the

Table 4: Results of the sensitivity and scenario analyses: difference in % versus the market price.

	PHN	Hunter syndrome	CF	CF	PBC	SMA	CLN2	Alpha-man. Lys.	Lipo Dys.
	Eculizumab	Idursulfase	Lumacaftor/Ivacaftor	Ataluren				€200.000 - €800.000	
Price	€358,000	€600,000	€169,386	€270,000	€38,021	€240,000	€595,971	€800,000	€480,000
Break-even price base case	-22%*	-44%	157%	6%	-19%	150%	-25%	0%	-6%
Cost of capital 9%	-1%	-29%	225%	34%	3%	217%	-6%	27%	21%
Cost of capital 18%	-58%	-70%	39%	-43%	-56%	35%	-60%	-46%	-51%
Include non-Western markets	40%	0%	363%	91%	47%	351%	34%	80%	69%
Reimbursement 80%	-41%	-58%	183%	-20%	-39%	88%	-44%	-25%	-29%
Failures: 20% higher	-60%	-71%	32%	-45%	-58%	29%	-62%	-49%	-52%
Costs 20% R&D lower	-17%	-35%	202%	25%	-4%	193%	-12%	18%	11%
Costs 20% R&D higher	-36%	-56%	101%	-17%	-36%	96%	-42%	-22%	-26%
Cost sales 20% lower	-29%	-41%	174%	13%	-13%	167%	-21%	7%	0%
Cost sales 20% higher	-36%	-55%	110%	-14%	-34%	104%	-39%	-19%	-23%
Delay	-37%	-55%	107%	-14%	-34%	102%	-40%	-19%	-25%
Drug price 30% higher	9%	-22%	258%	48%	13%	249%	4%	39%	31%
Uptake 60-70-80%	-28%	-50%	129%	-5%	-27%	98%	-34%	-11%	-2%
Uptake 70-80-95%	-15%	-41%	171%	12%	-14%	134%	-22%	5%	15%

*A positive difference indicates that actual prices are higher than break-even prices and a negative difference indicates that actual prices are lower than break-even prices.

Discounted Cash Flow Model to orphan drugs, whose prices have been challenged by reimbursement authorities, because they are considered unacceptably high. The primary goal of the current analysis was not to judge if the prices for these orphan drugs really are excessive, but rather to test the feasibility of our published concept using recently assessed drugs, whereas the initial publication was only based on a hypothetical drug [1]. The outcomes of this feasibility analysis may guide further conceptual research. Nevertheless, the outcomes of this analysis already provide information to put the actual drug price in a broader perspective. If the actual drug price is below the break-even price, we may at this stage already conclude that the actual drug price seems reasonable and that no further justification is required from the pharmaceutical company. However, if the actual drug price is substantially higher than the break-even price, more information is needed to determine if the price is reasonable. In our analysis, the price of one of the CF drugs and the price of the SMA drug were more than two times higher than the break-even prices. Therefore, these findings would indicate that further exploration is required to judge if these prices really were necessary to satisfy investors. This further exploration could reveal that a higher price is justified; for example, production costs may be substantially higher for these drugs.

Sensitivity analyses assess the uncertainty associated with the statistical distribution of the input parameters, whereas scenario analyses are based on methodological assumptions in our approach [19]. The statistical distribution is common uncertainty, which does not depend on the stage of development of our concept. The methodological assumptions in our approach require further research. The scenario analyses show the impact on the results of a future change in these assumptions, for example the most appropriate hurdle rate for orphan drugs. The hurdle rate, market size, and risk of failure of clinical trials are the most critical parameters in the model. A recent paper by Prasad showed that the median cost of drug development was €544 million (US$648 million) for oncology drugs, which was close to our input parameter of £590 million [20]. The authors report that their costs are significantly lower than prior estimates. Therefore, our analysis based on of €590 million, may be considered realistic conservative approach [20]. Future research may lead to better estimates of disease-specific costs and probabilities of failures. We do not intend to use internal bookkeeping data but recommend

the use of published costing data for R&D and costs of marketing. Therefore, we recommend the use of standard costs for the development (phase I, II and III) and marketing of a new innovative product, which should reflect the actual costs for development that can be applied in every business valuation.

In this model the assumption is that there is 11 years of sales left for orphan drugs. After a patent expiries pharmaceutical companies may have a monopoly, when there are no competitors entering the market. For orphan drugs, biosimilars/generics may not always enter the market because of the small market sizes and thus prices remain high. Even if biosimilars would enter the market, the uptake of these drugs might be limited, because of small price differential and issues with switching. Hence, in reality manufacturers have a much longer period of sales than 11 years. On the other hand, most of new orphan drugs may improve the functional status of the patients, but there is still need for more efficacious drugs.

The hurdle rate is another important topic for further research. While a start-up or a company that is still in the discovery stage faces a high cost of capital of over 20%, a clinical stage company can use a lower discount rate. When a company already has a drug on the market, the cost of capital is usually already close to the discount rate of a pharmaceutical company, i.e. between 8% and 10%. So, the hurdle rate seems to depend mainly on the stage of a company. Knowledge of stage-dependent discount rates may be included to improve estimates of the specific costs of capital for each stage of clinical development. Another topic for further consideration is that often early access programs are used for innovative orphan drugs to achieve earlier patient access so commercial timelines and uptake are influenced by these early access program to some extent.

The current analyses also show the impact of epidemiological data, especially the number of eligible patients and market size. The market size in the base case analysis is based on 872.5 million patients based on Western European, US, Australia, Japan and Canada markets. The scenario analysis also included Eastern Europe and South America, leading to almost twice as many patients (1,670 million). A more accurate estimate of the number of eligible patients requires more detailed epidemiological data and analyses. Part of the deviations between market and break-even prices may be due to lack of detailed epidemiological knowledge in the financial environment.

Practical issues in handling data input and uncertainty in a budget impact analysis are described in the literature, which can provide guidance on the calculation of the forecast of the number of eligible patients for budget impact analyses [13].

We developed the concept from the narrow perspective of the investor in the pharmaceutical market to see if drug prices for innovative ("expensive") drugs are justified based on business valuation theory. This analysis does not include all other monetary and non-monetary values for society (patients, physicians, payers, providers and employers), which may be included in a broader analysis.

We notice that the current price negotiations for Orkambi and Spinraza in The Netherlands show the increasing hurdles for market access for orphan drugs and therefore investors for new clinical programs may add these parameters in the equation leading to higher break-even price, as shown in our scenario analysis. Therefore, current inappropriate price discounts following price negotiations will have a boomerang effect, because current price containment measures to minimize "excessive" pricing may even lead to more expensive pricing. The use of the current Discounted Cash Flow model may also minimize these future consequences of price negotiations.

Conclusion

The application of the Discounted Cash Flow to orphan drugs shows that it may be a valuable tool for both reimbursement authorities and pharmaceutical companies to assess the price of orphan drugs from an investor's perspective and help to put the high ICERs seen with these drugs in a broader perspective. This approach is applied to The Netherlands but is relevant for most European countries, as central reimbursement procedures are increasingly followed by price negotiations. Although there is no formal legal framework for this concept, it may already be useful in informal price negotiations between health authorities and pharmaceutical companies.

Declarations

A. Ethics approval and consent to participate: Not applicable.

B. Consent for publication: Not applicable.

C. Availability of data and material: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

D. Funding: This study was not funded by any person or company.

E. Acknowledgements: Not applicable.

References

1. Nuijten MJC, Vis J (2016) Evaluation and valuation of innovative medicinal products. J Rare Dis Res Treat 2: 1-11.

2. Nuijten MJ, Dubois DJ (2011) Cost-utility analysis: Current methodological issues and future perspectives. Front Pharmacol 2: 29.

3. Mark Nuijten (2013) Pitfalls in the valuation of a pharmaceutical company. Journal of Private Equity Fall 16: 57-66.

4. https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know

5. http://www.sozialgesetzbuch-sgb.de/sgbv/130b.html

6. http://apps.who.int/medicinedocs/documents/s20974en/s20974en.pdf

7. Mark Nuijten (2014) The potential impact of current and future pharmaceutical policy changes on cash flows for innovative medicines. The Journal of Private Equity Winter 18: 34-45.

8. Fugel HJ, Nuijten M, Postma M (2016) Economic viability of Stratified Medicine concepts: An investor perspective on drivers and conditions that favour using Stratified Medicine approaches in a cost-contained healthcare environment. N Biotechnol 25: 860-867.

9. Harrington S (2012) Cost of capital for pharmaceutical, biotechnology, and medical device firms. In: Danzon PM, Nicholson S, The oxford handbook of the economics of the biopharmaceutical industry. Oxford University Press, New York, 75-99.

10. https://www.horizonscangeneesmiddelen.nl/binaries/content/assets/horizonscan/horizonscan-vws-uittreksel-december-2016.pdf

11. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0781&from=SV

12. DiMasi JA, Hansen RW, Grabowski HG (2003) The price of innovation: New estimates of drug development costs. J Health Econ 22: 151-85.

13. Nuijten MJ, Mittendorf T, Persson U (2010) Practical issues in handling data input and uncertainty in a budget impact analysis. Eur J Health Econ 12: 231-241.

14. Sabir S (2009) The economical and ethical consideration and implications of the stratification of future oncology therapeutics. Massachusetts Institute of Technology, MA, USA.

15. http://flipper.diff.org/apptagsaccount/items/6782

16. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=168491

17. Elaine Chiquette, Elif A Oral, Abhimanyu Garg, David Araújo-Vilar, Praveen Dhankhar (2016) Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. Dove Press 10: 375-383.

18. Nuijten MJC, Vis J (2018) Economic comments on proposal for a novel cancer drug pricing model. Nat Rev Clin Oncol 15: 587.

19. Task Force on Principles for Economic Analysis of Health Care Technology (1995) Economic analysis of health care technology: A Report on Principles. Ann Intern Med 122: 61-70.

20. Prasad V, Mailankody S (2017) Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med 177: 1569-1575.