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# The use of generic medications in thalassemia and hemoglobinopathies: challenges, benefits, and economic impact

## Abstract

Thalassemia and hemoglobinopathies necessitate lifelong disease management, leading to significant treatment costs. Generic medications offer potential cost savings, but concerns persist regarding their comparative effectiveness and safety compared to brand-name drugs. This comprehensive review evaluates the evidence concerning the utilization of generics for transfusion-dependent thalassemia and hemoglobinopathies. Quality-assured generics can offer substantial cost savings for both health systems and patients, contingent upon ensuring bioequivalence, efficacy, pharmacovigilance, and addressing stakeholder concerns.

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## Introduction

Thalassemia constitutes a group of inherited disorders characterized by the reduced or absent production of normal hemoglobin owing to mutations in the synthesis of globin chains. The intricate balance between α and β chains is disrupted, leading to ineffective erythropoiesis and anemia. The severity of thalassemia varies based on the specific mutations, with β-thalassemia major being the most severe form, necessitating lifelong therapy. While the survival of individuals has been extended through modern management, the economic burden remains substantial, posing a challenge to global healthcare systems.[1] Chronic transfusions, a crucial aspect of management, lead to iron overload, necessitating iron chelation therapy to mitigate associated complications.

### Transfusion complications and chelation requirements

Regular red blood cell transfusions serve as the cornerstone of treatment for β-thalassemia major. However, these transfusions lead to progressive iron overload, resulting in complications such as cirrhosis, cardiac dysfunction, and endocrine disorders. Consequently, effective iron chelation therapy is imperative to remove excess iron and prevent organ damage. The efficacy of chelating agents lies in their high iron binding affinity, specificity for iron, appropriate pharmacokinetics, and low toxicity. Despite modern treatments, iron overload continues to significantly impact the morbidity and mortality of thalassemia major patients, emphasizing the critical need for safe, effective, and affordable chelation options.[2,3]

### Evidence on generic medications in thalassemia

The lifetime cost of TDT patients is estimated to be USD 606,665. In Malaysia, a TDT patient is expected to incur a total lifetime cost of USD 561,208, with iron-chelating therapy (ICT) being the main driver of cost and accounting for 56.9% of the total cost.[4] However, there is no information available on the annual financial cost of a patient with thalassemia in general or specifically with regard to iron chelation. The annual direct medical cost for patients with transfusion-dependent thalassemia (TDT) in Dubai, UAE, is estimated to be AED 131,156 (USD 35,713). The main driver of the medical costs for the participants is iron chelation therapy, which accounts for AED 78,372 (59.8%) of the total direct medical costs.[5] However, it is important to note that the financial cost of thalassemia may vary depending on the healthcare system, country, and individual patient factors. The considerable economic burden poses challenges for ensuring sustained access to optimal therapy for patients in Europe. Affordability is a major concern given the need for lifelong disease management.[6] Brand-name drugs, especially newer iron chelators like deferasirox, account for a substantial proportion of expenses. This underscores the potential value of quality-assured, therapeutically equivalent generic medications to help reduce costs and expand access to essential thalassemia treatments in Europe.The total economic burden is substantial given the global disease prevalence. Access to treatment remains poor in limited-resource settings. Generic medications typically cost 20–90% less than brand-name equivalents, providing an attractive option to reduce expenditures. However, there are lingering concerns about the true comparative effectiveness and safety of generics versus originators, especially in patient populations.[7]

This review summarized current evidence regarding the risks, benefits, and economic impacts of using generic medications to treat transfusion-dependent thalassemia. Searches were conducted in PubMed, Google Scholar, and Cochrane databases for relevant English-language reviews, trials, observational studies, and pharmacoeconomic analyses published from 2010–present. Additional citations were identified from reference lists. Overall, the literature suggests clinical outcomes are generally similar between generic and branded medications, provided appropriate regulatory approval requirements are met.[8,9] However, direct comparative evidence in thalassemia patients remains quite limited. Most data comes from small trials in developing countries comparing locally produced generic iron chelators to original brands over 6–12 months. These found non-inferiority for reducing iron burden short-term. But studies on long-term survival, cardiac outcomes, complications, and safety are lacking.[10–12] While generics can substantially lower costs, realized savings depend on utilization rates, pricing policies,

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availability, and other health system factors. There is a need for expanded comparative effectiveness research directly in thalassemia populations and standardized bioequivalence criteria tailored to these patients.[13] Accordingly, there are many differences and complexities in the regulatory procedures for drug development and clinical use between the EU and the USA. These differences include, amongst others, the areas of drug post-marketing surveillance, emergency medicines, and orphan drugs such as deferasirox, deferiprone, and deferoxamine. The development of the FDA was based on the premise of serving as a centralized consumer protection agency in the USA, while the purpose of the development of the EMA was to harmonize inter-state commercial interests and legislation regulations among the 27 member states of the EU. However, both the EMA and FDA are discussing programs of collaboration and exchange of information to strengthen efforts on drug safety in both their regions and worldwide.[14]

## Key evidence and considerations by drug class

### Deferoxamine

As the first approved chelator, deferoxamine has over 40 years of clinical experience demonstrating efficacy for iron overload in thalassemia major.[15] Studies from developed countries show that brand-name deferoxamine and generic versions have similar effects on things like liver iron, serum ferritin, heart function, and side effects. However, the subcutaneous infusion mode limits compliance, often resulting in inadequate dosing. Oral chelators provide an appealing alternative. There is also more limited evidence from developing nations where regulatory quality control may be less stringent. One concerning study in India reported elevated liver enzymes in patients who switched from brand to generic deferoxamine. Overall, the literature supports generic deferoxamine efficacy if appropriate regulatory approval and manufacturing quality standards are in place. However, continued pharmacovigilance is advised. Longer-term data would provide helpful reassurance, given the lifelong treatment course.

### Deferiprone

The oral chelator deferiprone was introduced in Europe and India in 1999. Compared to deferoxamine, it shows similar or greater efficacy for iron removal at comparable doses.[16] Deferiprone also appears to better protect cardiac function, based on some studies. However, agranulocytosis remains a concern, requiring weekly blood monitoring.[17] Small trials in India found locally produced generic deferiprone non-inferior to the brand name for iron reduction over 6–12 months.[18] But data on long-term clinical outcomes is extremely limited. As the use of generic deferiprone increases, larger studies on efficacy, toxicity, appropriate bioequivalence criteria, and the need for therapeutic drug monitoring will be important.[19,20]

### Deferasirox

Deferasirox is the newest oral chelator, approved in 2005. It provides convenient once-daily dosing and demonstrates dose-dependent efficacy. However, renal and hepatic toxicities are concerns requiring regular monitoring.[21] Given its recent introduction, there is little published evidence on generic deferasirox.[22] One prospective study in Indonesia found locally produced generic deferasirox non-inferior to the brand name for reducing iron levels and serum ferritin over 1 year. Affordability was improved.[23] However, larger studies on long-term outcomes and appropriate bioequivalence criteria are critically needed.

### Supportive care

Managing thalassemia also requires extensive supportive care to screen for and treat complications like infections, endocrine disorders, heart disease, liver disease, and bone abnormalities. Generic drugs are commonly used to improve affordability, but comparative effectiveness evidence versus brands is limited.

### Economic benefits and challenges

The chronic transfusion and chelation requirements make lifelong thalassemia treatment extremely costly, resulting in substantial economic burdens for health systems and patients.[24–26] Brand-name drugs, especially newer agents like deferasirox, account for a major portion of expenses. Generics present an opportunity to alleviate economic burdens through lower prices, typically 20–90% below brand-name equivalents.[27] However, realizing substantial savings depends on factors like generic utilization rates, pricing policies, market availability, and prescriber acceptance. There are also notable challenges around demonstrating bioequivalence, monitoring long-term clinical outcomes, ensuring consistent manufacturing quality, and building confidence in generics among stakeholders.[28] Appropriately implemented substitution policies paired with pharmacovigilance can facilitate cost savings without compromising effectiveness or tolerability compared to originators. Guidelines are needed to promote safe, effective generic use for thalassemia.

## Conclusion

In summary, quality-assured generic medications can play an important role in thalassemia care by improving affordability and reducing economic burdens. However, work remains to gather direct comparative effectiveness data in patient populations, standardize bioequivalence criteria, address misperceptions, and ensure stringent regulatory oversight. If these conditions are met, generics present a valuable opportunity to extend access without compromising outcomes compared to more costly branded options.

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## Conflicts of interest

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