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April 6, 2023

Subject: A.40 Risdiplam - spinal muscular atrophy - EML and EMLc

Dear WHO EML Secretariat and Expert Committee on the Selection and Use of Essential Medicines:

I am writing with regard to the EML application for risdiplam for the WHO Model List of Essential Medicines (EML) and the Model List of Essential Medicines for Children (EMLc), for the treatment of spinal muscular atrophy (SMA). I am currently finishing my PhD (defending May 2023) at Harvard University. I have published extensively on pharmacoeconomics and have served as a consultant on pharmaceutical policy for WHO, Médecins Sans Frontières (MSF), the Clinton Health Access Initiative (CHAI), the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the World Bank.

I have received no funding related to this work, nor do I have any other conflicts of interest to declare.

This comment contextualizes the risdiplam application within existing policy as set forth by the Expert Committee and includes additional information relevant to considerations of cost and cost-effectiveness.

1) **The question of whether or not medicines for rare diseases should be included on the EML is not a new one. The public health relevance of risdiplam is comparable with other medicines/indications currently included on the EML.**

   For the 2005 update, the Expert Committee invited a discussion paper on how the Model List should engage "rare essentials", that is, drugs for rare diseases (1). The 2005 paper reflected on some inconsistencies in recent decisions, namely the deletion of fludrocortisone for adrenal insufficiency in 2003 "because its rare indication did not meet the criterion of 'satisfying the priority health-care needs of the population'", while just 2 years later factor VIII and IX concentrates were maintained on the EML even though hemophilia is also a rare disease (1). A complementary Orphan Medicines Model List was proposed, but ultimately rejected by the 2007 Expert Committee, who decided to maintain the criteria at the time of "comparative effectiveness, safety, cost and need, taking overall public health into consideration" (2).

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Faced with this challenge again in 2013, the Expert Committee reaffirmed that it would pursue a case-by-case approach in considering public health relevance, and would consider incidence and prevalence, evidence of the burden of disease, effectiveness, "as well as the potential for advocacy purposes" (3).

SMA is a rare disease caused by one or more related genetic disorders. Estimates of incidence range from 1 in 3,900 – 16,000 live births (Verhaart 2017) and 1 in 6,000 - 10,000 live births (d'Amico 2011), or expressed as incidence 6–27 per 100,000 people per year (Everhart 2017) and 10–17 per 100,000 people per year (d'Amico 2011) (4,5). There is no strong evidence of significant regional or ethnic differences in disease prevalence.

This puts it at a higher or comparable incidence than CML, MDR-TB, and rabies, for which treatments are included in the EML.

- Chronic myeloid leukaemia (CML):
    - Imatinib, added to the EML in 2015, is the first-line treatment for CML. CML was estimated in 2020 to have a global incidence of 0.85 per 100,000 people (6). For the 2015 application, the Expert Committee references Rohrbacher and Hasford (2009), who estimated annual incidence to be 1 or 2 cases per 100,000 people (7).
    - Dasatinib and nilotinib, added to the EML in 2017, are treatments for imatinib-resistant CML, which represents about 50% of CML cases (8). A rough estimate of the incidence of imatinib-resistant CML can thus be put at 0.43 cases per 100,000 people.
    - Even if prevalence is considered, instead of incidence, the comparison is similar: CML has a global prevalence of 3.25 per 100,000 people. Dasatinib and nilotinib, treating about 50% of CML cases that are imatinib-resistant thus would be used for about 1.625 per 100,000 people. People born with more severe forms of SMA have a short life expectancy, bringing prevalence of CMA closer to incidence. Even despite this, the prevalence of SMA is likely higher than the prevalence of the disease treated with dasatinib or nilotinib. (4). Of course, if there were wider access to treatments like risdiplam, the prevalence of SMA would rise as life expectancy is extended.
- Multi-drug resistant tuberculosis (MDR-TB):
    - Bedaquiline and delamanid, added to the EML in 2015, are treatments for multi-drug resistant tuberculosis (9). At the time, there were an estimated

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517,000 new cases per year of rifampicin-resistant or multidrug-resistant TB (10). Assuming a 2020 global population of 7.4 billion, this is equivalent to global incidence of 6.8 cases per 100,000 people (11).

  - These medicines were also included in 2019 on the WHO Model List of Essential Medicines for Children (EMLc) for MDR-TB, for use in children aged 6 years and above. The WHO TB department referenced Jenkins et al (2014) and Dodd et al (2016) to estimate a total burden of 30,000 cases in children each year (12,13). 5506 children and adolescents <15 years were reported to be initiated on second-line treatment for MDR/RR-TB (14). Assuming a population of 1.5 billion children aged 6-17, and assuming all 30,000 children in Jenkins et al (2014) were also aged 6-17, the incidence can be estimated as 2.0 cases per 100,000 per year.

- Rabies
  - Rabies has an incidence of 0.18 cases per 100,000, though a higher number of people may use these products in post-exposure prophylaxis (8). Equine rabies immunoglobulin, anti-rabies immunoglobulin, and anti-rabies virus monoclonal antibodies added to the EML in 1977, 1992, and 2021, respectively (15–17).

2) Risdiplam is an archetypal case of a low production cost, high price medicine, for which the Expert Committee has laid out helpful guidance for review, including consideration of data on production costs.

In response to applications for direct-acting antivirals for hepatitis C, cancer medicines, and novel oral anticoagulants, the 2015, the Expert Committee's report offered some useful commentary on how the Expert Committee would review medicines that are currently very highly priced (9). A helpful distinction was made between "high cost" and "high price" medicines, where the 'cost' of medicines was defined as production costs, and prices were defined as the amount paid by the purchaser (9). The potential budgetary impact of medicine *prices* could be controlled by lowering *prices* to be closer to *costs*, using established policy tools:

"While noting that high price is not necessarily a barrier to inclusion of a medicine on the Essential Medicines List, the Committee discussed the following matters in relation to consideration of high-priced medicines in general. Firstly, it is important to distinguish between high-priced medicines and high-cost medicines. "Cost" in this context refers to the production or

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manufacturing cost of the medicines, whereas "price" is the amount paid by the purchaser, whether a patient, an insurance or a government. Prices can be subject to negotiation and controls. Countries considering whether to make high-priced medicines available may need to manage expenditure by adopting price control policies, which may include generic substitution; controls on the ex-manufacturer price charged; controls on supply chain mark-ups; and price-setting, using internal or external reference pricing, or cost effectiveness evaluation to set affordable ceiling prices …

Alternative policy approaches, such as voluntary or compulsory licenses, or government use, may be considered. Voluntary licenses have increased the availability of generic versions of several HIV treatments and are starting to be used for the new hepatitis C treatments. A number of countries have gained experience of implementing compulsory licenses for both HIV and cancer treatments. Requirements include an appropriate national legislative framework and availability of a local or foreign manufacturer that can supply a good quality generic product, as well as the political will to implement a compulsory licence." (9)

The Expert Committee has affirmed the relevance of considering costs of production in relation to EML applications, particularly where production costs were low and prices very high for a number of products:

- Imatinib (2015):
    - *"For small molecule drugs for cancer treatment, such as imatinib, the cost of production has been estimated, generics are now available in some settings, and price reductions of the order of 90% are considered possible."* (9)
- Direct-acting antivirals for hepatitis C (2015):
    - *"Nevertheless, widespread access to interferon-free combinations is limited by high total costs in most healthcare systems. Evidence from two recent studies suggests that the manufacturing costs for a 12-week all-oral DAA regimen could be a fraction of current market prices[.] Specifically, the analyses suggest that 12-week regimens could cost as little as US$ 118 for the as-yet unapproved Merck DAA combination, US$ 149 for treatment with sofosbuvir plus ribavirin and US$ 193 for sofosbuvir + ledipasvir. This cost analysis has not been completed for the ombitasvir + paritaprevir + ritonavir and dasabuvir combination, but it is reasonable to suppose that similar manufacturing costs might result. The Expert Committee saw reason to believe that significant price reductions could be achieved."* (9)

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- Alcohol-based hand rub (2015):
  - *"The production cost per 100-mL bottle of ABHR was US$ 0.37 in Kenya, US$ 0.30 in Bangladesh and US$ 0.30 in Mali. Prices of some commercially available [alcohol-based hand rubs] may be much higher and vary greatly."* (9)
- Entecavir (2015):
  - *"Although studies presented in the application showed entecavir to be either cost–effective or the preferred strategy, the Committee noted that the production cost of entecavir has been estimated to be far below the price currently charged."* (9)

Also relevant are the 2015 WHO pharmaceutical pricing policy guidelines, which strongly recommend that "countries use multiple pricing policies to achieve low prices for generic and biosimilar medicines that are informed by the cost of production. These policies may include: internal reference pricing, mark-up regulation, direct price controls, tendering, promoting price transparency and lower patient co-payments" (18).

3) There is reason for optimism that there may be affordable access to quality assured generic risdiplam in the near term.

Risdiplam is a small-molecule medicine, with less complex manufacture than other treatments for SMA. Production in small volumes is both feasible and cost-effective, and active pharmaceutical ingredient (API) costs for even relatively small quantities (20kg) are estimated to cost $8700/kg. Given the low dose of this treatment (not more than 5 mg/day) a favorable annual treatment cost per-patient is likely achievable even at a cost of $40,000/kg for the API (the maximum range cited in the application estimated by KEI's consultant).

The cost of production for risdiplam is estimated below, following methods developed and reported in earlier work. This work was originally commissioned by WHO for the Fair Pricing Forum in 2017 (19), and has since been expanded and further developed to include all solid oral dosage and injectable formulations on the EML, recombinant human insulin and insulin analogues (20), HIV medicines and treatments for opportunistic infections (21,22), direct-acting antivirals for hepatitis C (23), antihypertensive medicines (24), cancer medicines (25,26), tuberculosis medicines (27), and investigational treatments for COVID-19 (molnupiravir, nirmatrelvir/ritonavir, and baricitinib) (28–30).

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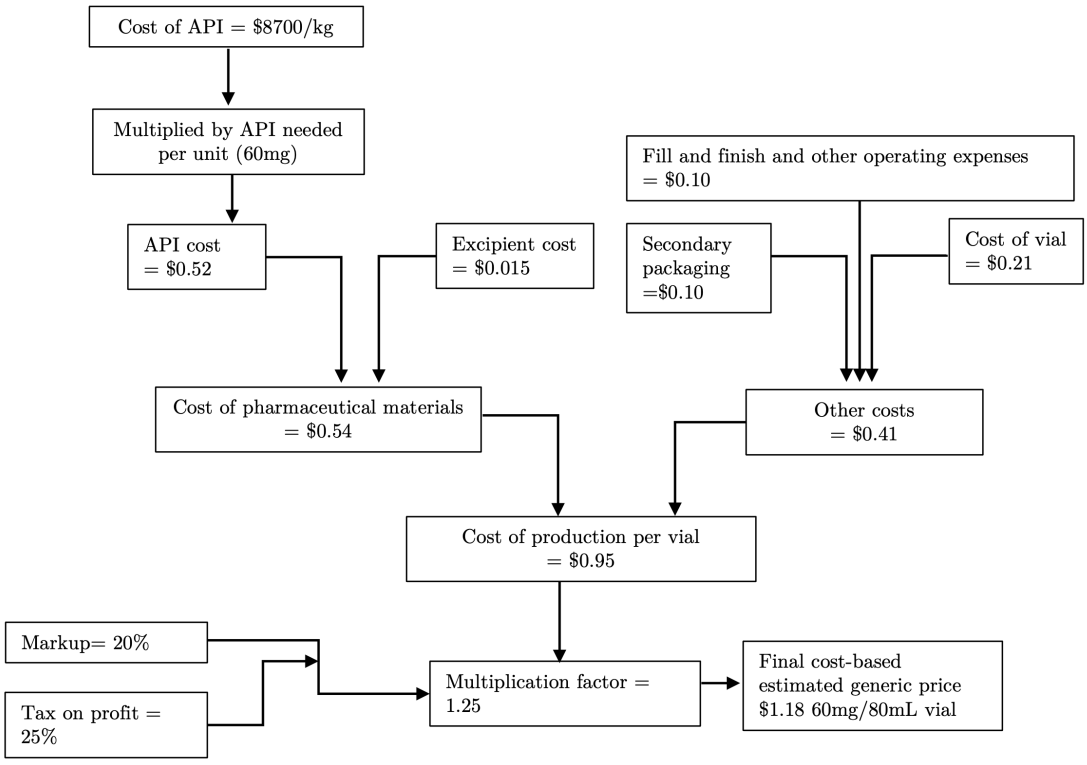
The costing algorithm includes costs of materials (active pharmaceutical ingredient, excipients, vial), formulation and secondary packaging costs, a 20% mark-up, and tax on profit (Figure 1).[1] A detailed table of cost input variables and their sources is available in Appendix Table 1.

Figure 1. Risdiplam cost-based estimated generic price (powder for oral solution 60mg/80mL vial (0.75mg/mL)



[1] A higher markup (20%) is used here instead of the 10% average profit margin assumed in robust generic markets used other publications to account for the small market size. Even a markup of 1000% (unit price $12.83 per 60mg/80mL vial) would result in a 99% decrease relative to the lowest price reported in the applicant's price survey ($213,525).

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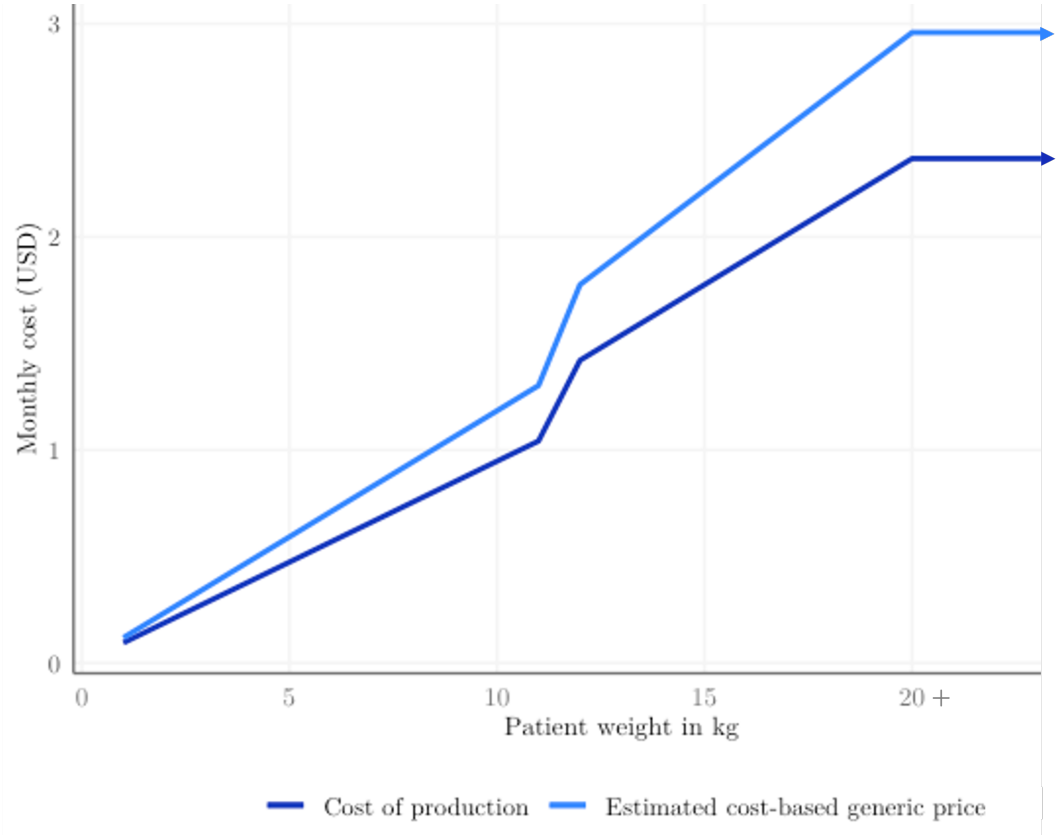
Figure 2. Production cost and estimated cost-based generic prices for 1 month supply of risdiplam, by patient weight



Risdiplam also has a number of other considerations that are attractive from a production and supply chain standpoint: dry powder is recommended to be stored at 20°C to 25°C (68°F to 77°F), but can also withstand 15°C to 30°C (59°F to 86°F), that is, it does not need to be refrigerated, in most climates (31). Reconstitution is done with purified water, which could be easily done within the home, as it is an oral medicine. Once reconstituted, risdiplam can be stored in a typical household refrigerator at 2°C to 8°C (36°F to 46°F), and even without refrigeration, can withstand temperatures of up to 40°C (up to 104°F) for a combined total of 5 days (31).

Compared to other treatments, which may require injections or specialist care, risdiplam is well-suited to treatment administration by family members and in a low-resource context.

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The risdiplam application provides detailed cost-effectiveness analyses, which I will not duplicate here. Nevertheless, I emphasize the point made in the application that manufacturing costs for other SMA treatments - onasemnogene abeparvovec (Zolgensma) or nusinersen (Spinraza) - are likely to be far lower than current observed prices, but much higher than risdiplam. Risdiplam is comparatively simple to produce, offers many advantages in terms of supply chain and health system efficiencies, and is easily administered. Risdiplam is therefore likely to be the only treatment for which access in LMICs could be realistically possible in the short- to medium-term.

4) **The Expert Committee has affirmed that inclusion of medicines into the Model List of Essential Medicines can in itself be an important step in catalyzing policy actions that may lead to more affordable pricing.**

As I have described above, risdiplam is a medicine for which low-cost generic production is feasible, even considering the relatively small expected market size. At present, generic risdiplam is not currently available. The applicant (Knowledge Ecology International) has disclosed that they are currently in confidential discussions with manufacturers, who have provided price quotes comparable to the estimated cost-based generic prices presented above.

Historically, the Expert Committee has been open to including medicines for which no generic options are available at the time of review (or for which generic options are not available in most countries). Recognizing the role that inclusion in the EML can play in in catalyzing policy actions directed at affordable access, the Expert Committee has historically included high-priced medicines for which affordable products may be available in the near to medium term.

This understanding of the bi-directional relationship between EML inclusion and affordability has been consistently highlighted in commentary by the Expert Committee:

- 2013: "*Adding a medicine to the WHO EML might precipitate a 'special intervention' before the normal processes of patent expiry and could be used as an advocacy tool to reduce the price of the medicine. This would be an additional consideration regarding the public health relevance of the medicine.*" (3)

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- 2015: "*In summary, at its meeting in April 2015, the 20th WHO Expert Committee approved inclusion of several new medicines on the EML in spite of their high price. These decisions were made on the basis of the public health need and evidence that the medicines are both highly effective and safe. It is expected that their addition to the EML will support efforts to reduce the prices.*" (9)
- 2017: "*The issue of affordability of a number of high-priced medicines, specifically those for cancer, hepatitis C and diabetes, was raised. The Committee has added high-priced medicines, such as those for hepatitis C and cancer, to the EML and/or EMLc as an important step in making them more affordable and more widely accessible. The Committee highlighted the need for continuing assessment, at country level, of pricing mechanisms for, availability of and access to high-priced medicines that are added to the EML and/or EMLc.*" (32)

This is not just an abstract policy position taken by the Expert Committee: a commentary published in the Bulletin of the World Health Organization by authors affiliated with the EML process highlighted cases where EML inclusion has stimulated the entry of new manufacturers for medicines that were not widely available at the time of inclusion, including, for example, zinc sulfate in 2005 and rectal artesunate in 2005. The authors concluded that "[i]nclusion of effective but expensive medicines in the model list may also focus the attention of all stakeholders on the need to increase affordability and access to essential medicines" (33).

In preparing this comment, I reviewed comments submitted by parents of children with SMA. The Expert Committee has not historically considered submissions by patients, though you will likely be as moved as I was to read of the stress and heartbreak patients and parents face in trying to source this medicine. What struck me in reviewing these comments is that there is already a global network of patients and parents engaged in access issues related to risdiplam, not just for themselves or their own children, but also for those around the world they know could benefit for the drug but cannot access it because it is not affordable.

I am a health economist, so in my technical capacity I can comment only on why I believe that risdiplam could be profitably and sustainably manufactured and distributed at a price that could enable global access. Many of the esteemed members of the Expert Committee who will review this application have long histories working in access to medicines, and many have played instrumental roles in some of the great

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public health success stories of the last 50 years. HIV and hepatitis C drugs were, at launch, the most expensive drugs in history. And yet, today, we have global treatment programs, with prices having fallen 95-99%. Addressing and overcoming monopolies in manufacture was a prerequisite to generic access, and inclusion on the EML was an important step. But history has demonstrated that the key catalyst in these movements were movements of people affected by these diseases. There is a gap between "identified potential" and a repertoire of policy options that WHO has described as next steps on the path from EML inclusion to affordable access. As you read their testimonies, I encourage you to factor in the power of organized patients as they relate to the likelihood that countries may pursue voluntary or compulsory licenses necessary to enable generic production in jurisdictions where patents are in force.

5) Conclusion and future considerations

In 2021, the Expert Committee recommended "establishing a standing EML Working Group to support the Expert Committee to provide advice to WHO on policies and rules to make highly priced essential medicines more affordable and accessible." To my knowledge, no such group has materialized. I encourage the Expert Committee to continue to motivate for such a body. However, the current lack of such a body should not lead the Expert Committee to postpone decisions involving high-priced medicines. They retain a mandate, and the Expert Committee has in the last 45 years developed a rich set of nuanced policy considerations that weigh these different factors, while defining a vision for how the EML can promote broader access.

This comment outlines how a decision to include risdiplam would be consistent with past decisions. Much has changed over the last two decades in terms of the economics of production technology and global markets, with small batch processing becoming more economically efficient and therefore global treatment programs for rare diseases more feasible. WHO has demonstrated leadership in coordinating smaller markets, for example, in WHO's important work on markets for childhood cancers.

Some have argued that rare diseases should not be included in the EML because they will divert national resources from other disease programs. Experience has shown that there is no cause for alarm: the addition of high-cost cancer medicines was not associated with LIC health systems divesting from maternal health or childhood immunization, for example. The Expert Committee should place greater trust in

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countries to budget responsibly, along locally defined priorities. I invite the Expert Committee to consider that providing WHO guidance on medicines for rare indications is warranted, as these are the diseases for which under-resourced national authorities may lack the expertise or resources to evaluate available treatment options.

In conclusion, I recommend that the 24th Expert Committee on the Selection and Use of Essential Medicines include risdiplam for SMA. Should members of the Committee or Secretariat have further inquiries on the content of this comment, including questions about cost of production methods and their application, I attach my contact information below and am available to support as may be helpful.

Sincerely,

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Appendix Table 1. Cost input variables.

Component	Cost per unit (USD)	Notes and data source
API	$8700/kg	Assuming 20kg batch sizes produced in a 200L reactor and prepared under international standards of GMP. The synthesis work was undertaken by Dr Woldegebriel Yeibyo and Professor Joseph Fortunak, both of Howard University, USA. Both Dr Yeibyo and Dr Fortunak have extensive experience in small molecule synthesis. Dr Fortunak has 35+ years in new/generic medicine development and developing capacity for producing quality-assured medicines in LMICs, including with the Global Fund, USAID, UNITAID, MSF, MPP, the African Union, UNIDO, UNAIDS, and UN ANDI.
Excipients	$0.015	Bulk commercial supplier (Sigma Aldrich) and analysis of import-export data. See Appendix Table 2.
Vial	$0.21	Upper end of estimates in Clendinen et al, 2016, and CEPI 2020 (0.155-0.21)(34,35)
Fill-and-finish and other operating expenses.	$0.10	Cost of 10mL vial of water for injection in South Africa public procurement (0.07-0.09 USD)(36). As an oral formulation, costs may be lower than parenteral formulations so this is a conservative estimate.
Secondary packaging	$0.10	Clendinen et al, 2016 (35)
Markup	20%	Derived from average profit margins across generic companies (10%), and doubled to account for small volume.
Allowance for tax	25%	Global average corporate tax rate(37)

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Appendix Table 2. Detailed excipient costs

Ingredient name	strength (mg/mL)	Unit cost (USD/kg)	Data source
mannitol	16.81	7.75	API analysis
isomalt	2.97	6.04	API analysis
maltodextrin	1.88	0.62	API analysis
tartaric acid	1.51	5.29	API analysis
sodium benzoate	0.38	15.98	Sigma Aldrich
polyethylene glycol	0.25	49.6	Sigma Aldrich
sucralose	0.2	42.73	Sigma Aldrich
ascorbic acid	0.18	5.79	API analysis
edetate disodium	0.09	11.75	API analysis

API analysis: Data on the cost of active pharmaceutical ingredient (API) were extracted from Panjiva, a commercial trade database that systematically archives shipment-level import/export records. Data were collected for exports from India, Jan 2019 – Jan 2023.

Sigma Aldrich: A major commercial supplier of fine chemicals for commodity and pharmaceutical use.

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