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The impact of capping health system cost savings on the projected cost-effectiveness of etranacogene dezaparvovec compared with factor IX prophylaxis for the treatment of hemophilia B

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Plain language summary

This article discusses a case in which there is a new drug that is being compared with a current drug that has a very high cost. If nothing is done, the new therapy will appear to be worth a very high cost even if it provides a small gain in health. The article proposes limiting cost offsets associated with using the new drug.

Implications for managed care pharmacy

This study provides insight into formulary decisions of a new gene therapy for hemophilia B. It further illustrates potential methods for considering adoption and pricing of a new therapy generally in a context where the existing standard of care is very costly. The article can be used to assist in policymaking around value-based pricing and efficiency-based formulary decisions in the context of hemophilia B and similar contexts.

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ABSTRACT

This viewpoint discusses cost-effectiveness estimates for EtranaDez, a gene therapy for hemophilia B, using the Institute for Clinical and Economic Review's (ICER) framework for single and short-term therapies (SSTs). EtranaDez offers long-term benefits from a single administration, in contrast to the high costs and frequent dosing required by current factor IX prophylaxis. However, the projected gains in health from EtranaDez are small relative to the cost implications of the therapy, and consequently, how the cost offsets associated with EtranaDez are counted has a substantial impact on assessing its cost-effectiveness.

Strategies for assessing cost offsets used in the ICER SST framework include a 50/50 cost-sharing model between the health care system and the manufacturer and a cap of $150,000 annually on health care cost offsets. Results from the standard full cost-offset analysis as reported by ICER depicted EtranaDez as a dominant therapy with substantial cost savings compared with factor IX prophylaxis. However, while considering the ICER SST framework, particularly the $150,000 annual cap scenario, the cost-effectiveness was significantly reduced. The incremental cost-effectiveness ratio varied notably between these scenarios, challenging the conventional perception of value of gene therapy in health care.

These cost-sharing scenarios highlight the potential of the ICER SST framework to help curtail inefficient health care spending. In cases in which the cost of existing treatment is exceedingly high, the application of such frameworks would improve efficiency in resource allocation, fostering a balance between incentives for innovation and economic sustainability in managed care systems.

Hemophilia B is an X-linked genetic disorder in which there is partial or complete deficiency of coagulation factor IX.[1,2] In the United States, hemophilia B is reported in 5.3 out of 100,000 male live births, and the prevalence of the condition in the male population is estimated to be 3.7 per 100,000 based on patients receiving treatment in hemophilia treatment centers.[3,4]

Currently, prophylactic treatment with factor IX (FIX) (clotting factor concentrate) products is used to maintain factor levels above 1% in patients with severe hemophilia B, reducing bleeding and preventing arthropathy and subsequent disability.[5-7] However, the very high cost, typically upward of $500,000 per year in patients with severe disease, and frequent intravenous administration (typically weekly) of these products are a substantial concern.[5,8-11] Single administration of gene therapy can overcome the limitations of conventional factor prophylaxis in patients with hemophilia as it offers the possibility of stable long-term expression of functional endogenous clotting factors in the liver by modifying the hemophilia phenotype.[8,12-14] Etranacogene dezaparvovec is the first gene therapy approved in the United States for hemophilia and worldwide for hemophilia B treatment.[15,16] Interim analysis of ongoing clinical trials has shown that etranacogene dezaparvovec can produce stable expression of endogenous factor IX in patients with hemophilia B at 18 months in a phase 3 study and 3 years in a phase 2b study.[14,17]

Near the time of approval for etranacogene dezaparvovec, the Institute for Clinical and Economic Review (ICER) published an evidence report that included the results of a cost-effectiveness analysis.[18,19] The traditional base-case analysis was conducted from a US health care sector perspective with a threshold of $150,000 per quality-adjusted life-year (QALY) gained as the top end of the range representing reasonable cost-effectiveness. For this report, ICER also conducted a scenario analysis applying the method adaptations from its assessment framework for high-impact single and short-term therapies (SSTs), which itself is an effort to incorporate past considerations of value-based pricing for potential cures of particular diseases.[20]

The ICER SST method framework includes 2 analytic strategies for sharing the value of cost offsets between the manufacturer and the health care system: a 50/50 split of the cost savings to the health system and a limit of $150,000 per year of health system cost savings. The cap of $150,000 was chosen because it is a typical willingness-to-pay (WTP) threshold for 1 QALY and hence any treatment that cost more than $150,000 per year could not possibly be considered efficient by that threshold. The 50/50 split is taken as a potential market of "fairness" in terms of giving credit to the new treatment while trying not to perpetuate

inefficient levels of costs. In the case of FIX, however, the 50/50 split of cost savings results in cost savings well above $150,000 per year. The overarching rationale is that manufacturers of one-time therapies should not necessarily receive 100% of the value of estimated lifetime cost offsets, especially when those cost offsets arise from eliminating the need for current care that is priced at levels that are not cost-effective. Traditional incremental cost-effectiveness methods can misleadingly depict these therapies as exceptionally cost-effective, even at astronomical prices, if they offer only marginal improvements in effectiveness coupled with the potential to eliminate extremely high costs of standard care. If no adjustment is made, it serves to perpetuate extremely high costs of care relative to the respective health gain being provided.

The objective of this viewpoint article is to highlight the impact of these "shared savings" approaches on evaluating the cost-effectiveness and value-based pricing of etranacogene dezaparvovec and discuss implications to managed care decision-makers.

The underlying semi-Markov model was developed to simulate a group of patients receiving etranacogene dezaparvovec, taking into account the length of time the treatment remains effective. The outcomes evaluated in the model included overall costs, QALYs, and number of total bleeds averted. The model uses Pettersson scores as health states to best allow for the direct impact of the number of bleeds along with joint deterioration associated with bleeds. The model has 6-month cycles, uses a 3% discount rate, and follows patients over a lifetime. Further details of the model can be found in the report along with several scenario analyses and both deterministic and probabilistic sensitivity analyses.[18] In the model, the base-case price for etranacogene dezaparvovec was $3.5 million dollars, and the current market price–based projected annual costs of FIX prophylaxis were more than $600,000.[11,21]

Because etranacogene dezaparvovec involves a one-time intervention and has the potential to provide substantial and sustained health benefits to patients, it meets the requirements for the high-impact SST framework proposed by ICER.[20] This framework includes a scenario that uses a shared savings model, where 50% of the cost savings generated by a new treatment over a patient's lifetime would go to the health system, rather than all of it being given credit to the treatment alone.[20] Another SST scenario restricts any health care cost offsets from a new treatment to $150,000 annually, where any additional savings would not be used in constructing incremental cost-effectiveness ratios for the new treatment. Further detail on the rationale for these 2 strategies is available in the ICER SST methods framework white paper.[20]

TABLE 1	Results for Cost-Effectiveness of Etranacogene Dezaparvovec Compared With Factor IX in the Full Cost-Offset Analysis				
Treatment	**Drug cost**	**Total cost**	**Bleeds**	**Quality-adjusted life-years**	**Life-years**
Etranacogene dezaparvovec	$8,500,000	$9,454,000	182	20.03	27.13
Factor IX	$14,029,000	$15,797,000	247	19.39	27.13

The standard full cost-offset analysis had etranacogene dezaparvovec costing $9.5 million and FIX prophylaxis costing $15.8 million per patient over a lifetime time horizon (Table 1).[18] In addition, etranacogene dezaparvovec resulted in a decrease in the total number of bleeds, with 65 fewer bleeds occurring over the course of a lifetime. Patients who underwent gene therapy had a total of 20.03 QALYs, whereas patients continuing FIX prophylaxis had only 19.39 QALYs. Hence, the full cost-offset results were that gene therapy with etranacogene dezaparvovec at a price of $3.5 million was a dominant treatment with modest health gains and large cost savings.

The 50:50 cost-sharing scenario shows etranacogene dezaparvovec at a price of $3.5 million still having lower projected total costs than FIX prophylaxis, with cost savings of $1.5 million. However, in the scenario in which cost offsets are limited to $150,000 per year, patients taking etranacogene dezaparvovec face an additional lifetime cost of $638,000. In both of these scenarios, the outcomes in terms of QALYs and bleeds averted remain unchanged from the base case. The incremental cost-effectiveness ratio for etranacogene dezaparvovec in the $150,000-limit cost-offset scenario was $997,000 per QALY. In the 50:50 cost-sharing scenario, etranacogene dezaparvovec was still a dominant therapy.

To achieve cost-effectiveness at a WTP threshold of $150,000 per QALY under the $150,000 cap scenario, the threshold price for this therapy would have to be $2.96 million. At the same WTP threshold, the threshold price would be $5.13 million under the 50:50 shared savings.

Importantly, it is because the existing treatments for hemophilia B cost more than $600,000 per year that traditional cost-effectiveness projections imply large cost savings. Putting a cap on potential cost offsets at $150,000 per year resulted in etranacogene dezaparvovec not being cost-effective at a price of $3.5 million, and the threshold price for etranacogene dezaparvovec to meet a WTP threshold of $150,000 per QALY is $3 million per year.

Etranacogene dezaparvovec demonstrates the dilemma of allocating full cost offsets to the value of a new one-time treatment because doing so perpetuates inefficient levels of health care spending. This also introduces the risk of incentivizing development of gene therapies for conditions that already have treatments, particularly expensive treatments, rather than conditions that currently lack effective treatments. As such, it is imperative to recognize the importance of implementing carefully considered pricing strategies for novel therapies, which take into account the cost savings associated with such treatments, while ensuring that they promote fair and effective allocation of health care resources toward optimizing health outcomes. If an inappropriate comparator, which itself is not cost-effective at a standard WTP threshold, is used in cost-effectiveness comparison, it can lead to the adoption of new technologies at prices that do not provide enough health benefits to fully compensate for the benefits that are taken away from other areas of the health care system.[22] Therefore, it is critical to implement appropriate cost-effectiveness thresholds and pricing structures that accurately reflect the value of new technologies while considering the uncertainties and evidence behind them to ensure that the adoption of new technologies ultimately leads to improved health care outcomes for patients within the health system.[22] It is beyond the scope of this article to evaluate the state of cost-effectiveness and value-based prices generally. In addition to the ICER report on etranacogene dezaparvovec, the SST framework has only been used in 3 other reports, where it had an impact in 2 of them.[23-25] In many instances, the cost caps discussed here are unnecessary as current therapies have relatively low cost. Nonetheless, the health system should be mindful of cases such as etranacogene dezaparvovec where current care exhibits extremely high costs.

ICER's SST framework methods to share the savings from cost offsets are not the only methods that have been proposed to address this issue. Some health economists have suggested that cost-effectiveness modeling "re-price" health care services that are rendered unnecessary by a new treatment, so that they conform to the overall cost-effectiveness threshold that guides pricing decisions.[20,26] Functionally, the 50/50 scenario would be akin to repricing FIX at half its current cost, and there is an even lower price that would lead to a cost of FIX of $150,000 per year.[20,26] These approaches involve sharing the economic surplus gained from adopting the new treatment proportionally

between the innovator and the health sector, where the health sector includes those responsible for paying for health insurance in the United States, such as patients, payers, and health plan sponsors. The specific cost-offset scenario of $150,000 was chosen because it is at the upper limit of ICER's range for WTP threshold for an additional QALY, and the upper bound treatment effect per year for a treatment is 1 QALY.[20,26] The 50/50 scenario was selected as a "fair" way to split costs. The impact of the two can be very different, as in the case shown here involving the very high annual costs of the standard of care.

Readers should consult the report for a full description of model limitations and assumptions.[18] The scenario limiting cost offsets to $150,000 highlighted here is based on a WTP threshold of $150,000 per QALY as an upward bound on what a system "should" pay annually for a therapy, and thereby what a new treatment should be allowed to "save" annually. However, there is no proven optimal level to optimize overall patient welfare. Similarly, there is nothing normatively optimal about a 50:50 sharing of cost offsets between the manufacturer and the health system. Policymakers may favor different levels of cost-offset caps and of sharing of savings, and economic assessments should remain open to different perspectives on which scenario should serve as the "base case."

Overall, when more therapies with similar profiles to etranacogene dezaparvovec emerge, the SST framework can foster consideration of a balance in the pricing of one-time therapies between the goals of promoting innovative therapies and affordability. The overall goal should be efficient resource allocation across patients, positioning managed care organizations and other stakeholders to provide superior care while maintaining economic sustainability.

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