



**PATIENT INFORMATION LEAFLET  
ON REBLOZYL®**

**A BREAKTHROUGH IN THALASSAEMIA  
MANAGEMENT!**



THALASSAEMIA INTERNATIONAL FEDERATION  
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## THALASSAEMIA INTERNATIONAL FEDERATION

Thalassaemia International Federation (TIF) is a non-profit, non-governmental umbrella organisation working to improve the lives of patients with thalassaemia in all affected countries.

Together with patient/parent organisations, the medical community as well as international, regional and national health bodies/authorities, TIF promotes the establishment of new, and the strengthening of existing policies that aim to provide the highest quality of care for all.



**220**  
members

**132** National Thalassaemia Associations

**60** Countries

**90+** Volunteers

**67** International Patient Advocates

**23** International Medical Advisors

**7** Staff members

**1986**

Founded

**2015**

Awarded 'Dr Lee Jong-Wook Memorial Prize' of the WHO for outstanding contribution to public health

**1996**

Official Relations with WHO

**2017**

Consultative Status of UN ECOSOC

**2018**

European Commission partner in the field of Health

### Mission

The development and implementation of National Control Programmes, including both prevention and management, in every affected country

### Vision

The establishment of equal access to quality health, social and other care for all patients with thalassaemia globally, in truly patient-centred healthcare systems

## INTRODUCTION

**Thalassaemia** is a hereditary, non-malignant disorder that belongs to a family of genetic conditions affecting the human blood, known as Haemoglobin disorders or Haemoglobinopathies. These conditions affect *haemoglobin*, an important substance or protein of the human blood contained in the red blood cells. It is estimated that 7% of the world population is a carrier of a severe haemoglobin disorder and 300-500.000 children are born each year with a severe haemoglobin disorder.

A life-long **chronic** disorder found in the indigenous populations of malaria endemic or previously endemic regions including South East Asia, the Middle East, Mediterranean countries, and Northern Africa. However, as a result of the mass migration of populations through the years from high prevalence areas, thalassaemia today occurs widely across the world, constituting one of the commonest **rare** diseases in Europe and North America.

Associated with high mortality, morbidity and disability rates when not effectively treated and contributing significantly to the global and national toll of birth defects and disease burden when not appropriately prevented, thalassaemia constitutes perhaps one of the only rare disease for which effective management and prevention strategies have been **well explored** and identified.

Research and clinical efforts throughout the decades, particularly after the 1960s, have provided tools to effectively address the accurate and early diagnosis, the effective and appropriate prevention and the clinical management of  $\beta$ -thalassaemia major. Indeed, for many years the cornerstones of management have been (i) **lifelong transfusion** with filtered, pathogen screened, well-matched, properly stored, fresh red blood cells (RBCs) to keep haemoglobin at appropriately sufficient levels in order to counter the consequences of the genetic defect (e.g. bone marrow hyperactivity, anaemia) and (ii) **iron chelation** with authorized chelation drugs taken daily orally, subcutaneously or intravenously.

Adherence to quality care and implementation of disease-specific national prevention and management strategies, as described in the '*Guidelines for the Management of Transfusion Dependent Thalassaemia (3<sup>rd</sup> edition, 2014*)' and the '*Guidelines of Thalassaemia and other Haemoglobin Disorders (2<sup>nd</sup> edition, 2013*)' published by the Thalassaemia International Federation (TIF), in the context of universal coverage healthcare (UHC) systems, have indeed brought about dramatic improvements in the survival, health and quality of life of patients – a fact documented vastly in published literature.

Such achievements, however, have occurred only in a very limited number of countries outside the western world. Subsequently, the situation regarding survival, quality of life and the establishment of disease-specific national control programmes remain extremely heterogeneous across the world, despite the adoption of specific resolutions by the World Health Organization (WHO) since 2006, and the significant benefits that the effective control (prevention and clinical management) of thalassaemia have demonstrated in all areas of the wider repercussions of the disorder, including those of public health, social integration, occupational assimilation, public healthcare expenditure etc.

Thus, it is of vital importance for TIF and every national thalassaemia association across the world, in addition to global medical community, to continue to work unwaveringly to achieve the provision of the best possible care for thalassaemia patients in the context of UHC healthcare systems, which do not require any out-of-pocket payments for any health service received by chronic patients including those with thalassaemia. Hence, promoting the UN2030 Sustainable Development Goal for the global implementation of UHC thus ensuring access of all patients to quality healthcare and '*leaving no-one behind*'.

## BREAKING NEWS:

Milestones achieved throughout the decades in the management of transfusion dependent  $\beta$ -thalassaemia have been the:

- (i) Improvement in the quality of blood provided;
- (ii) Development of the first subcutaneous life-saving chelator (Deferoxamine) in the 1960s;
- (iii) Development of oral chelators, contributing not only to the effectiveness of management and better health, but also very importantly to the quality of life, albeit unfortunately only a fraction of the global patient community has access to them to-date.

**Reblozyl® (luspatercept-aamt) has received, after many years of clinical trials, approval from the major global regulatory authorities, the Food and Drug Administration (FDA) in the USA, on 8 November 2019, followed by the European Medicines Agency (EMA) on 25 June 2020.**

This drug promises immense improvements to the quality of life and health of thalassaemia patients in addition to significant wider public health benefits stretching from health expenditure to work/school days lost, etc.

## ABOUT REBLOZYL:

1. Reblozyl® is an **erythroid maturation agent**. This means that it works by regulating or controlling late-stage RBC maturation, thus delaying the production of thalassaemia RBCs. It is noted that thalassaemia RBCs produced by the bone marrow, have a high  $\alpha$ -chain content that results in their fast destruction (within days), hence requiring patients to be transfused frequently between 15 – 30 days. Delaying this process of production, therefore **extends the period between transfusions**.
2. Reblozyl® is NOT indicated for use as a substitute of RBC transfusions in patients who require immediate correction of anaemia, i.e. acute transfusion needs.
3. The approval of the drug received PRIORITY REVIEW designation from the FDA, and a POSITIVE OPINION by the Committee for Medicinal Products for Human Use (CHMP) of the EMA, based on results from the pivotal Phase III randomized, double blind, placebo-controlled, multicentre global trial called BELIEVE.

**Priority Review** is a programme of the FDA that ensures the quick assessment of drugs that are intended to treat a serious disease or condition, for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies.

EMA's Committee for Medicinal products for Human Use (CHMP) carries out a scientific assessment of the application and gives a recommendation (**Positive/Negative Opinion**) on whether the medicine should be marketed or not. However, **the European Commission is the authorising body for all centrally authorised medicinal products**, who takes a legally binding decision based on EMA's recommendation.

4. The BELIEVE trial **evaluated the safety and efficacy** of luspatercept in 336 adult patients with thalassaemia who require regular transfusions.

**Regular transfusions** are defined as 2-20 RBC units per 24 weeks, and no transfusion-free period of more than 35 days during the period of 24 weeks.

5. BELIEVE Trial Results

- i. The BELIEVE trial achieved the primary endpoint i.e. a clinically meaningful and statistically significant improvement in transfusion intervals. This is translated as an achievement of  $\geq 33\%$  reduction in RBC transfusion burden i.e. a reduction of at least 2 units of blood (RBCs) during weeks 13-24 after the initiation of the trial in **21.4%** of the patients in the trial (n = 48). From those who did not receive this drug, called the placebo group, only **4.5%** (n=5) showed similar reductions.
- ii. Secondary end and other efficacy end points included:
  - a. at least **33%** reduction (at least reduction of 2 units of RBCs) during weeks 37-48 after receiving the drug achieved in **19.6%** of the patients (n=44) [versus **3.6%** (n=4) in the placebo] and
  - b.  **$\geq 50\%$**  reduction (of at least 2 units of RBCs) during weeks **13-24 in 7.6%** (n=17) [versus **1.8%** (n = 2) in the placebo] and in **10.3%** of patients (n = 23) versus **0.9%** (n = 1) of patients at weeks **37-48**.

Long term safety and efficacy results from the phase III BELIEVE trial were presented at the EHA25 Congress in June, showing that more than 33% reduction of required transfusions for: 2% of  $\beta 0/\beta 0$  patients, 39% of  $\beta 0/\beta +$  patients, 6% of  $\beta +/\beta +$  patients, and 7% of HbE/ $\beta$ -thalassaemia patients.

More than 50% reductions of required transfusion for: 3% of  $\beta 0/\beta 0$  patients, 3% of  $\beta 0/\beta +$  patients, 2% of  $\beta +/\beta +$  patients, and 8% of HbE/ $\beta$ -thalassaemia patients.

6. The BEYOND Phase II double-blind, randomized, placebo-controlled, multicentre trial in adult patients with **Non-Transfusion Dependent  $\beta$ -Thalassaemia** is ongoing, with topline results expected by year-end 2020 or early 2021.
7. Other clinical trials are currently on-going, in different phases, for evaluating the safety and efficacy of the drug in Myelodysplastic Syndromes and Myelofibrosis, disorders which are characterised by disruption in the normal production of RBC's, although in a different way than those occurring in  $\beta$ -thalassaemia.

**POTENTIAL BENEFITS FOR PATIENTS WHO RECEIVE THE DRUG:**

- a) Reduction of transfusion and disease-related iron deposition load. Consequent relative change/ reduction of iron chelation dose or scheme.
- b) Reduced dependency on transfusion therapy and attendance to transfusion clinics and consultation.
- c) Amelioration of deep concerns and challenges for blood donations and blood adequacy.
- d) Consequent potential reduction/minimizing of transfusion related infections and reactions.
- e) Better allocation of blood resources by national transfusion systems to other disease needs.
- f) Lowering costs of chelation, as well as chelation and transfusion associated medical complications, reactions, and other unwanted effects.

8. The cost has been reported to be \$3.602 for a 25 mg vial / \$10.787 for a 75 mg vial in the US. Pricing and reimbursement negotiations in individual countries in Europe may vary.

9. Recommended Dose & Administration Methodology

- i. The recommended starting dose is 1mg/kg, once every 3 weeks, by subcutaneous injection;
- ii. The Haemoglobin level of the patient is reviewed before each administration;
- iii. There are two preparations:
  - Each vial containing 25mg powder to be reconstituted in 0.68ml of sterile water
  - Each vial containing 75mg powder to be reconstituted in 1.6ml of sterile water
  - After reconstitution the liquid is, clear and colourless to slightly yellow
  - The preparation can be stored at room temperature for up to 8 hours or refrigerated up to 24 hours and must NOT under ANY circumstances be frozen.

10. Indications for Discontinuation

1. **Thrombosis / Thromboembolism:** In adult patients with beta thalassaemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) Reblozyl®-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Thromboprophylaxis in patients with beta thalassaemia at increased risk of TEE should hence be considered in patients receiving Reblozyl® who should be monitored for signs and symptoms of thromboembolic events for their prompt treatment.
2. **Hypertension:** Hypertension was reported in 10.7% (61/571) of Reblozyl®-treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult patients with beta thalassaemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) > 130mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) > 80 mm Hg. Blood pressure should thus be monitored prior to each administration and new-onset hypertension or exacerbation of pre-existing hypertension should be promptly monitored using anti-hypertensive agents.
3. **Embryo-Fetal toxicity:** Based on findings from animal reproductive studies, Reblozyl® may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aapt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.25 mg/kg.

**ENSURING ACCESSIBILITY – TIF'S ROLE:** The first and most important step in order to support the access of patients to such new developments is to engage in committed, well-structured and well-documented discussions with the pharmaceutical industry, the medical community and the national competent healthcare authorities in each country, including reimbursement agencies to highlight the cost vs real benefit to patients. Evidence-based

discussions, that are patient-centred, will enable TIF to support the drug's accessibility to patients globally.

## **CHANGING THE UNDERSTANDING OF THE DISEASE AND ITS CURRENT MANAGEMENT REGIME: THE POSITION OF TIF**

TIF is in support of every development that unequivocally benefits the health and the quality of life of the patients it represents. TIF is fully aware of the daily concerns, uncertainties, fears and challenges with regard to adequate and safe blood, access to effective iron chelation treatment and comprehensive and appropriate monitoring. We look forward to fully identifying with the support of the medical experts and the industry the potential benefits of the drug. We are convinced that this new drug constitutes another huge milestone towards better and more quality care for our patients.

We fervently believe that healthcare professionals need to fully understand the properties and consequences of the drug as well as its potential side-effects and risks so that an update of the guidelines and monitoring protocols can be developed. Healthcare professionals, academia and industry need to continue to work for the collection of more information regarding the post-authorization and use of this drug and the patients' involvement and the promotion of patient reported outcomes tool are considered an important contribution to the better understanding of the effects of this drug in the short and long-term to ensure the health and quality of life of patients. Health regulators need to obtain knowledge and work with treating physicians, pharmaceutical teams, health economists, patients and the industry to produce value versus lost studies / models to allow the integration of this as any other innovative drug into the array of drugs for the management of the patients' needs and the identification of new trends such as personalized care. Such studies will contribute to the better management of costs and the accessibility of the drug to patients.

New monitoring parameters will have to be integrated, including for:

1. Side effects and adverse reactions;
2. 'New' laboratory or other tests deemed necessary in the protocol of monthly/periodical/annual monitoring agenda for adequacy and safety of patients taking the drug;
3. The close monitoring of the effectiveness of drug with clinical, laboratory investigations;
4. The evaluation of reported outcomes of patients taking the drug;
5. Post licensing reports of adverse effects, reactions to establish better and long-term safety and efficacy profile of the drug.



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