Fair pricing of "old" orphan drugs: considerations for Canada's orphan drug policy

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New Canadian regulations for orphan drugs are expected soon, after implementation of the orphan drug framework proposed in 2012 was delayed because of patient safety legislation that has now passed.[1] Traditionally, laws for orphan drugs have been intended to encourage research and development of new treatments for diseases that, because of their rarity in the population, manufacturers would otherwise ignore.[1,2] The United States' *Orphan Drug Act*, for example, offers special tax credits and supplementary exclusivity to the developers of qualifying products. What these laws do not do is address the needs of patients using older established drugs for rare diseases. In this article, we discuss an "old" orphan drug, trientine, which is important in the treatment of Wilson disease, to illustrate a particular problem in the pricing and procurement of orphan drugs. This problem requires careful consideration as Canadian legislation and policies are being designed.

The trientine story

Wilson disease was first described in 1912; at the time, it was an invariably fatal neurologic disorder associated with liver cirrhosis. In the 1950s and 1960s, D-penicillamine (1956) and trientine (1969) were developed as oral treatments, largely by researchers in the United Kingdom.[3] Now, medical treatment is highly effective in Wilson disease, permitting good health and a normal life span in most patients.[4] However, D-penicillamine causes major adverse effects in 30%–40% of patients with Wilson disease.[5]

Trientine is traditionally the second-line drug used for patients who cannot tolerate D-penicillamine. Trientine is chemically and mechanistically distinct from D-penicillamine,[3] and adverse effects of D-penicillamine typically resolve with trientine treatment. For selected patients, trientine is the preferred first-line oral chelator. For some, it is the only safe and effective treatment.[4] In an Italian series, trientine not being available, 11 patients with Wilson disease (31% of the cohort) who did not respond to D-penicillamine or zinc had poor outcomes: four underwent liver transplantation, one died and six had persistently abnormal liver tests.[6]

The regulatory status of D-penicillamine (Cuprimine) and trientine (Syprine) differs in Canada. Cuprimine, recognized as the first-line drug for Wilson disease, was approved for sale in Canada in 1964. Syprine, by contrast, never received regulatory approval and thus has no Drug Identification Number (DIN). Physicians must apply for access to trientine through Health Canada's Special Access Programme, and the cost of purchasing the drug is typically borne by the patient.

Until the end of 2013, the price of Syprine in Canada was about $963 per month ($11 556 per year), so it already represented a considerable financial burden for patients.[7] In 2010, the pharmaceutical company Valeant purchased Aton Pharma, which had previously acquired the US licence for Syprine from Merck and was the current supplier for Health Canada's Special Access Programme, and began to increase the price in the US. Around November 2013, Valeant Canada announced that, as of January 2014, the price of Syprine would match the US price: roughly Can$13 244 per month ($158 928 per year), which is about 13 times the previous price.

The reason Valeant offered for this price increase was financial. In a letter to physicians and pharmacists (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140308/-/DC1), Valeant noted that making Syprine "available free of charge [through a compassionate use program] ... was no longer sustainable. ... From that date [Jan. 1, 2014], Syprine™ was only available at the commercial US price, as the product is not commercially available in Canada."

Key points

- Orphan drug laws fail to distinguish between new drugs for rare diseases and older established orphan drugs, whose indications, safety and efficacy are well-researched.
- In January 2014, the cost of trientine, an "old" orphan drug that is essential for treating Wilson disease in a subgroup of patients, increased by about 13-fold.
- In future, as high-priced treatments for rare diseases are developed, regulations should facilitate competitive access to older, unpatented drugs. Failure to do so puts the effective availability of the drugs at risk.

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Nothing about the drug itself changed, and Valeant did not publish any new clinical studies to justify the price increase (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140308/-/DC1). As noted in Valeant's 2014 second-quarter presentation for investors, Syprine revenues were growing, with the primary driver being pricing (the assessment includes US revenues).[8]

Because it lacks a DIN, Syprine is not eligible for routine government subsidy in Canada, although some provinces, including British Columbia and Saskatchewan, make individual exceptions. The change in price thus presented immediate and possibly life-threatening difficulties for the about 40 Canadian patients with Wilson disease known to require trientine. With Valeant the only Canadian supplier, trientine, although still available, effectively ceased to be a reasonable therapeutic option for Wilson disease in Canada because of the inordinately high cost. A complete count of all Canadian patients taking Syprine is not available, but the effective non-availability of Syprine forced changes in drug treatment regimens in most of these patients.

Because pharmacologic treatment for Wilson disease must be consistent and lifelong, access to an alternative supply of trientine through the Special Access Programme was urgently needed. A different formulation of trientine, which cost less than Syprine did in 2013, was identified by some specialist clinicians with help from the Patented Medicine Prices Review Board, Alberta Health and Wellness, and the Canadian Organization for Rare Disorders, and this formulation was added to the list of drugs authorized under the Special Access Programme. Valeant Canada chose to reduce Syprine's price to its previous (2013) level, subsequent to public outcry initiated by Canadian hepatologists.[9] Whether Syprine's price will remain fixed at that level is unknown; in the US, Valeant raised the drug's price again in July 2014.[10]

Considerations for Canada's orphan drug regulations

Although we seem to have overcome the trientine crisis for now, the situation described calls attention to important problems related to access to orphan drugs. Problems with access can arise with both older orphan drugs like trientine and newer orphan drugs like ivacaftor, the recently developed treatment for a subset of patients with cystic fibrosis,[11] albeit perhaps somewhat differently. The challenge is that many drugs for rare diseases have small volumes and simply do not attract generic competition. As a result, competition cannot be relied on to ensure long-term access at reasonable prices. Generally, higher prices for rare-disease treatments are tolerated on the assumption that they permit manufacturers to recoup costs. But when generic competition fails to arrive, as in the case of trientine, an older drug with established safety and effectiveness, manufacturers remain free to charge what the market will bear. Valeant did not have to justify the price change in terms of expenditures or value. Payers tend to decide on reimbursement of new drugs with a view to their therapeutic value, and for orphan drugs, rarity is sometimes a consideration.[12] But for older drugs, prices should reflect the cost of secure, stable and safe production, and nothing more.

Trientine is not the only example of an older orphan drug being priced strategically on the heels of minimal research and development efforts. The price of colchicine, a time-honoured treatment for gout, increased 50-fold when a company began marketing it as a treatment for acute gout after a minor reformulation, coupled with small clinical trials highlighting its efficacy, and received exclusivity at the same time to market it as the prophylaxis for familial Mediterranean fever.[13] A similar scenario is unfolding with a reformulated version of the "old" established treatment for urea cycle disorders (glycerol phenylbutyrate; Ravicti). Although the reformulation is expected to improve patient tolerance, in the US it has been priced at five times the cost of the original drug despite carrying development costs of only one-tenth of a typical drug.[14,15] Given the potential financial returns, repurposing older drugs for treating new diseases is an enticing business strategy, especially in the orphan drug market.[16] On a larger scale, many of the orphan drugs approved in the US during the 1990s and later are losing patent protection and orphan drug exclusivity, yet without their prices falling.

Thus, whereas orphan drug laws may encourage new efforts in drug research and development in the rare disease market, they are also likely to invite strategic pricing. Although the pricing change for Syprine happened in the absence of a Canadian law for orphan drugs, three decades' experience with the US *Orphan Drug Act* suggests that such activities may well be expected. No additional North American manufacturer of trientine has emerged since the drug's market exclusivity expired in 1992. Generic orphan drugs are rarely made;[17] therefore, the price of many orphan drugs often remains exceptionally high.

The fundamental point is that the price of orphan drugs, like many other drugs, is not based on performance.[18,19] Assembling existing evidence

and negotiating the regulatory process requires resources, and the repurposing of drugs that have been in clinical use for other conditions merits some reward. Developing a first-in-class drug like ivacaftor probably merits more reward. Manufacturing and marketing an established orphan drug not subject to further research and development, like trientine, merits less reward. However, pricing of drugs has less to do with what the manufacturer invested and more with what it believes the market will bear.[11,19] Notwithstanding the lifesaving nature of many treatments for rare diseases, if the elevated prices of Syprine and ivacaftor represent the new norm, spending on any orphan drugs will clearly not be sustainable. If a new framework for orphan drugs is needed in Canada to encourage and support research and development, it should also ensure reasonable access to these critical therapies.

Proposals for policy

To address this and related policy problems connected to orphan drugs,[2] serious efforts must be made to calibrate market rewards with manufacturers' actual performance in research and development. Existing mechanisms such as the Patented Medicine Prices Review Board are inadequate, given how the board determines price ceilings;[20] moreover, its price-control function is limited to patented drugs. Canada's forthcoming framework for orphan drugs should therefore be reworked to address the need to support both innovation and access. Moreover, strategies to address problems with access may differ depending on whether an older or newer orphan drug is involved. For older drugs, such as trientine, the focus should be on ensuring safety and availability at a reasonable price. An orphan drug framework should clarify that patient access to essential drugs should not be vulnerable to prices that reflect neither costs of production nor rewards for innovation.

When there is only one supplier, as was the case for trientine, availability at a reasonable price is at risk. Although there were other possible suppliers for trientine globally, the barriers to entering the Canadian market were too large to make it attractive. Generic manufacturers may have felt that the market was too small if they were going to split the market and offer a low price.

In these circumstances, what is the right strategy for ensuring a competitively priced supply? Patients, disease-focused nongovernmental organizations, and physicians do not have the expertise or the capacity to scour world markets. Insured patients may have no incentive to do so. Insurers benefit from lower prices and have expertise to assess capability to supply, but they may not monitor international prices. To reduce the danger that access to drugs is compromised by unreasonable pricing, we believe that the Patented Medicine Prices Review Board could extend its data collection program to unpatented drug pricing for all products that are sole-sourced in Canada. In cases where the Canadian price proves excessive, relative to prices in all other markets, the board could generate the information required for assisting patients, clinicians and insurers to identify competitive suppliers. This would not be outside the current activities of the Patented Medicine Prices Review Board, which, despite its name, also periodically monitors generic drug prices.

Second, the orphan drug framework should address the needs of Canadians who rely on the Special Access Programme to obtain essential medicines. The program is used for several hundred drugs, in part because the Canadian market is not large enough to attract some very specialized drugs. Facilitating the process of obtaining a Health Canada Notice of Compliance through the creation of a regulatory pathway for orphan drugs could, in theory, help to increase insurability of essential drugs and also help to increase competition. Given the experience under the US orphan drug system, however, additional measures may be required to ensure meaningful competition and achieve greater control of prices. One strategy for older, unpatented yet essential orphan drugs may be for the provinces and territories to work together to seek out alternative suppliers from international markets, with assistance from the Patented Medicine Prices Review Board. Another strategy, applicable to future orphan drugs developed in whole or in part with public research funds, is to attach stipulations for reasonable pricing to those funds, as recently proposed in the US.[12] Downstream, manufacturers of orphan drugs could be required to account for their research and development expenditures to determine an appropriate rate of return[20] for new orphan drugs. As Canada moves to design its framework for orphan drugs, it must provide for sustainable access to essential products on reasonable terms, and this will likely involve a set of innovative strategies.

In the end, all orphan drugs should be priced fairly. Fair pricing should be defined as what is fair for society and Canadian health care systems, and fair given the contribution of the company to developing and producing the product. It was clearly unfair to increase the price of trientine, a drug that has been used to treat Wilson disease for nearly 50 years, by 13-fold overnight. This price increase carried serious risks for

patients. Canada's orphan drug framework and regulations should face head-on the pricing challenges posed by orphan drugs.

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