

Short Communication



Pricing Zolgensma – the world’s most expensive drug

Mark Nuijten

Department Pricing and Valuation, A2M, Amsterdam, The Netherlands

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A heated discussion has recently broken out in Europe about the price of Zolgensma, ‘the most expensive drug ever’. The National Institute for Health and Care Excellence (NICE) approved Zolgensma in March this year, which is set to become the most expensive treatment ever approved by NICE. Zolgensma is a gene therapy medicine for treating spinal muscular atrophy (SMA), a serious and rare condition of the nerves that causes muscle wasting and weakness [1]. It is estimated that the drug will cost approximately €1.9 million per course of treatment [2]. Patients with SMA have a defect in a gene known as *SMN1*, which the body needs to make a protein essential for the normal functioning of nerves that control muscle movements. Zolgensma is a gene therapy containing a functional copy of this gene which, after injection, passes into the nerves from where it provides the correct gene to make enough of the protein and, thereby, restore nerve function [1]. At first impression, the price level of Zolgensma raises many understandable questions, because €1.9 million sounds exorbitantly high in the public domain (often driven by emotions and lack of specialised knowledge of the costs and risk of the development of a new pharmaceutical). However, there are many factors that may justify NICE’s decision to approve the intervention for use.

In the Netherlands, since the debate in 2013 about the high price of medicines for Fabry and Pompe diseases, ‘expensive’ medicines are increasingly only reimbursed after tough price negotiations with the Ministry of Health [3]. This usually concerns medicines for the treatment of rare diseases, the so-called ‘orphan drugs’ such as Zolgensma. For example, it is estimated that only one in 11,000 children is born with SMA [4]. These price negotiations have since become a permanent and important part of the market access process for new ‘expensive’ orphan drugs, where expenditure weighed against patient suffering, a difficult and ethically difficult task for all parties [3].

The current choice for ‘expensive’ medicines is based on clinical and economic criteria, whereby in The Netherlands the Ministry of Health is willing to pay a maximum of €80,000 for each extra life year gained with perfect quality of life, the so-called quality-adjusted life year” (QALY). It often concerns orphan drugs which, due to their high price, have a ‘cost per QALY’ that is much higher than the Dutch threshold value of €80,000. However, the price per patient for an orphan drug is often much higher, because the fixed research and development (R&D) costs, which are not much different than the R&D costs for non-orphan drugs, are recouped on far fewer patients.

For example, the reimbursement of Spinraza, the first effective drug for SMA, was also initially denied due to an excessively high ‘cost per QALY’ of €600,000. Finally, Spinraza became available for Dutch SMA patients in 2018 after much delay due to lengthy price negotiations resulting in a heavily enforced price discount.

In contrast to the current assessment of the drug price based on the ‘cost per QALY’, we also take the investor’s perspective into account. A price, whereby the ‘cost per QALY’ remains below the Dutch upper threshold of €80,000, reflects what the Dutch society wants to pay for the health benefits through new health-care treatments. However, clinical research requires significant investments and, therefore, there is an investor who deserves a financial reward for the capital that he has made available for the development of the new drug according to economic valuation theory. Investing in pharmaceuticals and biotech companies is very risky, as only one in 20 drugs eventually hits the market. In addition, the investor’s patience is being tested, as it takes an average of eight to ten years before the drug can be sold, while some €660 million has already been spent on clinical research [5]. For Spinraza, the Ministry of Health demanded a discount of 85%, which meant a price drop from €240,000 to just

CONTACT Mark Nuijten  mark@a2m.nl  Blokstallen 2, 4611 WB Bergen op Zoom, Amsterdam, The Netherlands

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€36,000, while the minimum investor price was at least €100,000 according to our calculation [3].

We applied our Pricing Model to Zolgensma to estimate if the treatment is still cost-effective when priced at €1.9 million per treatment, when considering the investor's perspective [6–8]. This Pricing Model is based on the future cash flows and cost of capital according to the discounted cash flow method. The free cash flows correspond with future Zolgensma sales, and costs for R&D, production and marketing. We are relying for this forecast on epidemiology and budget impact figures from the joint assessment report of Zolgensma, which was drawn up as part of the Beneluxa initiative and is a co-production of The Netherlands, Belgium and Ireland [2]. The goal of the Beneluxa initiative is that the participating countries conduct joint HTA-assessment of innovative medicinal products, including budget and pricing assessments for new 'expensive' medicines. The budget impact analysis for The Netherlands is based on treatment of only symptomatic patients with SMA type 1, representing 60% of the SMA population [9]. However, in this calculation, we assume a broader patient population including pre-symptomatic SMA patients with type 2 or type 3 SMA. The rationale is to make a conservative estimate of the price of Zolgensma, because the more patients, the lower the required price for the investor. These numbers were extrapolated to the global number of potential patients in the Western economies, where 'expensive' drugs, such as Zolgensma, could be to some extent affordable. The probabilities of failure during the development phases (phases I, II and III), costs for R&D, production and marketing are derived from published literature [10,11].

Our analysis leads to a minimum price of €1.7 million for Zolgensma, which is close to the actual price of €1.9 million. The difference is only 11% lower, which seems within an acceptable range of uncertainty, because the Pricing Model is based on a deterministic approach, which does not reflect any spread in the distributions of the parameters and any other non-statistical uncertainty, e.g., assumptions on uptake curve for the new pharmaceutical.

However, the chance of successfully completing the different phases of clinical research and reaching the finish line of registration is lower for new innovative medicines than for traditional medicines and it is also known that the R&D costs for innovative medicines are significantly higher [12]. Production costs will also be higher than normal, because manufacturing is not just a matter of 'rolling a pill', but the production of gene therapy is time-consuming and

requires specific, expensive materials and equipment. This much more complex manufacturing process leads to additional production costs. If we do an analysis based on a 10% lower clinical success rate and 10% higher costs [8], Zolgensma's minimum price increases from €1.7 million to €2.6 million compared with an actual price of €1.9 million.

The cost of capital, which represents the required return for the investor, is 12% in our analysis, which represents the risk of the R&D project. In the absence of data on the cost of capital at project level, we took as a proxy the average cost of capital of 12% for the biotech sector. In addition, at the time of investment, Zolgensma was owned by the biotech company Avexis, and did not become owned by Novartis until 2018. The applied cost of capital of 12% reflects the average required return on an R&D project, which can be even 20% in the early phase of clinical research due to operational leverage. Therefore, we also conduct an analysis in which the cost of capital decreases step-by-step from 20% to 12% over the development phases until reimbursement of Zolgensma. In this analysis, Zolgensma's minimum price increases from €1.7 million to €2.1 million compared with an actual price of €1.9 million.

The latter analysis is conservative, because we have not included other risks in the cost of capital. The therapeutic area and competitive environment have an influence on the risk profile and lead to higher cost of capital. Therefore, the cost of capital for current R&D projects may not reflect the cost of capital for a new high risk-profile research area, like gene therapy and, therefore, the investor may add a premium to the cost of capital based on his judgment. An additional risk at the time of investment was the knowledge that another competitive innovative drug, Spinraza, was further in development phase with promising intermediate clinical results and would enter the market approximately 3 years earlier. At the time, it was anticipated that Spinraza may not only capture a large part of the market, because of lack of any alternative treatment options for SMA, but Biogen (the manufacturer) may also set the precedent price for innovative products in this market, along with the conditions of reimbursement following its reimbursement. Another risk is that, at the time of registration of Zolgensma, no long-term effects on lasting efficacy and safety may be known. The authorities would, therefore, be hesitant because gene therapy was a new treatment concept and no long-term data was available for other gene therapies. Finally, it was expected that a price of around €2 million would provoke primary public responses,

because drug prices of 'only' €200,000 were already leading to tough price negotiations with demands for large discounts and/or staggered payments.

The price of Zolgensma is about ten times higher than that of Spinraza, and this big difference can be explained by the fact that it is administered only once, whereas Spinraza is an annual treatment with continuous revenues for the remainder of each patient's life. The market for Zolgensma therefore only consists of the new ('incident') patients, while the market for Spinraza also includes existing ('prevalent') patients. In the initial period after launch, there is still a cohort of existing prevalent SMA patients, and a proportion of these patients are also eligible for Zolgensma. This consistency between prices of Zolgensma and Spinraza validates the concept of the described Pricing Model, but it should also be noted that it is based on long-term maintained treatment effect of Zolgensma following a single administration.

In conclusion, at €1.9 million, the price of Zolgensma is more justified than it first seems. The minimum price for the investor to break even is around €1.7 million, but scenario analyses using our Pricing Model show that the price is more possible to be around €2.6 million. At €1.9 million, the current price of Zolgensma is somewhere in between and, therefore, seems reasonable from this perspective. However, the price discount of 50%, which the Dutch National Health Care Institute is advising the Minister, leads to price of €0.95 million, which is far below the lower limit of €1.7 million from the investor's perspective. On the other hand, it is understandable that an up-front payment of almost €2 million is difficult for a drug with unknown long-term effects. Therefore, staggered payment arrangements linked to 'pay-for-performance' could be a starting point for the upcoming negotiations in The Netherlands.

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References

- [1] Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma>.
- [2] Onasemnogene abeparvovec (Zolgensma®) bij spinale musculaire atrofie (SMA). 2021 April 23. Zorginstituut Nederland, Reference ACP92-4.** Source of specific data for Zolgensma.
- [3] Nuijten M, Fugel HJ, Vis J. Evaluation and valuation of the price of expensive medicinal products: application of the discounted cash flow to orphan drugs. *J Rare Dis Disord* 2018, 1:005. Volume 1 | Issue 1 *.
- [4] Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy – a literature review. *Orphanet J Rare Dis*. 2017;12:124.
- [5] Nuijten M, Van Wilder P. The impact of early phase price agreements on prices of orphan drugs. *BMC Health Serv Res*. 2021 Mar 12;21(1):222. PMID: 33711994; PMCID: PMC7953706.
- [6] Nuijten M, Vis J. Economic comments on proposal for a novel cancer drug pricing model. *Nat Rev Clin Oncol*. 2018 Sep;15(9):587.* Source of more in-depth considerations of economic valuation of pharmaceuticals
- [7] Nuijten MJC, Vis J. Evaluation and valuation of innovative medicinal products. *J Rare Dis Res Treat*. 2016;2(1):1–11. ** Source of introduction to concept and Pricing Model based on DCF method
- [8] Nuijten M, Capri S. Pricing of orphan drugs in oncology and rare diseases. *Mark Access Health Policy*. 2020 Dec 1;8(1):1838191. PMID: 33312455; PMCID: PMC7717868.
- [9] Verhaart IEC, Robertson A, Leary R, et al. A multisource approach to determine SMA incidence and research ready population. *J Neurol*. 2017;264(7):1465–1473.
- [10] Sloand J. Assessing the financial viability of stratified medicine using decision tree analysis. Working paper. Bethlehem. Lehigh University; 2014.
- [11] Fugel HJ, Nuijten M, Postma M. 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. *New Biotechnol*. 2016;33(6):860–867. Epub 2016 Sep 21. 113. eCollection 2016.
- [12] Mestre-Fernandez J, Sussex J, Towse A. The R&D cost of a new medicine - office of health economics; 2012 December. 978–1–899040–19–3.