# PHARMACOECONOMIC OF TREATMENT OF FABRY DISEASE WITH AGALSIDASE ALFA

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***Summary.*** Fabry disease is a rare lysosomal disorder connected with accumulation of globotriaosylceramide and other glycosphingolipids in the body. The main clinical manifestations of the disease are pain, angiokeratoma, proteinuria, cardiovascular, cochlea-vestibular and cerebrovascular disorders. Enzyme replacement therapy with agalsidase alfa or agalsidase beta is critically for slowing the progression and complications of the disease. This publication is focused on the use of agalsidase alfa in the treatment of Fabry disease in comparison with treatment with agalsidase beta which is reimbursed by National Health Insurance Fund (NHIF) in Bulgaria. The current analysis was conducted from the perspective of payer – NHIF – and it is based on clinical trials, pharmacoeconomic studies and budget impact analysis. Implementation of enzyme replacement therapy with agalsidase alfa in Positive Drug List in Bulgaria is associated with little higher costs for NHIF in comparison with the alternative drug agalsidase beta - 2 373 866.00 BGN (= 1 209 488.07 Euro) and 2 243 401.12 BGN (=1 143 016.03 Euro) respectively. The higher drug costs could be justified by significant advantages of the new drug agalsidase alfa: better immunogenic profile, reduced time for infusion– 40 minutes with agalsidase alfa and 75 minutes with agalsidase beta; adequate and unproblematic delivery of drug with INN agalsidase alfa.

***Key words:*** agalsidase alfa, pharmacoeconomics, Fabry disease.

## INTRODUCTION:

Fabry disease is a rare progressive X-linked recessive disorder of lysosomal depots due to deficient activity of enzyme called α-galactosidase A. This leads to accumulation of globotriaosylceramide and other glycosphingolipids in the body. As a

result there are cell dysfunction, microvascular pathology, and progressive tissue and organ damages – cardiovascular, neurological (pain), renal (proteinuria) and cerebrovascular.[1, 14]

The disease affects all ethnic groups and more frequently is occurred in males. It's estimated that Fabry disease affects 1 in every 40 000 to 60 000 males.[1]

Because of the progression of Fabry disease and absorption of the complications there is a need of implementation of antihypertensive, non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressant and other pharmacotherapy methods to relieve the symptoms.[2, 3]

There are a lot of studies which show that enzyme replacement therapy could prevent or slow the progression and could increase the expected duration of life and improve quality of life of patients.[4, 5]

Objective of the current study is to evaluate the budget impact of the introduction of agalsidase alfa for the treatment of Fabry disease in national setting.

MATERIALS AND METHODS:

The current pharmacoeconomic analysis was conducted from the perspective of payer and it is based on the results of clinical trials and cost of therapy compared with an alternative drug for treatment of Fabry disease which is paid by National Health Insurance Fund.

The study was performed as three step analysis. First was analyzed systematically the available literature for the effectiveness and cost effectiveness of both alternatives by searching the PubMed and Google Scholar. Randomized clinical trials with data for products efficacy were selected and compared. Then was calculated the cost of therapy with the alternatives by multiplying the patients weight with the recommended doses. At the end was performed budget impact analysis with the assumption that every year within the 5 year period 2 new patients were treated with agalsidase alfa.

RESULTS AND DISCUSSION:

**I. Clinical trials results**

The safety and efficacy of drug with INN agalsidase alfa are defined in 4 clinical studies: *TKT003, TKT005, TKT010, TKT028*. There are 3 additional clinical trials for safety and efficacy in special groups of patients: *TKT014* in female with Fabry disease and *TKT023* and *TKT029* in pediatric patients. (Table 1)

The goal of the study TKT003 was to investigate the effect of drug on the pain using Brief Pain inventory method in 6-th month and to assess the renal function and pathology. 26 men over 18 years old were randomized in two groups: 14 patients receive alfa galactosidase A and 12 – placebo. In the first group there is progressive drop of pain points – 3.8 in the beginning to 2.7 in the end of 24$^{th}$ week in comparison with placebo group. There is increasing of normal glomeruli in the first group – 20%. [6]

Clinical trial TKT005 with duration of 6 months covers 15 male patients, randomized in 2 groups: patients in first group receive 0.2mg/kg aglasidase alfa i.v. for 40 minutes and the patients in the second group are placebo group. In the patients receiving drug the level of Gb3 (globotriaosylceramide ) is reduced with 45% in plasma. There is approved cardiac function – the level of Gb3 in heart is decreased with 19% as well as reduction of left ventricular mass with 6.2%. [7]

15 female patients are included in clinical trial TKT014 and they have at least three affected by the disease organs and systems: neuropathic pain, cerebrovascular accident, and hypertrophy of left ventricle or renal dysfunction. They receive 0.2mg/kg i.v. aglasidase alfa for 55 weeks.

| **Clinical trial** | **Goal of clinical trial** | **Design of the study** | **Results** | **Serios adverse drug reactions** |
|---|---|---|---|---|
| ***TKT003*** | **Phase II/III**: assessment of safety and clinical efficacy (pain) | Randomized double blind, placebo controlled, single centre | Decrease of pain;<br>Reduction of number of patients taking pain killers;<br>Reduction of number of days of taking pain killers;<br>Increase of number of normal glomeruli; | Bleeding in injection site, allergic reaction, chest pain,, hearing decreased, anaemia, fever; TKT006: ataxia, chest pain, viral hepatitis, deficiency of Vit B12, muscle weakness, |

| | | | | |
|---|---|---|---|---|
| | | | Reduction of average duration of QRS complex. | cerebrovascular disorder |
| ***TKT005*** | **Phase II/III**: assessment of safety and clinical efficacy (cardiac function) | Randomized double blind, placebo controlled, single centre | Decreased level of Gb3;<br>Reduction of left ventricular mass | Pharyngitis |
| ***TKT010*** | **Phase II/III** | Randomized double blind, placebo controlled | Statistically insignificant | |
| ***TKT028*** | **Phase III:** comparison the effects of several dosage regimens on cardiac function and structure | Prospective multicenter open label design | No results | |
| ***TKT014*** | **Phase II:** to assess safety and efficacy in female patients | Open label, placebo controlled | Decreased levels of Gb3;<br>Reduction of left ventricular mass;<br>Increased average assessment of quality of life of patients | Hypertension, Хипертензия, exacerbation of COPD; myocardial infarction; cerebrovascular accident; acute hearing loss |
| ***TKT023*** | **Phase I/II:** to assess the safety and efficacy in pediatric patients | Prospective multicenter open-label | Normal renal function;<br>Normal quality of life;<br>Normalization of sweating | |

**Table 1** Clinical trials for drug with INN agalsidase alfa

The average level of Gb3 is decreased as well as left ventricular mass - with 23g/m$^2$ on 27$^{th}$ week from the beginning. The average points for quality of life, measured by SF-36 form, are higher than in the beginning. [8]

The clinical efficacy is measured by the level of Gb3, renal and cardiac function, sweating and quality of life in pediatric patients with Fabry disease (clinical trial TKT023). Renal function is stable after 6 months as well as the average level of albumin

excretion is decreased from 50mg/24h to 27.6mg/24h. The most of patients have normal or closely to normal level of quality of life. [9]

## II. Published pharmacoeconomic studies

There are two models for agalsidase alfa which are designed in Italy and Norway.

In Italy the number of patients with Fabry disease are 220 – 32% take agalsidase alfa and 41% - agalsidase beta. The costs for clinical visits, tests, ERT, co-medication, dialysis are calculated on the basis of price in the period 2008-2009: 28 299 832 Euro for all patients. This sum represents 0.03% of Italian healthcare budget. Sensitivity analysis experiences the influence of change the therapy – from agalsidase beta to agalsidase alfa. The results indicate that the annual costs are reduced by 1% to 28.1 million Euro. This change of pharmacotherapy release hospital resources because of shorter time of infusion of agalsidase alfa than agalsidase beta. In Norway the patients are 60 – 23% take aglasidase alfa and 30% - aglasidase beta. Total costs are 6 695 645 Euro which are 0.05% of the total healthcare budget of Norway. [10, 11]

Model includes 1000 hypothetical patients from Wales and their average weight is 50kg. The additional costs for ERT with agalsidase alfa is £887 858 and increasing of QALY with 3.51. This leads to ICER equal to £252 951 per QALY. ICER for agalsidase beta is £252 112 per QALY. [12]

| Average costs for untreated patients | Average costs for treated patients | Average QALY for treated patients | Average QALY for untreated patients | Incremental costs | Incremental QALY | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| 34 329 | 2 572 122 | 24.76 | 14.69 | 2 537 792 | 10.07 | 252 112 |

**Table 2** Cost-effectiveness of ERT in patients with Fabry disease

## III. Pharmacotherapy costs

### 1. Pharmacotherapy costs for Agalsidase alfa

| INN | Pharnaceutical form | Dosage | CIP manufacturer price |
|---|---|---|---|
| Agalsidase alfa | concentrate for solution for infusion | 0,2mg/kg every other week | 14 343,43BGN (for 4 fl.) |

**Table 3** Dosage and and price for drug with INN agalsidase alfa

1 ml concentrate for solution for infusion contain 1 mg agalsidase alfa. Each vial of 3.5ml of concentrate contains 3.5mg aglasidase alfa. It is administered every other week by intravenous infusion, i.e. in 26 weeks in 1 year. The price of 4 vials is 14 343.43 BGN (= 7308.00 Euro) and of 1 vial is 3585.90BGN (=1827.02 Euro). (**Table 4)** There are data that the number of patients with Fabry disease who are treated with ERT in Bulgaria is 7. Their age and weight, which is consistent with the norms for the age of the patients due to lack of actual data, are presented in Table. Total amount of pharmacotherapy with Agalsidase alfa for 7 patients for 1 year is 2 373 866.00 BGN (=1 209 488.07 Euro).

| Age (years) | Weight (кg) | Single dose (мg) | Number of vials for 1 year | Cost of pharmacotherapy/year (BGN) |
|---|---|---|---|---|
| 12 | 30 | 30*0,2 = 6 | ~52 | 52*3585,9 = 186 466,8 |
| 18 | 50 | 50*0,2 = 10 | ~78 | 78*3585,9 = 279 700,2 |
| 19 | 55 | 55*0,2 = 12 | ~78 | 78*3585,9 = 279 700,2 |
| 23 | 60 | 60*0,2 = 12 | ~90 | 90*3585,9 = 322 731 |
| 50 | 70 | 70*0,2 = 14 | ~104 | 104*3585,9 =372 933,60 |
| 55 | 80 | 80*0,2 = 16 | ~130 | 130*3585,9 =466 167,00 |
| 55 | 85 | 85*0,2 = 17 | ~130 | 130*3585,9 =466 167,00 |
| **Total cost for pharmacotherapy for 7 patients/year** | | | | ***2 373 866,00*** |

**Table 4** Cost of ERT with agalsidase alfa in 7 bulgarian patients with Fabry disease

## 2. Pharmacotherapy costs for Agalsidase beta

| INN | Pharnaceutical form | Dosage | CIP manufacturer price |
|---|---|---|---|
| Agalsidase beta | powder for concentrate for solution for infusion . | 1mg/kg every other week | 6986,30 BGN for 1 vial |

**Table 5** Dosage and and price for drug with INN agalsidase beta

The content of Agalsidase beta in 1 vial of 7 ml is 35mg (5mg/1ml). The infusion is realized every other week, i.e. for 26 weeks in 1 year. The price for 1 vial is 6986.30 BGN (=3559.53 Euro). (**Table 5**)

The data for treated Bulgarian patients with Fabry disease are presented in **table 6**. Total pharmacotherapy cost with agalsidase beta for 7 patients for 1 year is 2 243 401.12 BGN (=1 143 016.03 Euro).

| Age (years) | Weight (кg) | Single dose (мg) | Number of vials for 1 year | Cost of pharmacotherapy/year (BGN) |
|---|---|---|---|---|
| 12 | 30 | 1*30=30 | ~26 | 22*5811,92=127 862,24 |
| 18 | 50 | 1*50=50 | ~52 | 52*5811,92=302219,84 |
| 19 | 55 | 1*55=55 | ~52 | 52*5811,92=302219,84 |
| 23 | 60 | 1*60=60 | ~52 | 52*5811,92=302219,84 |
| 50 | 70 | 1*70=70 | ~52 | 52*5811,92=302219,84 |
| 55 | 80 | 1*80=80 | ~78 | 78*5811,92=453 329,76 |
| 55 | 85 | 1*85=85 | ~78 | 78*5811,92=453 329,76 |
| **Total cost for pharmacotherapy for 7 patients/year** | | | | ***2 243 401,12*** |

**Table 6** Cost of ERT with agalsidase beta in 7 bulgarian patients with Fabry disease

## 3. Comparison between pharmacotherapy cost for ERT

There are higher costs for treatment with aglasidase alfa than agalsidase beta (86 748.70 BGN (= 44 198.58 Euro) is the difference). (**Chart 1**)

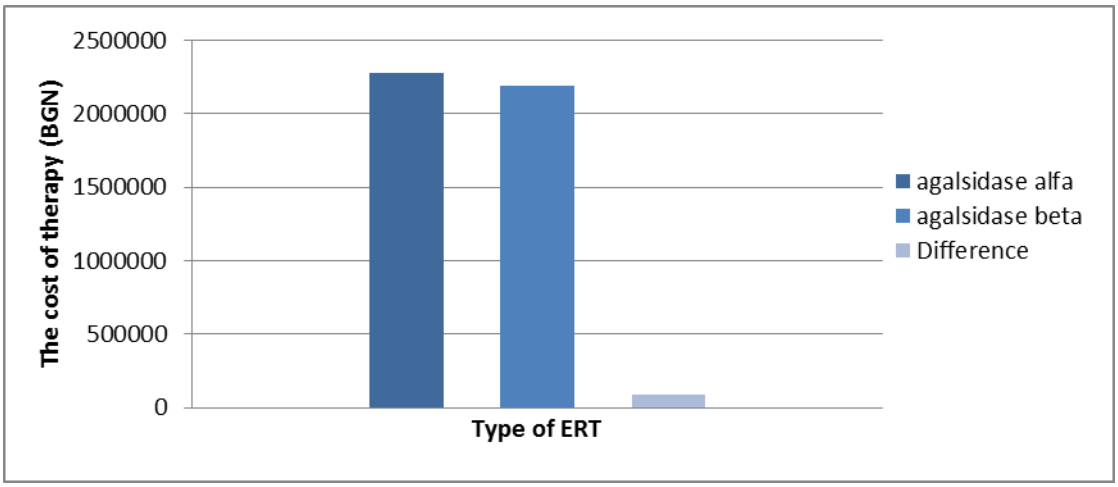


**Chart 1** Pharmacotherapy costs for 7 patients with Fabry disease in Bulgaria and the amount of cost savings for NHIF

**4. Including new patients**

The implementation of 2 new patients every year leads to increasing in pharmacotherapy costs for two group of patients. If the weight of these 2 new patients is 50kg, the annual pharmacotherapy costs for their treatment are:

- For afalsidase alfa: 74 vials/year => 265 356.60 BGN (=135 199.56 Euro)
- For aglasidase beta: 37 vials/year => 258 493.10 BGN ( = 131 702.60 Euro)

On the **chart 2** is followed the increasing of pharmacotherapy costs for period of 5 years. The value for aglasidase alfa is higher than agalsidase beta.

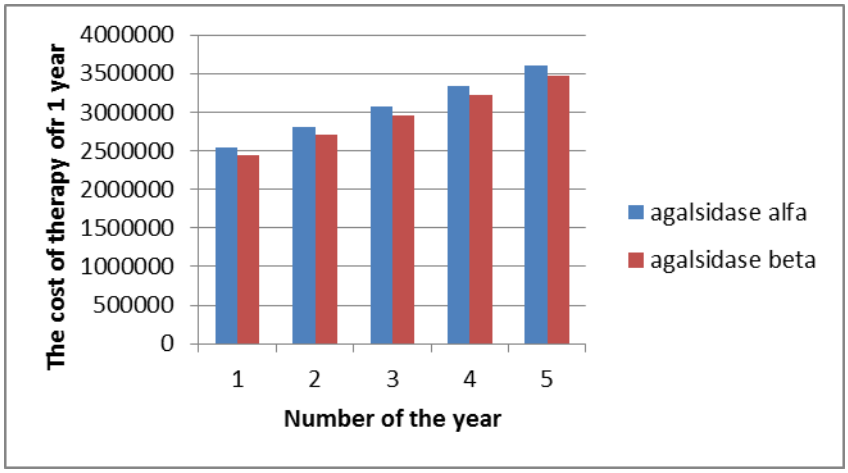

**Chart 2** Costs for Enzyme replacement therapy (ERT) as a result of implementation of new patients for 5 year period

CONCLUSIONS:

Implementation of enzyme replacement therapy with agalsidase alfa in Positive Drug List in Bulgaria is associated with little higher costs for NHIF in comparison with the alternative drug agalsidase beta. These higer drug costs could be justified by significant advantages of the new drug agalsidase alfa:

- Better immunogenic profile because of the use of human cell line to obtain the enzyme product. For comparison – for the alternative drug the cell line is from Chinese hamster;
- The time for infusion is reduced – 40 minutes with agalsidase alfa and 75 minutes with agalsidase beta;
- There is adequate and unproblematic delivery of drug with INN agalsidase alfa. For comparison: EMA reports for lack of delivery of drug with INN aglasidase beta because of manufacturing problem. This is associated with risks for providing of timely treatment for patients with Fabry disease.[13]

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