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What is the relationship between price and prevalence in non-oncology rare disease?

Introduction

With a recent flurry of headline grabbing high prices for medicines in non-oncology rare diseases, this article investigates whether there is a relationship between prevalence and price.

High development costs and low patient numbers have often been presented as justifications for high prices in rare diseases. Payers have traditionally accepted this narrative for two reasons. First, because the individual budget impact of each product remains low relative to high budget impact categories. And, second, because of high unmet need and a regulatory environment that supports investment in orphan indications – often driven by broader societal support built on the back of emotional stories of patient hardship.

However, the environment is changing as the collective budget impact of treatments for rare diseases is rising. Despite the provision of alternative funding mechanisms for orphan drugs, payers are taking a tougher line on prices, negotiating rebates, and setting budget impact thresholds. Rather than accepting the labelled indication de facto, payers are increasingly scrutinising the patient population as a means of reducing economic uncertainties. In the past, payers always recognised rarity in their pricing decisions. Is this still true or, with the rise of treatments for rare diseases, are other factors contributing more to the price-setting process?

Methods

Our analysis included 16 orphan drugs that received European Medicines Agency (EMA) approval since July 2012. These drugs were sorted into two categories: rare and ultra-rare. As proposed by the European Commission,[1] drugs indicated for diseases with a prevalence of less than 1 in 50,000 were categorised as ultra-rare; the remainder, all of which met the EU orphan definition of a prevalence below 5 in 10,000, were categorised as rare (see Table 1).

Table 1: Prevalence estimates and sources used

Brand name	Molecule name	EMA approval date	Prevalence	Prevalence sources
Kalydeco	ivacaftor	July, 2012	1:30,000	Maiuri et al., 2015[2]
Opsumit	macitentan	December, 2013	1:5,500	EMA
Adempas	riociguat	March, 2014	1:5,000	EMA
Cerdelga	eliglustat tartrate	January, 2015	1:35,000	EMA
Ofev	nintedanib	January, 2015	1:3,500	EMA
Strensiq	asfotase alfa	August, 2015	1:300,000	Orphanet; Mornet et al., 2011[3]; Conti et al., 2017[4]
Kanuma	sebelipase alfa	August, 2015	1:90,000	Desai et al., 2016[5], Carter et al., 2019[6]
Raxone	ibedenone	September, 2015	1:35,000	NORD, LHON Society, Man et al., 2002[7]
Orkambi	lumacaftor/ivacaftor	October, 2015	1:5,000	Maiuri et al., 2015[2]
Wakix	pitolisant	April, 2016	1:2,500	Scheer et al., 2018[8]
Uptravi	selexipag	May, 2016	1:5,500	EMA
Galafold	migalastat hydrochloride	May, 2016	1:10,000	EMA
Ocaliva	obeticholic acid	December, 2016	1:2,500	EMA
Spinraza	nusinersen	May, 2017	1:65,000	Verhaart et al., 2017[9]
Brineura	cerliponase alfa	May, 2017	1:2,000,000	Williams et al., 2017[10]
Crysvita	burosumab	February, 2018	1:20,000	Orphanet

Rare Ultra-rare

Source: EMA; CRA analysis

In this study, we used prevalence rather than incidence as the measure of disease rarity, as it typically provides a better representation of the patient population. Despite this, we understand that in diseases with high mortality rates, incidence may provide a better proxy than prevalence for the number of patients eligible for treatment and can therefore be used in health technology assessments (HTAs).

We used a pragmatic approach to calculate prevalence: EMA prevalence rates served as a foundation for our calculations and were compared against estimates in the literature. Where EMA prevalence differed substantially from the literature, an average was taken from the estimates.

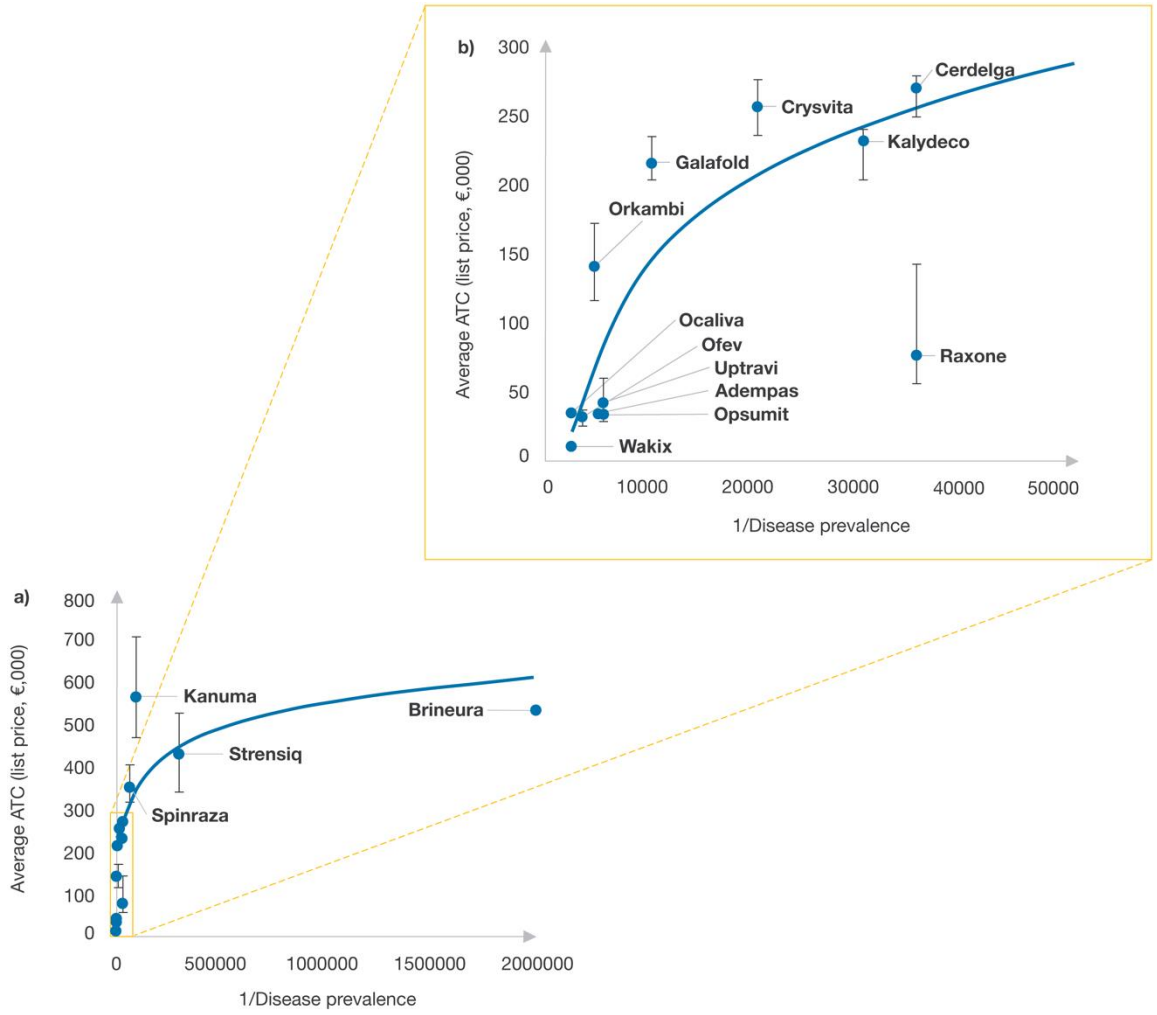
We calculated the average annual treatment cost (AATC) of each drug across EU5 (France, Germany, Italy, Spain and the UK) and Japan using launch list prices where possible. While we used list prices, we understand that confidential net price discounts may have been negotiated in France, Italy, Spain and the UK, which would affect actual budget impact. Where variable dosing strategies applied for a given drug, a pragmatic approach was taken using the literature or calculations made by HTA bodies (see Table 2).

Table 2: Pack sizes, prices, dosing strategy and assumptions used in average annual treatment cost (AATC) calculations

Brand name	Pack name	List price per pack (€)						Dosing strategy and assumptions
		DE	FR*	IT	ES	UK*	JP*	
Kalydeco	56 x 150 mg	18,177	18,000	18,000	18,000	15,400	–	150 mg BID
Opsumit	**EU:** 30 x 10 mg **JP:** 1 x 10 mg	2,300	–	2,850	2,450	2,536	114	10 mg QD
Adempas	**DE, ES, IT, UK:** 42 x 0.5-2.5 mg (flat) **FR:** 1 x 0.5-2.5 mg (flat) **JP:** 1 x 0.5-2.5 mg (variable)	1,220	28	1,396	1,369	1,376	27 (2.5 mg)	2.5 mg TID (maintenance)
Cerdelga	**DE, ES, IT:** 56 x 84 mg **FR, UK:** 1 x 84 mg	20,712	337	20,856	20,712	376	–	84 mg QD or BID (majority of patients BID)
Ofev	60 x 150 mg	2,967	2,060	2,719	2,404	2,624	–	150 mg BID
Strensiq	12 x 40 mg	40,320	25,954	–	–	32,175	–	2 mg/kg 3 times per week or 1 mg/kg 6 times per week Average weight 19.3 kg (NICE)
Kanuma	1 x 20 mg	5,927	–	6,567	8,980	–	–	1 mg/kg every other week Average weight based on 10-year average assuming treatment start at age 11 (NICE)
Raxone	180 x 150 mg	4,544	–	11,553	–	7,000	–	900 mg per day
Orkambi	112 tablets (variable conc.)	10,128	–	12,994	–	8,800	–	Two lumacaftor/ivacaftor tablets every 12 hours
Wakix	30 x 4.5-18 mg (flat)	465	–	–	–	353	–	4.5 mg to 36 mg QD Assumes two tablets per day
Uptravi	**EU:** 60 tablets (variable conc., flat pricing) **JP:** 1 x 400 µg	2,548	2,548	4,847	3,864	3,300	23	EU: 200-1,600 µg BID JP: 1000 µg BID
Galafold	14 x 123 mg	15,419	15,610	17,000	16,154	17,769	15,978	123 mg QAD
Ocaliva	30 x 10 mg	2,721	–	3,060	2,762	2,622	–	5 mg / 10 mg QD
Spinraza	1 x 12 mg	89,600	–	70,000	70,000	75,000	72,600	**Loading:** 12 mg on days 0, 14, 28, 63; **Maintenance:** 12 mg every 4 months Assumes average annual treatment cost of years 1 and 2
Brineura	2 x 150 mg	20,385	–	–	–	–	–	300mg every other week
Crysvita	1 x 10 mg	2,550	–	–	–	2,992	–	0.4-2 mg/kg biweekly admin; Maintenance: range from 10-60mg (NICE)

Pricing sources: Germany: Lauertaxe; France: Codage, Legifrance, Theriaque; Italy: Gazzetta Ufficiale; Spain: BotPlus, Vademecum; UK: NICE, BNF; Japan: MHLW
Dosing sources: Electronic Medicines Consortium (eMC), The National Institute of Health and Care Excellence (NICE), Pharmaceuticals and Medical Devices Agency (PMDA)
*Variable pack sizes to other markets for some brands

Figure 1: Relationship between average annual treatment cost (AATC) and disease prevalence for a) all diseases and b) diseases with a prevalence of at least 1 in 50,000



Source: CRA analysis

Discussion

Relationship between average annual treatment cost (AATC) and prevalence

We found that there is a relationship between AATC and disease prevalence, in which AATC tends to increase as the prevalence decreases (see Figure 1). While this is true for rare diseases as payers' major focus is on budget impact, the correlation between AATC and prevalence is not as apparent for ultra-rare diseases. Though a trend cannot be established due to the limited number of ultra-rare disease products (n=4), the change in price-prevalence correlation may be symptomatic of a ceiling to payers' willingness to pay.

Deviations from the trend-line

Our research also highlighted that the relationship between price and prevalence can be influenced by several other factors. These include the robustness of clinical data, magnitude of clinical benefit, demonstrated mortality benefit, level of unmet need, disease burden and lack of available treatments. To determine the relative importance of these factors, we conducted an in-depth review of Kanuma, Strensiq and Brineura, three ultra-rare products, as well as analysed the cystic fibrosis (CF) and pulmonary hypertension (PH) treatment clusters.

Ultra-rare diseases:

1. Kanuma

Kanuma is an enzyme replacement therapy used to treat patients of all ages with lysosomal acid lipase deficiency (LAL-D), a chronic disease for which the previous treatment options were limited to stem cell or liver transplant. LAL-D can be life-threatening, with infants who show signs of disease within the first weeks of life typically dying within 6-12 months. There are several factors that would influence the high AATC of Kanuma.

A key driver of the Kanuma annual treatment cost in every market is its strong clinical profile, having demonstrated both an increase in survival and growth improvements in infants, as well as meeting its primary endpoint in a placebo-controlled study in children and adults. In this case, the mortality and developmental benefit in a life-threatening disease affecting paediatric patients may have led to the average list price of Kanuma exceeding prevalence-based expectations according to the trend-line in Figure 1.

However, there is variation in the Kanuma annual treatment cost across the three markets in which it is available (Germany, Italy and Spain). The annual treatment costs in Italy and Spain are markedly higher than in Germany, which could be in part accounted for by confidential net price discounts.

The annual treatment cost variation across markets and the high AATC of Kanuma may also be due to variable epidemiology estimates used in pricing calculations and negotiations (see Table 3). The estimate used in this analysis, 1 in 90,000, is based on our interpretation of literature estimates. In Germany, the patient number estimates used in pricing negotiations were 4 to 5 for the infantile form and 27 to 838 for children and adolescents. This corresponds to a total prevalence range between approximately 1 in 2.5 million and 1 in 100,000; given that German pricing considerations accounted for an indication involving patients of all ages, the use of lower prevalence estimates (relative to 1 in 90,000) may explain why the AATC achieved is above the trend-line. The patient number estimates used in the Spanish Informe de Posicionamiento Terapeutico were 90 to 370, equivalent to a prevalence range between 1 in 120,000 and 1 in 100,000.

Table 3: Comparison between CRA prevalence estimates and those used in German and Spanish HTAs for Kanuma[11]

Market	Prevalence estimate
Our estimate	1 in 90,000
Germany	1 in 2.5M to 1 in 100,000
Spain	1 in 120,000 to 1 in 100,000

Sources: CRA analysis, GBA, AEMPS
Note: Prevalence estimate not included for Italy as it is not publicly available

2. Strensiq

Strensiq is an enzyme replacement therapy used to treat patients with childhood-onset hypophosphatasia, a chronic disease with high morbidity in most patients, and, in the most severe forms, a lethal outcome within days or weeks of birth. Prior to Strensiq, there was no indicated treatment and disease management involved symptomatic approaches. Strensiq was tested in a single-arm clinical trial, in which an improvement in X-ray appearance of the wrists and knees was demonstrated versus historic controls. Strensiq was authorised by the EMA under exceptional circumstances.

The approval of Strensiq was driven by the recognised unmet need in hypophosphatasia and the promising clinical profile. While in some countries, such as Spain, the clinical trial design led to the request for additional data before granting reimbursement, Strensiq received an ASMR II in France (Important Improvement, allowing free pricing up to the average price across Germany, the UK, Spain and Italy, with only volume negotiated with CEPS - Comité Économique des Produits de Santé).

As with Kanuma (LAL-D), prevalence estimates for Strensiq (hypophosphatasia) are highly varied and dependent on geography, method of calculation and severity of patients included in the review. While the prevalence estimate used in this analysis is 1 in 300,000, literature estimates for severe hypophosphatasia vary from 1 in 100,000 to 1 in 900,000. Prevalence estimates for milder forms of hypophosphatasia are several orders of magnitude higher than severe forms – as high as 1 in 6,370 in European populations.3 Although the EMA label does not exclude milder forms, payers appear to have based their pricing considerations on more severe forms, where Strensiq is expected to be most used. This is evident in France, where the Commission de la Transparence (CT) estimated a patient number between 50 and 80, broadly equivalent to a prevalence of 1 in 1,000,000.

3. Brineura

Brineura is indicated for the treatment of children with ceroid lipofuscinosis type 2 (CLN2), also known as Batten disease, an inherited condition that leads to progressive brain damage and death typically between the ages of 6 and 12 years old. Brineura is administered by infusion directly into the brain, which requires surgery for implantation of the device before the first administration. Brineura was authorised by the EMA under exceptional circumstances.

Brineura is reimbursed in Germany at an annual treatment cost of €530,000 following AMNOG (German HTA – Pharmaceutical Market Reform Act, or Arzneimittelmarkt-Neuordnungsgesetz) review and negotiations with statutory health insurance. In France, pricing negotiations are still ongoing but the initial nominative Autorisation Temporaire d'Utilisation (ATUn) annual treatment cost was set at €1,200,000. Interestingly, an initial ASMR IV (Minor Improvement, with price volume negotiations with CEPS) was upgraded to an ASMR III (Moderate Improvement, allowing free pricing up to the average price across Germany, the UK, Spain and Italy, with only volume negotiated with CEPS) in June 2018. This upgrade was due to a successful appeal that involved testimony from a French clinical trial investigator. The duration of pricing negotiation in France may be indicative of CEPS' lack of willingness to pay at the German price level, without a lower UK price to bring the European average down, given the recent NICE rejection (due to cost-effectiveness estimates exceeding those normally accepted for high specialised technologies and concerns over long-term effectiveness).

Although CLN2 is an ultra-rare disease based on prevalence (1:2,000,000), its incidence (1:200,000) suggests a higher number of treatable patients, which is likely to have featured highly in payers' decisions. This is illustrated in France, where the CT cited both prevalence and incidence to determine the size of the eligible patient population.[12]

Another consideration is that Brineura may have potentially reached payers' willingness to pay threshold in Germany. This is because Brineura and Strensiq reached a similar AATC even though the number of patients eligible for treatment was significantly different (20-40 patients for Brineura, compared with approximately 1,000 patients for Strensiq).[13]

Rare diseases:

1. CF drugs (Kalydeco, Orkambi)

Both Kalydeco and Orkambi have transformed the cystic fibrosis (CF) market, being positioned as precision medicines for treating specific mutations that cause CF. Kalydeco was the first approved precision medicine in 2012 for a single mutation, G551D, which has varying reports of prevalence within cases of CF (total prevalence of 1:2,500). Within the timeframe of price negotiation in some markets, Kalydeco was approved to treat further CF mutations that expanded the patient population. Interestingly, considering only the lower end of the prevalence estimates of the first approved mutation (1:100,000), the AATC would fall significantly below the trend-line. This suggests that payers may have considered the upcoming indication expansion during initial price negotiations.

Orkambi, a combination treatment that contains the active ingredient of Kalydeco (ivacaftor) as well as lumacaftor, was approved in 2015 to treat a different CF mutation, F508del. Based on the prevalence of the different mutations, Orkambi would be expected to treat more patients than Kalydeco, which is reflected in the lower AATC of Orkambi.

2. PH cluster (Opsumit, Adempas, Uptravi)

Analysis of the pulmonary hypertension[14] (PH) drugs shows similar price levels within a single rare disease area. Opsumit gained EMA approval in December 2013 and PMDA approval in March 2015 for the long-term treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO Functional Class II or III. PAH was one of the few rare diseases that already had effective treatments established as standard of care. These treatments included the endothelin receptor antagonists Tracleer (bosentan) and Volibris (ambrisentan), which had set price precedents. Adempas gained EMA approval four months after Opsumit but with two indications, PAH and chronic thrombo-embolic pulmonary hypertension (CTEPH). Additionally, EMA estimated only a minor addition to the PAH prevalence with the inclusion of CTEPH. The similar AATC of Opsumit and Adempas can therefore be attributed to a combination of the proximity of their respective launches and the comparable prevalence estimates.

In contrast, in Japan, Adempas was approved for CTEPH in January 2014 and then approved for PAH in February 2015. The AATC of Adempas in Japan is slightly lower than that in the EU markets, unlike the other products in this cluster, which suggests that the sequential approval of the two indications may have impacted payer discussions due to an expected increase in patient volume and budget impact. Furthermore, the AATC of Adempas in Japan is somewhat lower than that of Opsumit suggesting that the indication expansion and potential renegotiation of the former may have played a part in the price achieved.

Uptravi received EMA and PMDA approval two years later in May and September 2016, respectively, in a subset of the Opsumit and Adempas patient populations. By restricting its indication to those that are ineligible for, or who have failed, first line treatment options, Uptravi achieved higher prices than Opsumit and Adempas in all markets except Japan, where the AATC of Uptravi and Opsumit are similar. While the smaller patient population was likely factored into price negotiations in Europe, it is difficult to quantify its role due to the lack of epidemiology data in first line failure rates.

Conclusion

This study provides evidence that disease rarity may be a driver of price. However, there may be a prevalence threshold below which payer willingness to pay for a given treatment stops increasing. This has important implications for pharmaceutical companies wishing to launch in ultra-rare diseases, potentially including high profile gene and cell therapies.

Given the stronger relationship between AATC and prevalence seen in existing treatments for less rare diseases, payers will likely continue to expect similar price-prevalence relationships for new entrants. To differentiate on price, manufacturers can look to capitalise on several other factors, including the robustness of clinical data, magnitude of clinical benefit, mortality benefit, level of unmet need, burden of disease and lack of available treatments, and ensure these are captured in their payer negotiation strategies.

In conclusion, payers do value rarity, both emotionally and financially, but need to balance this with the clinical benefit and budget impact uncertainties that products for rare diseases present to ensure optimal price-to-value alignment. Ensuring that patient populations are well defined and that the patient journey is well understood will help to reduce some of that uncertainty. Manufacturers should also select indications with the highest clinical benefit and unmet need, and support submissions with compelling patient and/or physician advocacy.

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[11] The prevalence estimate used in this study (1 in 90,000) reflects an aggregated view of literature reports; however, country-specific HTA bodies may have used data from local registries or physician / key opinion leader estimates of actual patient numbers

[12] Commission de la Transparence, 2018. Available at: https://www.has-sante.fr/upload/docs/evamed/CT-16359_BRINEURA_PIC_INS_Avis3_CT16359.pdf

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[14] Pulmonary hypertension (PH) is a general term used to describe high blood pressure in the lungs from any cause, including but not limited to pulmonary arterial hypertension and chronic thrombo-embolic pulmonary hypertension