

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Galafold 123 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains migalastat hydrochloride equivalent to 123 mg migalastat. For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule.

Size 2 hard capsule (6.4x18.0 mm) with an opaque blue cap and opaque white body with “A1001” printed in black, containing white to pale brown powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease ( $\alpha$ -galactosidase A deficiency) and who have an amenable mutation (see the tables in section 5.1).

### 4.2 Posology and method of administration

Treatment with Galafold should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease. Galafold is not intended for concomitant use with enzyme replacement therapy (see section 4.4).

#### Posology

The recommended dosage regimen in adults and adolescents 16 years and older is 123 mg migalastat (1 capsule) once every other day at the same time of day.

#### Missed dose

Galafold should not be taken on 2 consecutive days. If a dose is missed entirely for the day, the patient should take the missed dose of Galafold only if it is within 12 hours of the normal time the dose is taken. If more than 12 hours has passed the patient should resume taking Galafold at the next planned dosing day and time according to the every other day dosing schedule.

#### Paediatric population

The safety and efficacy of Galafold in children aged 0 to 15 years has not yet been established. No data are available.

#### Special populations

##### *Elderly population*

No dosage adjustment is required based on age (see section 5.2).

#### *Renal impairment*

Galafold is not recommended for use in patients with Fabry disease who have estimated GFR less than 30 mL/min/1.73 m<sup>2</sup> (see section 5.2).

#### *Hepatic impairment*

No dosage adjustment of Galafold is required in patients with hepatic impairment (see section 5.2).

#### Method of administration

For oral use. Galafold exposure is decreased by approximately 40% when taken with food and therefore food should not be consumed at least 2 hours before and 2 hours after taking Galafold to give a minimum 4 hours fast. Clear liquids, including carbonated drinks, can be consumed during this period. Galafold should be taken every other day at the same time of day to ensure optimal benefits to the patient.

Capsules must be swallowed whole. The capsules must not be cut, crushed, or chewed.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

It is advised to periodically monitor renal function, echocardiographic parameters and biochemical markers (every 6 months) in patients initiated on or switched to Galafold. In case of meaningful clinical deterioration, further clinical evaluation or discontinuation of treatment with Galafold should be considered.

Galafold is not indicated for use in patients with non-amenable mutations (see section 5.1).

No reduction in proteinuria was observed in patients treated with Galafold.

Galafold is not recommended for use in patients with severe renal insufficiency, defined as estimated GFR less than 30 mL/min/1.73m<sup>2</sup> (see section 5.2).

Limited data suggest that co-administration of a single dose of Galafold and a standard enzyme replacement therapy infusion results in an increased exposure to agalsidase of up to 5-fold. This study also indicated that agalsidase has no effect on the pharmacokinetics of migalastat. Galafold is not intended for concomitant use with enzyme replacement therapy.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Based upon *in vitro* data, migalastat is not an inducer of CYP1A2, 2B6, or 3A4. Furthermore, migalastat is not an inhibitor or a substrate of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5. Migalastat is not a substrate for MDR1 or BCRP, nor is it an inhibitor of BCRP, MDR1, or BSEP human efflux transporters. In addition, migalastat is not a substrate for MATE1, MATE2-K, OAT1, OAT3, or OCT2, nor is it an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K human uptake transporters.

### **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential/Contraception in males and females

Galafold is not recommended in women of childbearing potential not using contraception.

### Pregnancy

There are limited data from the use of Galafold in pregnant women. In rabbits, developmental toxicity was observed only at maternally toxic doses (see section 5.3). Galafold is not recommended during pregnancy.

### Breast-feeding

It is not known whether Galafold is secreted in human milk. However, migalastat has been shown to be expressed in the milk of lactating rats. Accordingly, a risk of migalastat exposure to the breast-feeding infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Galafold, taking into account the benefit of breast-feeding for the child relative to the benefit of therapy for the mother.

### Fertility

The effects of Galafold on fertility in humans have not been studied. Transient and fully reversible infertility in male rats was associated with migalastat treatment at all doses assessed. Complete reversibility was seen after 4 weeks off-dose. Similar findings have been noted pre-clinically following treatment with other iminosugars (see section 5.3). Migalastat did not affect fertility in female rats.

## **4.7 Effects on ability to drive and use machines**

Galafold has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

The most common adverse reaction was headache, which was experienced by approximately 10% of patients who received Galafold.

### Tabulated list of adverse reactions

Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency within each System Organ Class.

**Table 1: Adverse reactions with Galafold in clinical trials**

| <b>System Organ Class</b>                        | <b>Very common</b> | <b>Common</b>  |
|--|--------------------|--|
| Psychiatric disorders                            |                    | Depression   |
| Nervous system disorders                         | Headache           | Paraesthesia<br>Dizziness<br>Hypoaesthesia                         |
| Ear and labyrinth disorders                      |                    | Vertigo  |
| Cardiac disorders                                |                    | Palpitations   |
| Respiratory, thoracic, and mediastinal disorders |                    | Dyspnoea<br>Epistaxis  |
| Gastrointestinal disorders                       |                    | Diarrhoea<br>Nausea<br>Abdominal pain<br>Constipation<br>Dry mouth |

|  |  |  |
|--|--|--|
|  |  | Defaecation urgency<br>Dyspepsia                             |
| Skin and subcutaneous tissue disorders               |  | Rash<br>Pruritus   |
| Musculoskeletal and connective tissue disorders      |  | Muscle spasms<br>Myalgia<br>Torticollis<br>Pain in extremity |
| Renal and urinary disorders                          |  | Proteinuria  |
| General disorders and administration site conditions |  | Fatigue<br>Pain  |
| Investigations                                       |  | Blood Creatine Phosphokinase increased<br>Weight increased   |

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

#### **4.9 Overdose**

In case of overdose, general medical care is recommended. Headache and dizziness were the most common adverse reactions reported at doses of Galafold of up to 1250 mg and 2000 mg, respectively.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Various alimentary tract and metabolism products ATC code: A16AX14

Fabry disease is a progressive X-linked lysosomal storage disorder which affects males and females. Fabry disease-causing mutations in the *GLA* gene result in a deficiency of the lysosomal enzyme  $\alpha$ -galactosidase A ( $\alpha$ -Gal A) that is required for glycosphingolipid substrate (e.g., GL-3, lyso-Gb<sub>3</sub>) metabolism. Reduced  $\alpha$ -Gal A activity is, therefore, associated with the progressive accumulation of substrate in vulnerable organs and tissues, which leads to the morbidity and mortality associated with Fabry disease.

#### Mechanism of action

Certain *GLA* mutations can result in the production of abnormally folded and unstable mutant forms of  $\alpha$ -Gal A. Migalastat is a pharmacological chaperone that is designed to selectively and reversibly bind with high affinity to the active sites of certain mutant forms of  $\alpha$ -Gal A, the genotypes of which are referred to as amenable mutations. Migalastat binding stabilizes these mutant forms of  $\alpha$ -Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes. Once in lysosomes dissociation of migalastat restores  $\alpha$ -Gal A activity, leading to the catabolism of GL-3 and related substrates.

The *GLA* mutations amenable and not amenable to treatment with Galafold are listed in Table 2 and Table 3 respectively below. The *GLA* mutations are also accessible by health care providers at [www.galafoldamenabilitytable.com](http://www.galafoldamenabilitytable.com).

The nucleotide changes listed represent potential DNA sequence changes that result in the amino acid mutation. The amino acid mutation (protein sequence change) is most relevant when determining amenability. If a double mutation is present on the same chromosome (males and females), that patient is amenable if the double mutation is present in one entry in Table 2 (e.g., D55V/Q57L). If a double mutation is present on different chromosomes (only in females) that patient is amenable if either one of the individual mutations is present in Table 2.

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change                | Nucleotide change             | Protein sequence change |
|----------------------------------|-------------------------------|-------------------------|
| c.7C>G                           | c.C7G                         | L3V                     |
| c.8T>C                           | c.T8C                         | L3P                     |
| c.[11G>T; 620A>C]                | c.G11T/A620C                  | R4M/Y207S               |
| c.37G>A                          | c.G37A                        | A13T                    |
| c.37G>C                          | c.G37C                        | A13P                    |
| c.43G>A                          | c.G43A                        | A15T                    |
| c.44C>G                          | c.C44G                        | A15G                    |
| c.53T>G                          | c.T53G                        | F18C                    |
| c.58G>C                          | c.G58C                        | A20P                    |
| c.59C>A                          | c.C59A                        | A20D                    |
| c.65T>G                          | c.T65G                        | V22G                    |
| c.70T>C or c.70T>A               | c.T70C or c.T70A              | W24R                    |
| c.70T>G                          | c.T70G                        | W24G                    |
| c.72G>C or c.72G>T               | c.G72C or c.G72T              | W24C                    |
| c.95T>C                          | c.T95C                        | L32P                    |
| c.97G>T                          | c.G97T                        | D33Y                    |
| c.98A>G                          | c.A98G                        | D33G                    |
| c.100A>C                         | c.A100C                       | N34H                    |
| c.100A>G                         | c.A100G                       | N34D                    |
| c.101A>C                         | c.A101C                       | N34T                    |
| c.101A>G                         | c.A101G                       | N34S                    |
| c.102T>G or c.102T>A             | c.T102G or c.T102A            | N34K                    |
| c.103G>C or c.103G>A             | c.G103C or c.G103A            | G35R                    |
| c.104G>A                         | c.G104A                       | G35E                    |
| c.104G>T                         | c.G104T                       | G35V                    |
| c.107T>C                         | c.T107C                       | L36S                    |
| c.107T>G                         | c.T107G                       | L36W                    |
| c.108G>C or c.108G>T             | c.G108C or c.G108T            | L36F                    |
| c.109G>A                         | c.G109A                       | A37T                    |
| c.110C>T                         | c.C110T                       | A37V                    |
| c.122C>T                         | c.C122T                       | T41I                    |
| c.124A>C or c.124A>T             | c.A124C or c.A124T            | M42L                    |
| c.124A>G                         | c.A124G                       | M42V                    |
| c.125T>A                         | c.T125A                       | M42K                    |
| c.125T>C                         | c.T125C                       | M42T                    |
| c.125T>G                         | c.T125G                       | M42R                    |
| c.126G>A or c.126G>C or c.126G>T | c.G126A or c.G126C or c.G126T | M42I                    |
| c.137A>C                         | c.A137C                       | H46P                    |

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change                | Nucleotide change             | Protein sequence change |
|----------------------------------|-------------------------------|-------------------------|
| c.142G>C                         | c.G142C                       | E48Q                    |
| c.152T>A                         | c.T152A                       | M51K                    |
| c.153G>A or c.153G>T or c.153G>C | c.G153A or c.G153T or c.G153C | M51I                    |
| c.[157A>C; 158A>T]               | c.A157C/A158T                 | N53L                    |
| c.157A>G                         | c.A157G                       | N53D                    |
| c.160C>T                         | c.C160T                       | L54F                    |
| c.161T>C                         | c.T161C                       | L54P                    |
| c.164A>G                         | c.A164G                       | D55G                    |
| c.164A>T                         | c.A164T                       | D55V                    |
| c.[164A>T; 170A>T]               | c.A164T/A170T                 | D55V/Q57L               |
| c.167G>A                         | c.G167A                       | C56Y                    |
| c.167G>T                         | c.G167T                       | C56F                    |
| c.170A>T                         | c.A170T                       | Q57L                    |
| c.175G>A                         | c.G175A                       | E59K                    |
| c.178C>A                         | c.C178A                       | P60T                    |
| c.178C>T                         | c.C178T                       | P60S                    |
| c.179C>T                         | c.C179T                       | P60L                    |
| c.196G>A                         | c.G196A                       | E66K                    |
| c.197A>G                         | c.A197G                       | E66G                    |
| c.207C>A or c.207C>G             | c.C207A or c.C207G            | F69L                    |
| c.214A>G                         | c.A214G                       | M72V                    |
| c.216G>A or c.216G>T or c.216G>C | c.G216A or c.G216T or c.G216C | M72I                    |
| c.218C>T                         | c.C218T                       | A73V                    |
| c.227T>C                         | c.T227C                       | M76T                    |
| c.239G>A                         | c.G239A                       | G80D                    |
| c.239G>T                         | c.G239T                       | G80V                    |
| c.247G>A                         | c.G247A                       | D83N                    |
| c.253G>A                         | c.G253A                       | G85S                    |
| c.[253G>A; 254G>A]               | c.G253A/G254A                 | G85N                    |
| c.[253G>A; 254G>T; 255T>G]       | c.G253A/G254T/T255G           | G85M                    |
| c.254G>A                         | c.G254A                       | G85D                    |
| c.261G>C or c.261G>T             | c.G261C or c.G261T            | E87D                    |
| c.265C>T                         | c.C265T                       | L89F                    |
| c.272T>C                         | c.T272C                       | I91T                    |
| c.288G>A or c.288G>T or c.288G>C | c.G288A or c.G288T or c.G288C | M96I                    |
| c.289G>C                         | c.G289C                       | A97P                    |
| c.290C>T                         | c.C290T                       | A97V                    |
| c.305C>T                         | c.C305T                       | S102L                   |
| c.311G>T                         | c.G311T                       | G104V                   |
| c.316C>T                         | c.C316T                       | L106F                   |
| c.320A>G                         | c.A320G                       | Q107R                   |
| c.322G>A                         | c.G322A                       | A108T                   |
| c.326A>G                         | c.A326G                       | D109G                   |
| c.334C>G                         | c.C334G                       | R112G                   |
| c.335G>A                         | c.G335A                       | R112H                   |
| c.337T>A                         | c.T337A                       | F113I                   |

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change                | Nucleotide change             | Protein sequence change |
|----------------------------------|-------------------------------|-------------------------|
| c.337T>C or c.339T>A or c.339T>G | c.T337C or c.T339A or c.T339G | F113L                   |
| c.352C>T                         | c.C352T                       | R118C                   |
| c.361G>A                         | c.G361A                       | A121T                   |
| c.368A>G                         | c.A368G                       | Y123C                   |
| c.373C>T                         | c.C373T                       | H125Y                   |
| c.374A>T                         | c.A374T                       | H125L                   |
| c.376A>G                         | c.A376G                       | S126G                   |
| c.383G>A                         | c.G383A                       | G128E                   |
| c.399T>G                         | c.T399G                       | I133M                   |
| c.404C>T                         | c.C404T                       | A135V                   |
| c.408T>A or c.408T>G             | c.T408A or c.T408G            | D136E                   |
| c.416A>G                         | c.A416G                       | N139S                   |
| c.419A>C                         | c.A419C                       | K140T                   |
| c.427G>A                         | c.G427A                       | A143T                   |
| c.431G>A                         | c.G431A                       | G144D                   |
| c.431G>T                         | c.G431T                       | G144V                   |
| c.434T>C                         | c.T434C                       | F145S                   |
| c.436C>T                         | c.C436T                       | P146S                   |
| c.437C>G                         | c.C437G                       | P146R                   |
| c.454T>C                         | c.T454C                       | Y152H                   |
| c.454T>G                         | c.T454G                       | Y152D                   |
| c.455A>G                         | c.A455G                       | Y152C                   |
| c.466G>A                         | c.G466A                       | A156T                   |
| c.466G>T                         | c.G466T                       | A156S                   |
| c.467C>T                         | c.C467T                       | A156V                   |
| c.471G>C or c.471G>T             | c.G471C or c.G471T            | Q157H                   |
| c.484T>G                         | c.T484G                       | W162G                   |
| c.493G>C                         | c.G493C                       | D165H                   |
| c.494A>G                         | c.A494G                       | D165G                   |
| c.496_497delinsTC                | c.496_497delinsTC             | L166S                   |
| c.496C>G                         | c.C496G                       | L166V                   |
| c.[496C>G; 497T>G]               | c.C496G/T497G                 | L166G                   |
| c.499C>G                         | c.C499G                       | L167V                   |
| c.506T>C                         | c.T506C                       | F169S                   |
| c.511G>A                         | c.G511A                       | G171S                   |
| c.520T>C                         | c.T520C                       | C174R                   |
| c.520T>G                         | c.T520G                       | C174G                   |
| c.525C>G or c.525C>A             | c.C525G or c.C525A            | D175E                   |
| c.539T>G                         | c.T539G                       | L180W                   |
| c.540G>C or c.540G>T             | c.G540C or c.G540T            | L180F                   |
| c.548G>A                         | c.G548A                       | G183D                   |
| c.548G>C                         | c.G548C                       | G183A                   |
| c.550T>A                         | c.T550A                       | Y184N                   |
| c.551A>G                         | c.A551G                       | Y184C                   |
| c.553A>G                         | c.A553G                       | K185E                   |
| c.559_564dup                     | c.559_564dup                  | p.M187_S188dup          |
| c.559A>G                         | c.A559G                       | M187V                   |
| c.560T>C                         | c.T560C                       | M187T                   |



**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change                | Nucleotide change             | Protein sequence change |
|----------------------------------|-------------------------------|-------------------------|
| c.561G>T or c.561G>A or c.561G>C | c.G561T or c.G561A or c.G561C | M187I                   |
| c.567G>C or c.567G>T             | c.G567C or c.G567T            | L189F                   |
| c.572T>A                         | c.T572A                       | L191Q                   |
| c.581C>T                         | c.C581T                       | T194I                   |
| c.584G>T                         | c.G584T                       | G195V                   |
| c.586A>G                         | c.A586G                       | R196G                   |
| c.593T>C                         | c.T593C                       | I198T                   |
| c.595G>A                         | c.G595A                       | V199M                   |
| c.596T>C                         | c.T596C                       | V199A                   |
| c.596T>G                         | c.T596G                       | V199G                   |
| c.599A>G                         | c.A599G                       | Y200C                   |
| c.602C>A                         | c.C602A                       | S201Y                   |
| c.602C>T                         | c.C602T                       | S201F                   |
| c.608A>T                         | c.A608T                       | E203V                   |
| c.609G>C or c.609G>T             | c.G609C or c.G609T            | E203D                   |
| c.611G>T                         | c.G611T                       | W204L                   |
| c.613C>A                         | c.C613A                       | P205T                   |
| c.613C>T                         | c.C613T                       | P205S                   |
| c.614C>T                         | c.C614T                       | P205L                   |
| c.619T>C                         | c.T619C                       | Y207H                   |
| c.620A>C                         | c.A620C                       | Y207S                   |
| c.623T>G                         | c.T623G                       | M208R                   |
| c.628C>T                         | c.C628T                       | P210S                   |
| c.629C>T                         | c.C629T                       | P210L                   |
| c.638A>G                         | c.A638G                       | K213R                   |
| c.638A>T                         | c.A638T                       | K213M                   |
| c.640C>T                         | c.C640T                       | P214S                   |
| c.641C>T                         | c.C641T                       | P214L                   |
| c.643A>G                         | c.A643G                       | N215D                   |
| c.644A>G                         | c.A644G                       | N215S                   |
| c.[644A>G; 937G>T]               | c.A644G/G937T                 | N215S/D313Y             |
| c.644A>T                         | c.A644T                       | N215I                   |
| c.646T>G                         | c.T646G                       | Y216D                   |
| c.647A>G                         | c.A647G                       | Y216C                   |
| c.655A>C                         | c.A655C                       | I219L                   |
| c.656T>A                         | c.T656A                       | I219N                   |
| c.656T>C                         | c.T656C                       | I219T                   |
| c.659G>A                         | c.G659A                       | R220Q                   |
| c.659G>C                         | c.G659C                       | R220P                   |
| c.662A>C                         | c.A662C                       | Q221P                   |
| c.671A>C                         | c.A671C                       | N224T                   |
| c.671A>G                         | c.A671G                       | N224S                   |
| c.673C>G                         | c.C673G                       | H225D                   |
| c.683A>G                         | c.A683G                       | N228S                   |
| c.687T>A or c.687T>G             | c.T687A or c.T687G            | F229L                   |
| c.695T>C                         | c.T695C                       | I232T                   |
| c.712A>G                         | c.A712G                       | S238G                   |
| c.713G>A                         | c.G713A                       | S238N                   |
| c.716T>C                         | c.T716C                       | I239T                   |

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change               | Nucleotide change               | Protein sequence change |
|---------------------------------|---------------------------------|-------------------------|
| c.717A>G                        | c.A717G                         | I239M                   |
| c.720G>C or c.720G>T            | c.G720C or c.G720T              | K240N                   |
| c.724A>G                        | c.A724G                         | I242V                   |
| c.724A>T                        | c.A724T                         | I242F                   |
| c.725T>A                        | c.T725A                         | I242N                   |
| c.725T>C                        | c.T725C                         | I242T                   |
| c.728T>G                        | c.T728G                         | L243W                   |
| c.729G>C or c.729G>T            | c.G729C or c.G729T              | L243F                   |
| c.730G>A                        | c.G730A                         | D244N                   |
| c.730G>C                        | c.G730C                         | D244H                   |
| c.733T>G                        | c.T733G                         | W245G                   |
| c.740C>G                        | c.C740G                         | S247C                   |
| c.747C>G or c.747C>A            | c.C747G or c.C747A              | N249K                   |
| c.749A>C                        | c.A749C                         | Q250P                   |
| c.749A>G                        | c.A749G                         | Q250R                   |
| c.750G>C                        | c.G750C                         | Q250H                   |
| c.758T>C                        | c.T758C                         | I253T                   |
| c.758T>G                        | c.T758G                         | I253S                   |
| c.760-762delGTT or c.761-763del | c.760_762delGTT or c.761_763del | p.V254del               |
| c.769G>C                        | c.G769C                         | A257P                   |
| c.770C>G                        | c.C770G                         | A257G                   |
| c.770C>T                        | c.C770T                         | A257V                   |
| c.772G>C or c.772G>A            | c.G772C or c.G772A              | G258R                   |
| c.773G>T                        | c.G773T                         | G258V                   |
| c.776C>A                        | c.C776A                         | P259Q                   |
| c.776C>G                        | c.C776G                         | P259R                   |
| c.776C>T                        | c.C776T                         | P259L                   |
| c.779G>A                        | c.G779A                         | G260E                   |
| c.779G>C                        | c.G779C                         | G260A                   |
| c.781G>A                        | c.G781A                         | G261S                   |
| c.781G>C                        | c.G781C                         | G261R                   |
| c.781G>T                        | c.G781T                         | G261C                   |
| c.788A>G                        | c.A788G                         | N263S                   |
| c.790G>T                        | c.G790T                         | D264Y                   |
| c.794C>T                        | c.C794T                         | P265L                   |
| c.800T>C                        | c.T800C                         | M267T                   |
| c.805G>A                        | c.G805A                         | V269M                   |
| c.806T>C                        | c.T806C                         | V269A                   |
| c.809T>C                        | c.T809C                         | I270T                   |
| c.810T>G                        | c.T810G                         | I270M                   |
| c.811G>A                        | c.G811A                         | G271S                   |
| c.[811G>A; 937G>T]              | c.G811A/G937T                   | G271S/D313Y             |
| c.812G>A                        | c.G812A                         | G271D                   |
| c.823C>G                        | c.C823G                         | L275V                   |
| c.827G>A                        | c.G827A                         | S276N                   |
| c.829T>G                        | c.T829G                         | W277G                   |
| c.831G>T or c.831G>C            | c.G831T or c.G831C              | W277C                   |
| c.832A>T                        | c.A832T                         | N278Y                   |
| c.835C>G                        | c.C835G                         | Q279E                   |

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change                | Nucleotide change             | Protein sequence change |
|----------------------------------|-------------------------------|-------------------------|
| c.838C>A                         | c.C838A                       | Q280K                   |
| c.840A>T or c.840A>C             | c.A840T or c.A840C            | Q280H                   |
| c.844A>G                         | c.A844G                       | T282A                   |
| c.845C>T                         | c.C845T                       | T282I                   |
| c.850A>G                         | c.A850G                       | M284V                   |
| c.851T>C                         | c.T851C                       | M284T                   |
| c.860G>T                         | c.G860T                       | W287L                   |
| c.862G>C                         | c.G862C                       | A288P                   |
| c.866T>G                         | c.T866G                       | I289S                   |
| c.868A>C or c.868A>T             | c.A868C or c.A868T            | M290L                   |
| c.869T>C                         | c.T869C                       | M290T                   |
| c.870G>A or c.870G>C or c.870G>T | c.G870A or c.G870C or c.G870T | M290I                   |
| c.871G>A                         | c.G871A                       | A291T                   |
| c.877C>A                         | c.C877A                       | P293T                   |
| c.881T>C                         | c.T881C                       | L294S                   |
| c.884T>G                         | c.T884G                       | F295C                   |
| c.886A>G                         | c.A886G                       | M296V                   |
| c.886A>T or c.886A>C             | c.A886T or c.A886C            | M296L                   |
| c.887T>C                         | c.T887C                       | M296T                   |
| c.888G>A or c.888G>T or c.888G>C | c.G888A or c.G888T or c.G888C | M296I                   |
| c.893A>G                         | c.A893G                       | N298S                   |
| c.897C>G or c.897C>A             | c.C897G or c.C897A            | D299E                   |
| c.898C>T                         | c.C898T                       | L300F                   |
| c.899T>C                         | c.T899C                       | L300P                   |
| c.901C>G                         | c.C901G                       | R301G                   |
| c.902G>A                         | c.G902A                       | R301Q                   |
| c.902G>C                         | c.G902C                       | R301P                   |
| c.902G>T                         | c.G902T                       | R301L                   |
| c.907A>T                         | c.A907T                       | I303F                   |
| c.908T>A                         | c.T908A                       | I303N                   |
| c.911G>A                         | c.G911A                       | S304N                   |
| c.911G>C                         | c.G911C                       | S304T                   |
| c.919G>A                         | c.G919A                       | A307T                   |
| c.922A>G                         | c.A922G                       | K308E                   |
| c.924A>T or c.924A>C             | c.A924T or c.A924C            | K308N                   |
| c.925G>C                         | c.G925C                       | A309P                   |
| c.926C>T                         | c.C926T                       | A309V                   |
| c.928C>T                         | c.C928T                       | L310F                   |
| c.931C>G                         | c.C931G                       | L311V                   |
| c.935A>G                         | c.A935G                       | Q312R                   |
| c.936G>T or c.936G>C             | c.G936T or c.G936C            | Q312H                   |
| c.937G>T                         | c.G937T                       | D313Y                   |
| c.[937G>T; 1232G>A]              | c.G937T/G1232A                | D313Y/G411D             |
| c.938A>G                         | c.A938G                       | D313G                   |
| c.946G>A                         | c.G946A                       | V316I                   |
| c.947T>G                         | c.T947G                       | V316G                   |
| c.950T>C                         | c.T950C                       | I317T                   |
| c.955A>T                         | c.A955T                       | I319F                   |

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change      | Nucleotide change    | Protein sequence change |
|------------------------|----------------------|-------------------------|
| c.956T>C               | c.T956C              | I319T                   |
| c.958A>C               | c.A958C              | N320H                   |
| c.959A>T               | c.A959T              | N320I                   |
| c.962A>G               | c.A962G              | Q321R                   |
| c.962A>T               | c.A962T              | Q321L                   |
| c.963G>C or c.963G>T   | c.G963C or c.G963T   | Q321H                   |
| c.964G>A               | c.G964A              | D322N                   |
| c.964G>C               | c.G964C              | D322H                   |
| c.966C>A or c.966C>G   | c.C966A or c.C966G   | D322E                   |
| c.967C>A               | c.C967A              | P323T                   |
| c.968C>G               | c.C968G              | P323R                   |
| c.973G>A               | c.G973A              | G325S                   |
| c.973G>C               | c.G973C              | G325R                   |
| c.978G>C or c.978G>T   | c.G978C or c.G978T   | K326N                   |
| c.979C>G               | c.C979G              | Q327E                   |
| c.980A>T               | c.A980T              | Q327L                   |
| c.983G>C               | c.G983C              | G328A                   |
| c.989A>G               | c.A989G              | Q330R                   |
| c.1001G>A              | c.G1001A             | G334E                   |
| c.1010T>C              | c.T1010C             | F337S                   |
| c.1012G>A              | c.G1012A             | E338K                   |
| c.1013A>T              | c.A1013T             | E338V                   |
| c.1016T>A              | c.T1016A             | V339E                   |
| c.1027C>A              | c.C1027A             | P343T                   |
| c.1028C>T              | c.C1028T             | P343L                   |
| c.1033T>C              | c.T1033C             | S345P                   |
| c.1046G>C              | c.G1046C             | W349S                   |
| c.1055C>G              | c.C1055G             | A352G                   |
| c.1055C>T              | c.C1055T             | A352V                   |
| c.1061T>A              | c.T1061A             | I354K                   |
| c.1066C>G              | c.C1066G             | R356G                   |
| c.1066C>T              | c.C1066T             | R356W                   |
| c.1067G>A              | c.G1067A             | R356Q                   |
| c.1067G>C              | c.G1067C             | R356P                   |
| c.1072G>C              | c.G1072C             | E358Q                   |
| c.1073A>C              | c.A1073C             | E358A                   |
| c.1073A>G              | c.A1073G             | E358G                   |
| c.1074G>T or c.1074G>C | c.G1074T or c.G1074C | E358D                   |
| c.1076T>C              | c.T1076C             | I359T                   |
| c.1078G>A              | c.G1078A             | G360S                   |
| c.1078G>T              | c.G1078T             | G360C                   |
| c.1079G>A              | c.G1079A             | G360D                   |
| c.1082G>A              | c.G1082A             | G361E                   |
| c.1082G>C              | c.G1082C             | G361A                   |
| c.1084C>A              | c.C1084A             | P362T                   |
| c.1085C>T              | c.C1085T             | P362L                   |
| c.1087C>T              | c.C1087T             | R363C                   |
| c.1088G>A              | c.G1088A             | R363H                   |
| c.1102G>A              | c.G1102A             | A368T                   |
| c.1117G>A              | c.G1117A             | G373S                   |

**Table 2: Galafold (migalastat) amenability table**

| Nucleotide change    | Nucleotide change    | Protein sequence change |
|----------------------|----------------------|-------------------------|
| c.1124G>A            | c.G1124A             | G375E                   |
| c.1139C>T            | c.C1139T             | P380L                   |
| c.1153A>G            | c.A1153G             | T385A                   |
| c.1168G>A            | c.G1168A             | V390M                   |
| c.1172A>C            | c.A1172C             | K391T                   |
| c.1184G>A            | c.G1184A             | G395E                   |
| c.1184G>C            | c.G1184C             | G395A                   |
| c.1192G>A            | c.G1192A             | E398K                   |
| c.1202_1203insGACTTC | c.1202_1203insGACTTC | p.T400_S401dup          |
| c.1208T>C            | c.T1208C             | L403S                   |
| c.1225C>A            | c.C1225A             | P409T                   |
| c.1225C>G            | c.C1225G             | P409A                   |
| c.1225C>T            | c.C1225T             | P409S                   |
| c.1228A>G            | c.A1228G             | T410A                   |
| c.1229C>T            | c.C1229T             | T410I                   |
| c.1232G>A            | c.G1232A             | G411D                   |
| c.1234A>C            | c.A1234C             | T412P                   |
| c.1235C>A            | c.C1235A             | T412N                   |
| c.1253A>G            | c.A1253G             | E418G                   |
| c.1261A>G            | c.A1261G             | M421V                   |

NP GAL 0719

The mutations not amenable to treatment with Galafold are listed in Table 3 below.

UNKNOWN in the column of ‘protein sequence change’ indicate that the changes to the protein sequence caused by the mutations cannot be readily deduced from the nucleotide changes and need to be experimentally determined. In these cases, the question marks in the accompanying parentheses indicate that the changes provided therein have not been experimentally confirmed and may not be correct.

**Table 3: Mutations not amenable to Galafold (migalastat)**

| Nucleotide change          | Nucleotide change       | Protein Sequence change |
|----------------------------|-------------------------|-------------------------|
| c.1A>C or c.1A>T           | c.A1C or c.A1T          | M1L                     |
| c.1A>G                     | c.A1G                   | M1V                     |
| c.2T>A                     | c.T2A                   | M1K                     |
| c.2T>C                     | c.T2C                   | M1T                     |
| c.2T>G                     | c.T2G                   | M1R                     |
| c.3G>A or c.3G>T or c.3G>C | c.G3A or c.G3T or c.G3C | M1I                     |
| c.19G>T                    | c.G19T                  | E7X                     |
| c.41T>C                    | c.T41C                  | L14P                    |
| c.43G>C                    | c.G43C                  | A15P                    |
| c.44C>A                    | c.C44A                  | A15E                    |
| c.46C>G                    | c.C46G                  | L16V                    |
| c.47T>A                    | c.T47A                  | L16H                    |
| c.47T>C                    | c.T47C                  | L16P                    |
| c.47T>G                    | c.T47G                  | L16R                    |
| c.53T>C                    | c.T53C                  | F18S                    |
| c.56T>A                    | c.T56A                  | L19Q                    |

**Table 3: Mutations not amenable to Galafold (migalstat)**

| Nucleotide change                | Nucleotide change             | Protein Sequence change |
|----------------------------------|-------------------------------|-------------------------|
| c.56T>C                          | c.T56C                        | L19P                    |
| c.59C>T                          | c.C59T                        | A20V                    |
| c.61C>T                          | c.C61T                        | L21F                    |
| c.62T>C                          | c.T62C                        | L21P                    |
| c.62T>G                          | c.T62G                        | L21R                    |
| c.71G>A or c.72G>A               | c.G71A or c.G72A              | W24X                    |
| c.92C>T                          | c.C92T                        | A31V                    |
| c.109G>C                         | c.G109C                       | A37P                    |
| c.118C>G                         | c.C118G                       | P40A                    |
| c.118C>T                         | c.C118T                       | P40S                    |
| c.119C>A                         | c.C119A                       | P40H                    |
| c.119C>G                         | c.C119G                       | P40R                    |
| c.119C>T                         | c.C119T                       | P40L                    |
| c.127G>A                         | c.G127A                       | G43S                    |
| c.127G>C                         | c.G127C                       | G43R                    |
| c.128G>A                         | c.G128A                       | G43D                    |
| c.128G>T                         | c.G128T                       | G43V                    |
| c.131G>A or c.132G>A             | c.G131A or c.G132A            | W44X                    |
| c.132G>T or c.132G>C             | c.G132T or c.G132C            | W44C                    |
| c.134T>C                         | c.T134C                       | L45P                    |
| c.134T>G                         | c.T134G                       | L45R                    |
| c.136C>T                         | c.C136T                       | H46Y                    |
| c.137A>G                         | c.A137G                       | H46R                    |
| c.137A>T                         | c.A137T                       | H46L                    |
| c.[138C>G; 153G>T; 167G>T]       | c.C138G/G153T/G167T           | H46Q/M51I/C56F          |
| c.139T>C or c.139T>A             | c.T139C or c.T139A            | W47R                    |
| c.139T>G                         | c.T139G                       | W47G                    |
| c.140G>A or 141G>A               | c.G140A or G141A              | W47X                    |
| c.140G>T                         | c.G140T                       | W47L                    |
| c.141G>C or c.141G>T             | c.G141C or c.G141T            | W47C                    |
| c.142G>A                         | c.G142A                       | E48K                    |
| c.144G>T or c.144G>C             | c.G144T or c.G144C            | E48D                    |
| c.145C>A                         | c.C145A                       | R49S                    |
| c.145C>G                         | c.C145G                       | R49G                    |
| c.145C>T                         | c.C145T                       | R49C                    |
| c.146G>C                         | c.G146C                       | R49P                    |
| c.146G>T                         | c.G146T                       | R49L                    |
| c.148T>C or c.150C>G or c.150C>A | c.T148C or c.C150G or c.C150A | F50L                    |
| c.149T>G                         | c.T149G                       | F50C                    |
| c.154T>A or c.155G>C             | c.T154A or c.G155C            | C52S                    |
| c.154T>C                         | c.T154C                       | C52R                    |
| c.154T>G                         | c.T154G                       | C52G                    |
| c.155G>A                         | c.G155A                       | C52Y                    |
| c.155G>T                         | c.G155T                       | C52F                    |
| c.156C>A                         | c.C156A                       | C52X                    |
| c.156C>G                         | c.C156G                       | C52W                    |
| c.166T>A or c.167G>C             | c.T166A or c.G167C            | C56S                    |
| c.166T>G                         | c.T166G                       | C56G                    |
| c.168C>A                         | c.C168A                       | C56X                    |

**Table 3: Mutations not amenable to Galafold (migalstat)**

| <b>Nucleotide change</b>          | <b>Nucleotide change</b>         | <b>Protein Sequence change</b> |
|-----------------------------------|----------------------------------|--------------------------------|
| c.187T>A or c.188G>C              | c.T187A or c.G188C               | C63S                           |
| c.187T>C                          | c.T187C                          | C63R                           |
| c.188G>A                          | c.G188A                          | C63Y                           |
| c.194G>C (putative splicing site) | c.G194C (putative splicing site) | UNKNOWN (S65T)                 |
| c.194G>T (putative splicing site) | c.G194T (putative splicing site) | UNKNOWN (S65I)                 |
| c.196G>C                          | c.G196C                          | E66Q                           |
| c.[196G>C; 1061T>A]               | c.G196C/T1061A                   | E66Q/I354K                     |
| c.202C>T                          | c.C202T                          | L68F                           |
| c.206T>C                          | c.T206C                          | F69S                           |
| c.208A>G                          | c.A208G                          | M70V                           |
| c.215T>G                          | c.T215G                          | M72R                           |
| c.218C>A                          | c.C218A                          | A73E                           |
| c.227T>G                          | c.T227G                          | M76R                           |
| c.228G>C or c.228G>A or c.228G>T  | c.G228C or c.G228A or c.G228T    | M76I                           |
| c.233C>G or c.233C>A              | c.C233G or c.C233A               | S78X                           |
| c.235G>T                          | c.G235T                          | E79X                           |
| c.241T>C or c.241T>A              | c.T241C or c.T241A               | W81R                           |
| c.242G>A or c.243G>A              | c.G242A or c.G243A               | W81X                           |
| c.242G>C                          | c.G242C                          | W81S                           |
| c.243G>T or c.243G>C              | c.G243T or c.G243C               | W81C                           |
| c.244A>T                          | c.A244T                          | K82X                           |
| c.256T>C                          | c.T256C                          | Y86H                           |
| c.256T>G                          | c.T256G                          | Y86D                           |
| c.257A>G                          | c.A257G                          | Y86C                           |
| c.258T>G or c.258T>A              | c.T258G or c.T258A               | Y86X                           |
| c.262T>G                          | c.T262G                          | Y88D                           |
| c.266T>A                          | c.T266A                          | L89H                           |
| c.266T>C                          | c.T266C                          | L89P                           |
| c.266T>G                          | c.T266G                          | L89R                           |
| c.268T>C                          | c.T268C                          | C90R                           |
| c.269G>A                          | c.G269A                          | C90Y                           |
| c.270C>A                          | c.C270A                          | C90X                           |
| c.274G>A                          | c.G274A                          | D92N                           |
| c.274G>C                          | c.G274C                          | D92H                           |
| c.274G>T                          | c.G274T                          | D92Y                           |
| c.275A>G                          | c.A275G                          | D92G                           |
| c.275A>T                          | c.A275T                          | D92V                           |
| c.277G>A                          | c.G277A                          | D93N                           |
| c.277G>T                          | c.G277T                          | D93Y                           |
| c.278A>G                          | c.A278G                          | D93G                           |
| c.278A>T                          | c.A278T                          | D93V                           |
| c.279C>G or c.279C>A              | c.C279G or c.C279A               | D93E                           |
| c.280T>A or c.281G>C              | c.T280A or c.G281C               | C94S                           |
| c.[280T>A; 281G>C]                | c.T280A/G281C                    | C94T                           |
| c.280T>G                          | c.T280G                          | C94G                           |
| c.281G>A                          | c.G281A                          | C94Y                           |
| c.281G>T                          | c.G281T                          | C94F                           |
| c.283T>G                          | c.T283G                          | W95G                           |
| c.284G>A or c.285G>A              | c.G284A or c.G285A               | W95X                           |

**Table 3: Mutations not amenable to Galafold (migalstat)**

| <b>Nucleotide change</b> | <b>Nucleotide change</b> | <b>Protein Sequence change</b> |
|--------------------------|--------------------------|--------------------------------|
| c.284G>C                 | c.G284C                  | W95S                           |
| c.284G>T                 | c.G284T                  | W95L                           |
| c.285G>T or c.285G>C     | c.G285T or c.G285C       | W95C                           |
| c.295C>T                 | c.C295T                  | Q99X                           |
| c.299G>A                 | c.G299A                  | R100K                          |
| c.299G>C                 | c.G299C                  | R100T                          |
| c.305C>G or c.305C>A     | c.C305G or c.C305A       | S102X                          |
| c.307G>C                 | c.G307C                  | E103Q                          |
| c.307G>T                 | c.G307T                  | E103X                          |
| c.317T>G                 | c.T317G                  | L106R                          |
| c.319C>T                 | c.C319T                  | Q107X                          |
| c.320A>T                 | c.A320T                  | Q107L                          |
| c.331C>T                 | c.C331T                  | Q111X                          |
| c.334C>A                 | c.C334A                  | R112S                          |
| c.334C>T                 | c.C334T                  | R112C                          |
| c.338T>C                 | c.T338C                  | F113S                          |
| c.347G>T                 | c.G347T                  | G116V                          |
| c.350T>G                 | c.T350G                  | I117S                          |
| c.355C>T                 | c.C355T                  | Q119X                          |
| c.358C>G                 | c.C358G                  | L120V                          |
| c.[358C>T; 359T>C]       | c.C358T/T359C            | L120S                          |
| c.359T>C                 | c.T359C                  | L120P                          |
| c.[359T>C; 361G>A]       | c.T359C/G361A            | L120P/A121T                    |
| c.361G>C                 | c.G361C                  | A121P                          |
| c.369T>G or c.369T>A     | c.T369G or c.T369A       | Y123X                          |
| c.371T>A                 | c.T371A                  | V124D                          |
| c.374A>C                 | c.A374C                  | H125P                          |
| c.[374A>T; 383G>A]       | c.A374T/G383A            | H125L/G128E                    |
| c.379A>T                 | c.A379T                  | K127X                          |
| c.386T>C                 | c.T386C                  | L129P                          |
| c.388A>G                 | c.A388G                  | K130E                          |
| c.389A>G                 | c.A389G                  | K130R                          |
| c.392T>A                 | c.T392A                  | L131Q                          |
| c.392T>C                 | c.T392C                  | L131P                          |
| c.394G>A or c.394G>C     | c.G394A or c.G394C       | G132R                          |
| c.395G>A                 | c.G395A                  | G132E                          |
| c.395G>C                 | c.G395C                  | G132A                          |
| c.398T>A                 | c.T398A                  | I133N                          |
| c.400T>C                 | c.T400C                  | Y134H                          |
| c.400T>G                 | c.T400G                  | Y134D                          |
| c.401A>C                 | c.A401C                  | Y134S                          |
| c.402T>G or c.402T>A     | c.T402G or c.T402A       | Y134X                          |
| c.406G>C                 | c.G406C                  | D136H                          |
| c.406G>T                 | c.G406T                  | D136Y                          |
| c.412G>A or c.412G>C     | c.G412A or c.G412C       | G138R                          |
| c.413G>A                 | c.G413A                  | G138E                          |
| c.416A>C                 | c.A416C                  | N139T                          |
| c.422C>A                 | c.C422A                  | T141N                          |
| c.422C>T                 | c.C422T                  | T141I                          |
| c.424T>C                 | c.T424C                  | C142R                          |



**Table 3: Mutations not amenable to Galafold (migalstat)**

| <b>Nucleotide change</b>          | <b>Nucleotide change</b>         | <b>Protein Sequence change</b> |
|-----------------------------------|----------------------------------|--------------------------------|
| c.425G>A                          | c.G425A                          | C142Y                          |
| c.426C>A                          | c.C426A                          | C142X                          |
| c.426C>G                          | c.C426G                          | C142W                          |
| c.427G>C                          | c.G427C                          | A143P                          |
| c.439G>A or c.439G>C              | c.G439A or c.G439C               | G147R                          |
| c.440G>A                          | c.G440A                          | G147E                          |
| c.442A>C or c.444T>A or c.444T>G  | c.A442C or c.T444A or c.T444G    | S148R                          |
| c.443G>A                          | c.G443A                          | S148N                          |
| c.453C>G or c.453C>A              | c.C453G or c.C453A               | Y151X                          |
| c.456C>A or c.456C>G              | c.C456A or c.C456G               | Y152X                          |
| c.463G>C                          | c.G463C                          | D155H                          |
| c.467C>A                          | c.C467A                          | A156D                          |
| c.469C>T                          | c.C469T                          | Q157X                          |
| c.484T>C or c.484T>A              | c.T484C or c.T484A               | W162R                          |
| c.485G>A or c.486G>A              | c.G485A or c.G486A               | W162X                          |
| c.485G>T                          | c.G485T                          | W162L                          |
| c.486G>C or c.486G>T              | c.G486C or c.G486T               | W162C                          |
| c.488G>T                          | c.G488T                          | G163V                          |
| c.491T>G                          | c.T491G                          | V164G                          |
| c.493G>T                          | c.G493T                          | D165Y                          |
| c.494A>T                          | c.A494T                          | D165V                          |
| c.497T>C                          | c.T497C                          | L166P                          |
| c.500T>A                          | c.T500A                          | L167Q                          |
| c.500T>C                          | c.T500C                          | L167P                          |
| c.502A>C                          | c.A502C                          | K168Q                          |
| c.503A>G                          | c.A503G                          | K168R                          |
| c.504A>C or c.504A>T              | c.A504C or c.A504T               | K168N                          |
| c.508G>A                          | c.G508A                          | D170N                          |
| c.508G>C                          | c.G508C                          | D170H                          |
| c.509A>G                          | c.A509G                          | D170G                          |
| c.509A>T                          | c.A509T                          | D170V                          |
| c.511G>C                          | c.G511C                          | G171R                          |
| c.511G>T                          | c.G511T                          | G171C                          |
| c.512G>A                          | c.G512A                          | G171D                          |
| c.514T>A or c.515G>C              | c.T514A or c.G515C               | C172S                          |
| c.514T>C                          | c.T514C                          | C172R                          |
| c.514T>G                          | c.T514G                          | C172G                          |
| c.515G>A                          | c.G515A                          | C172Y                          |
| c.515G>T                          | c.G515T                          | C172F                          |
| c.516T>G                          | c.T516G                          | C172W                          |
| c.519C>A or c.519C>G              | c.C519A or c.C519G               | Y173X                          |
| c.522T>A                          | c.T522A                          | C174X                          |
| c.523G>A                          | c.G523A                          | D175N                          |
| c.530T>A                          | c.T530A                          | L177X                          |
| c.547G>A (putative splicing site) | c.G547A (putative splicing site) | UNKNOWN (G183S)                |
| c.548G>T                          | c.G548T                          | G183V                          |
| c.550T>G                          | c.T550G                          | Y184D                          |
| c.552T>A or c.552T>G              | c.T552A or c.T552G               | Y184X                          |
| c.553A>T                          | c.A553T                          | K185X                          |

**Table 3: Mutations not amenable to Galafold (migalstatat)**

| Nucleotide change                 | Nucleotide change                | Protein Sequence change |
|-----------------------------------|----------------------------------|-------------------------|
| c.557A>C                          | c.A557C                          | H186P                   |
| c.560T>G                          | c.T560G                          | M187R                   |
| c.572T>C                          | c.T572C                          | L191P                   |
| c.588A>T or c.588A>C              | c.A588T or c.A588C               | R196S                   |
| c.601T>C                          | c.T601C                          | S201P                   |
| c.604T>C                          | c.T604C                          | C202R                   |
| c.[604T>C; 644A>G]                | c.T604C/A644G                    | p.C202R/N215S           |
| c.605G>A                          | c.G605A                          | C202Y                   |
| c.606T>G                          | c.T606G                          | C202W                   |
| c.607G>A                          | c.G607A                          | E203K                   |
| c.610T>C or c.610T>A              | c.T610C or c.T610A               | W204R                   |
| c.611G>A or 612G>A                | c.G611A or G612A                 | W204X                   |
| c.612G>T or c.612G>C              | c.G612T or c.G612C               | W204C                   |
| c.614C>G                          | c.C614G                          | P205R                   |
| c.617T>C                          | c.T617C                          | L206P                   |
| c.620A>G                          | c.A620G                          | Y207C                   |
| c.626G>A                          | c.G626A                          | W209X                   |
| c.634C>T                          | c.C634T                          | Q212X                   |
| c.639G>A (putative splicing site) | c.G639A (putative splicing site) | UNKNOWN                 |
| c.[644A>G; 811G>A]                | c.A644G/G811A                    | N215S/G271S             |
| c.[644A>G; 811G>A; 937G>T]        | c.A644G/G811A/G937T              | N215S/G271S/D313Y       |
| c.648T>A or c.648T>G              | c.T648A or c.T648G               | Y216X                   |
| c.658C>T                          | c.C658T                          | R220X                   |
| c.661C>T                          | c.C661T                          | Q221X                   |
| c.666C>A or c.666C>G              | c.C666A or c.C666G               | Y222X                   |
| c.667T>C                          | c.T667C                          | C223R                   |
| c.667T>G                          | c.T667G                          | C223G                   |
| c.668G>A                          | c.G668A                          | C223Y                   |
| c.670A>G                          | c.A670G                          | N224D                   |
| c.674A>G                          | c.A674G                          | H225R                   |
| c.676T>C or c.676T>A              | c.T676C or c.T676A               | W226R                   |
| c.677G>A or c.678G>A              | c.G677A or c.G678A               | W226X                   |
| c.678G>T or c.678G>C              | c.G678T or c.G678C               | W226C                   |
| c.679C>T                          | c.C679T                          | R227X                   |
| c.680G>A                          | c.G680A                          | R227Q                   |
| c.680G>C                          | c.G680C                          | R227P                   |
| c.688G>A                          | c.G688A                          | A230T                   |
| c.691G>A                          | c.G691A                          | D231N                   |
| c.692A>G                          | c.A692G                          | D231G                   |
| c.692A>T                          | c.A692T                          | D231V                   |
| c.695T>G                          | c.T695G                          | I232S                   |
| c.700G>T                          | c.G700T                          | D234Y                   |
| c.701A>T                          | c.A701T                          | D234V                   |
| c.702T>G or c.702T>A              | c.T702G or c.T702A               | D234E                   |
| c.704C>A                          | c.C704A                          | S235Y                   |
| c.704C>G                          | c.C704G                          | S235C                   |
| c.704C>T                          | c.C704T                          | S235F                   |
| c.706T>C or c.706T>A              | c.T706C or c.T706A               | W236R                   |
| c.706T>G                          | c.T706G                          | W236G                   |
| c.707G>A or c.708G>A              | c.G707A or c.G708A               | W236X                   |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b>          | <b>Nucleotide change</b>         | <b>Protein Sequence change</b> |
|-----------------------------------|----------------------------------|--------------------------------|
| c.707G>T                          | c.G707T                          | W236L                          |
| c.708G>C or c.708G>T              | c.G708C or c.G708T               | W236C                          |
| c.712A>C or c.714T>A or c.714T>G  | c.A712C or c.T714A or c.T714G    | S238R                          |
| c.718A>T                          | c.A718T                          | K240X                          |
| c.734G>A or c.735G>A              | c.G734A or c.G735A               | W245X                          |
| c.734G>T                          | c.G734T                          | W245L                          |
| c.739T>C                          | c.T739C                          | S247P                          |
| c.748C>T                          | c.C748T                          | Q250X                          |
| c.751G>T                          | c.G751T                          | E251X                          |
| c.755G>C                          | c.G755C                          | R252T                          |
| c.770C>A                          | c.C770A                          | A257D                          |
| c.778G>C or c.778G>A              | c.G778C or c.G778A               | G260R                          |
| c.782G>A                          | c.G782A                          | G261D                          |
| c.782G>T                          | c.G782T                          | G261V                          |
| c.784T>A or c.784T>C              | c.T784A or c.T784C               | W262R                          |
| c.785G>A or c.786G>A              | c.G785A or c.G786A               | W262X                          |
| c.785G>T                          | c.G785T                          | W262L                          |
| c.786G>C or c.786G>T              | c.G786C or c.G786T               | W262C                          |
| c.789T>A or c.789T>G              | c.T789A or c.T789G               | N263K                          |
| c.[790G>T; 805G>A]                | c.G790T/G805A                    | D264Y/V269M                    |
| c.791A>C                          | c.A791C                          | D264A                          |
| c.791A>T                          | c.A791T                          | D264V                          |
| c.793C>T                          | c.C793T                          | P265S                          |
| c.794C>G                          | c.C794G                          | P265R                          |
| c.796G>A                          | c.G796A                          | D266N                          |
| c.796G>C                          | c.G796C                          | D266H                          |
| c.796G>T                          | c.G796T                          | D266Y                          |
| c.797A>C                          | c.A797C                          | D266A                          |
| c.797A>G                          | c.A797G                          | D266G                          |
| c.797A>T                          | c.A797T                          | D266V                          |
| c.798T>A or c.798T>G              | c.T798A or c.T798G               | D266E                          |
| c.800T>G                          | c.T800G                          | M267R                          |
| c.801G>A (putative splicing site) | c.G801A (putative splicing site) | UNKNOWN (M267I)                |
| c.803T>C                          | c.T803C                          | L268S                          |
| c.806T>A                          | c.T806A                          | V269E                          |
| c.[806T>G; 937G>T]                | c.T806G/G937T                    | V269G/D313Y                    |
| c.808A>T                          | c.A808T                          | I270F                          |
| c.811G>T                          | c.G811T                          | G271C                          |
| c.812G>T                          | c.G812T                          | G271V                          |
| c.815A>G                          | c.A815G                          | N272S                          |
| c.816C>A or c.816C>G              | c.C816A or c.C816G               | N272K                          |
| c.817T>C or c.819T>A or c.819T>G  | c.T817C or c.T819A or c.T819G    | F273L                          |
| c.820G>A                          | c.G820A                          | G274S                          |
| c.820G>T                          | c.G820T                          | G274C                          |
| c.821G>T                          | c.G821T                          | G274V                          |
| c.823C>T                          | c.C823T                          | L275F                          |
| c.824T>A                          | c.T824A                          | L275H                          |
| c.826A>G                          | c.A826G                          | S276G                          |

**Table 3: Mutations not amenable to Galafold (migalstatat)**

| <b>Nucleotide change</b> | <b>Nucleotide change</b> | <b>Protein Sequence change</b> |
|--------------------------|--------------------------|--------------------------------|
| c.826A>T                 | c.A826T                  | S276C                          |
| c.830G>A or c.831G>A     | c.G830A or c.G831A       | W277X                          |
| c.834T>G or c.834T>A     | c.T834G or c.T834A       | N278K                          |
| c.835C>A                 | c.C835A                  | Q279K                          |
| c.835C>T                 | c.C835T                  | Q279X                          |
| c.836A>G                 | c.A836G                  | Q279R                          |
| c.837G>C or c.837G>T     | c.G837C or c.G837T       | Q279H                          |
| c.838C>T                 | c.C838T                  | Q280X                          |
| c.845C>A                 | c.C845A                  | T282N                          |
| c.847C>T                 | c.C847T                  | Q283X                          |
| c.848A>C                 | c.A848C                  | Q283P                          |
| c.848A>G                 | c.A848G                  | Q283R                          |
| c.853G>C                 | c.G853C                  | A285P                          |
| c.854C>A                 | c.C854A                  | A285D                          |
| c.859T>C or c.859T>A     | c.T859C or c.T859A       | W287R                          |
| c.859T>G                 | c.T859G                  | W287G                          |
| c.860G>A or c.861G>A     | c.G860A or c.G861A       | W287X                          |
| c.861G>C or c.861G>T     | c.G861C or c.G861T       | W287C                          |
| c.863C>A                 | c.C863A                  | A288D                          |
| c.865A>T                 | c.A865T                  | I289F                          |
| c.871G>C                 | c.G871C                  | A291P                          |
| c.874G>A                 | c.G874A                  | A292T                          |
| c.874G>C                 | c.G874C                  | A292P                          |
| c.875C>T                 | c.C875T                  | A292V                          |
| c.877C>G                 | c.C877G                  | P293A                          |
| c.877C>T                 | c.C877T                  | P293S                          |
| c.878C>A                 | c.C878A                  | P293H                          |
| c.878C>T                 | c.C878T                  | P293L                          |
| c.881T>G or c.881T>A     | c.T881G or c.T881A       | L294X                          |
| c.890C>G                 | c.C890G                  | S297C                          |
| c.890C>T                 | c.C890T                  | S297F                          |
| c.892A>C                 | c.A892C                  | N298H                          |
| c.894T>G or c.894T>A     | c.T894G or c.T894A       | N298K                          |
| c.896A>G                 | c.A896G                  | D299G                          |
| c.899T>A                 | c.T899A                  | L300H                          |
| c.901C>T                 | c.C901T                  | R301X                          |
| c.916C>T                 | c.C916T                  | Q306X                          |
| c.929T>G                 | c.T929G                  | L310R                          |
| c.931C>T                 | c.C931T                  | L311F                          |
| c.932T>C                 | c.T932C                  | L311P                          |
| c.932T>G                 | c.T932G                  | L311R                          |
| c.934C>T                 | c.C934T                  | Q312X                          |
| c.935A>C                 | c.A935C                  | Q312P                          |
| c.947T>A                 | c.T947A                  | V316E                          |
| c.949A>T                 | c.A949T                  | I317F                          |
| c.950T>A                 | c.T950A                  | I317N                          |
| c.950T>G                 | c.T950G                  | I317S                          |
| c.958A>T                 | c.A958T                  | N320Y                          |
| c.960T>G or c.960T>A     | c.T960G or c.T960A       | N320K                          |
| c.961C>G                 | c.C961G                  | Q321E                          |

**Table 3: Mutations not amenable to Galafold (migalstat)**

| <b>Nucleotide change</b> | <b>Nucleotide change</b> | <b>Protein Sequence change</b> |
|--------------------------|--------------------------|--------------------------------|
| c.961C>T                 | c.C961T                  | Q321X                          |
| c.963_964GG>CA           | c.G963C/G964A            | Q321H/D322N                    |
| c.974G>A                 | c.G974A                  | G325D                          |
| c.979C>A                 | c.C979A                  | Q327K                          |
| c.980A>G                 | c.A980G                  | Q327R                          |
| c.982G>A or c.982G>C     | c.G982A or c.G982C       | G328R                          |
| c.982G>T                 | c.G982T                  | G328W                          |
| c.983G>A                 | c.G983A                  | G328E                          |
| c.983G>T                 | c.G983T                  | G328V                          |
| c.988C>T                 | c.C988T                  | Q330X                          |
| c.997C>T                 | c.C997T                  | Q333X                          |
| c.998A>G                 | c.A998G                  | Q333R                          |
| c.1012G>T                | c.G1012T                 | E338X                          |
| c.1016T>G                | c.T1016G                 | V339G                          |
| c.1018T>C or c.1018T>A   | c.T1018C or c.T1018A     | W340R                          |
| c.1019G>A or c.1020G>A   | c.G1019A or c.G1020A     | W340X                          |
| c.1019G>C                | c.G1019C                 | W340S                          |
| c.1021G>A                | c.G1021A                 | E341K                          |
| c.1021G>T                | c.G1021T                 | E341X                          |
| c.1022A>G                | c.A1022G                 | E341G                          |
| c.1023A >C or c.1023A>T  | c.A1023C or c.A1023T     | E341D                          |
| c.1024C>G                | c.C1024G                 | R342G                          |
| c.1024C>T                | c.C1024T                 | R342X                          |
| c.1025G>A                | c.G1025A                 | R342Q                          |
| c.1025G>C                | c.G1025C                 | R342P                          |
| c.1025G>T                | c.G1025T                 | R342L                          |
| c.1031T>C                | c.T1031C                 | L344P                          |
| c.1034C>G or c.1034C>A   | c.C1034G or c.C1034A     | S345X                          |
| c.1042G>C                | c.G1042C                 | A348P                          |
| c.1045T>C or c.1045T>A   | c.T1045C or c.T1045A     | W349R                          |
| c.1046G>A or c.1047G>A   | c.G1046A or c.G1047A     | W349X                          |
| c.1048G>C                | c.G1048C                 | A350P                          |
| c.1054G>C                | c.G1054C                 | A352P                          |
| c.1055C>A                | c.C1055A                 | A352D                          |
| c.1058T>G                | c.T1058G                 | M353R                          |
| c.1065C>A or c.1065C>G   | c.C1065A or c.C1065G     | N355K                          |
| c.[1067G>A; 1078G>C]     | c.G1067A/G1078C          | R356Q/G360R                    |
| c.1069C>T                | c.C1069T                 | Q357X                          |
| c.1072G>A                | c.G1072A                 | E358K                          |
| c.1081G>A or c.1081G>C   | c.G1081A or c.G1081C     | G361R                          |
| c.1081G>T                | c.G1081T                 | G361X                          |
| c.1088G>C                | c.G1088C                 | R363P                          |
| c.1095T>A or c.1095T>G   | c.T1095A or c.T1095G     | Y365X                          |
| c.1115T>A                | c.T1115A                 | L372Q                          |
| c.1115T>C                | c.T1115C                 | L372P                          |
| c.1115T>G                | c.T1115G                 | L372R                          |
| c.1117G>C                | c.G1117C                 | G373R                          |
| c.1118G>A                | c.G1118A                 | G373D                          |
| c.1124G>T                | c.G1124T                 | G375V                          |
| c.1130C>A                | c.C1130A                 | A377D                          |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b>            | <b>Nucleotide change</b>         | <b>Protein Sequence change</b> |
|-------------------------------------|----------------------------------|--------------------------------|
| c.1132T>C                           | c.T1132C                         | C378R                          |
| c.1133G>A                           | c.G1133A                         | C378Y                          |
| c.1133G>C                           | c.G1133C                         | C378S                          |
| c.1144T>C                           | c.T1144C                         | C382R                          |
| c.1145G>A                           | c.G1145A                         | C382Y                          |
| c.1146C>G                           | c.C1146G                         | C382W                          |
| c.1147T>C or c.1149C>G or c.1149C>A | c.T1147C or c.C1149G or c.C1149A | F383L                          |
| c.1151T>A                           | c.T1151A                         | I384N                          |
| c.1153A>C                           | c.A1153C                         | T385P                          |
| c.1156C>T                           | c.C1156T                         | Q386X                          |
| c.1157A>C                           | c.A1157C                         | Q386P                          |
| c.1160T>C                           | c.T1160C                         | L387P                          |
| c.1163T>C                           | c.T1163C                         | L388P                          |
| c.1165C>G                           | c.C1165G                         | P389A                          |
| c.1166C>G                           | c.C1166G                         | P389R                          |
| c.1166C>T                           | c.C1166T                         | P389L                          |
| c.1187T>A                           | c.T1187A                         | F396Y                          |
| c.1192G>T                           | c.G1192T                         | E398X                          |
| c.1193A>C                           | c.A1193C                         | E398A                          |
| c.1196G>A or c.1197G>A              | c.G1196A or c.G1197A             | W399X                          |
| c.1196G>C                           | c.G1196C                         | W399S                          |
| c.1202C>G or c.1202C>A              | c.C1202G or c.C1202A             | S401X                          |
| c.1215T>A                           | c.T1215A                         | S405R                          |
| c.1217A>G                           | c.A1217G                         | H406R                          |
| c.1219A>G                           | c.A1219G                         | I407V                          |
| c.1220T>A                           | c.T1220A                         | I407K                          |
| c.1220T>G                           | c.T1220G                         | I407R                          |
| c.1228A>C                           | c.A1228C                         | T410P                          |
| c.1229C>A                           | c.C1229A                         | T410K                          |
| c.1241T>C                           | c.T1241C                         | L414S                          |
| c.1243C>T                           | c.C1243T                         | L415F                          |
| c.1244T>C                           | c.T1244C                         | L415P                          |
| c.1246C>T                           | c.C1246T                         | Q416X                          |
| c.1247_1248CT>AA                    | c.C1247A/T1248A                  | L417K                          |
| c.1247A>C                           | c.A1247C                         | Q416P                          |
| c.1250T>C                           | c.T1250C                         | L417P                          |
| c.1250T>G                           | c.T1250G                         | L417R                          |
| c.1288T>C                           | c.T1288C                         | X430Q                          |
| c.18delA                            | c.18delA                         | p.P6fs*114                     |
| c.26delA                            | c.26delA                         | p.H9Lfs*111                    |
| c.32delG                            | c.32delG                         | p.G11Afs*109                   |
| c.33delC                            | c.33delC                         | p.G11fs*109                    |
| c.34_42del                          | c.34_42del                       | p.C12_L14del                   |
| c.34_57del                          | c.34_57del                       | p.C12_L19del                   |
| c.35_47del                          | c.35_47del                       | p.C12Ffs*104                   |
| c.42_48delTGCGCTT                   | c.42_48delTGCGCTT                | p.L14Sfs*12                    |
| c.58_72del                          | c.58_72del                       | p.A20_W24del                   |
| c.58_83del                          | c.58_83del                       | p.A20_G28delfs*2               |
| c.85dupG                            | c.85dupG                         | p.A29Gfs*1                     |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b>  | <b>Nucleotide change</b>  | <b>Protein Sequence change</b> |
|---------------------------|---------------------------|--------------------------------|
| c.89delG                  | c.89delG                  | p.R30Kfs*89                    |
| c.123_126dupCATG          | c.123_126dupCATG          | p.G43Hfs*13                    |
| c.123delC                 | c.123delC                 | p.T41fs*79                     |
| c.124_125del              | c.124_125del              | p.M42Gfs*12                    |
| c.125_137del              | c.125_137del              | p.M42Tfs*74                    |
| c.134_138delTGCACinsGCTCG | c.134_138delTGCACinsGCTCG | L45R/H46S                      |
| c.147_148insCCC           | c.147_148insCCC           | p.49insP                       |
| c.147_148insCGC           | c.147_148insCGC           | p.R49ins                       |
| c.154delT                 | c.154delT                 | p.C52Afs*68                    |
| c.157_160delAACC          | c.157_160delAACC          | p.C52fs*67                     |
| c.162delT                 | c.162delT                 | p.L54fs*66                     |
| c.172delG                 | c.172delG                 | p.E58Kfs*61                    |
| c.181_182dupA             | c.181_182dupA             | p.D61Efs*5                     |
| c.184delT                 | c.184delT                 | p.S62Pfs*58                    |
| c.186delC                 | c.186delC                 | p.S62fs*58                     |
| c.210insT                 | c.210insT                 | p.E71X                         |
| c.214delA                 | c.214delA                 | p.M72Wfs*47                    |
| c.256delT                 | c.256delT                 | p.Y88Mfs*42                    |
| c.259_276del              | c.259_276del              | p.87_92del                     |
| c.267_268dupCT            | c.267_268dupCT            | p.C90Sfs*31                    |
| c.270delC                 | c.270delC                 | p.C90X                         |
| c.281_286delinsT          | c.281_286delinsT          | p.C94Ffs*26                    |
| c.290delC                 | c.290delC                 | p.A97Vfs*22                    |
| c.297_298del              | c.297_298del              | p.Q99fs*22                     |
| c.297_300delAAGA          | c.297_300delAAGA          | p.Q99fs*19                     |
| c.305delC                 | c.305delC                 | p.S102X                        |
| c.317_327del              | c.317_327del              | p.S102fs*16                    |
| c.323_324insCAGA          | c.323_324insCAGA          | p.D109Rfs*14                   |
| c.336del18                | c.336del18                | p.113del6aa                    |
| c.354_368del              | c.354_368del              | p.Q119_Y123del                 |
| c.354_368del15            | c.354_368del15            | Q119_Y123del5                  |
| c.358del6                 | c.358del6                 | p.120del2aa/L120H              |
| c.363delT                 | c.363delT                 | p.A121fs*8                     |
| c.402delT                 | c.402delT                 | p.Y134X                        |
| c.409delG                 | c.409delG                 | p.V137Lfs*27                   |
| c.413dupG                 | c.413dupG                 | p.G138fs*2                     |
| c.421delA                 | c.421delA                 | p.T141Pfs*23                   |
| c.426dupC                 | c.426dupC                 | p.A143Rfs*13                   |
| c.428dupC                 | c.428dupC                 | p.G144Qfs*12                   |
| c.452delA                 | c.452delA                 | p.Y151Sfs*13                   |
| c.457_459del              | c.457_459del              | p.153delD                      |
| c.477delT                 | c.477delT                 | p.F159Lfs*5                    |
| c.486_498del              | c.486_498del              | p.W162Cfs*1                    |
| c.512delG                 | c.512delG                 | p.G171Vfs*19                   |
| c.516insGAC               | c.516insGAC               | p.152insD                      |
| c.520delT                 | c.520delT                 | p.C174Vfs*17                   |
| c.560delT                 | c.560delT                 | p.M187Sfs*3                    |
| c.568delG                 | c.568delG                 | p.A190Pfs*1                    |
| c.590delG                 | c.590delG                 | p.S197Tfs*42                   |
| c.606delT                 | c.606delT                 | p.C202Wfs*37                   |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b> | <b>Nucleotide change</b> | <b>Protein Sequence change</b> |
|--------------------------|--------------------------|--------------------------------|
| c.613_621del             | c.613_621del             | p.205_207del                   |
| c.614delC                | c.614delC                | p.P205Lfs*34                   |
| c.618_619del             | c.618_619del             | p.L206fs*24                    |
| c.621dupT                | c.621dupT                | p.M208Yfs*24                   |
| c.646delT                | c.646delT                | p.Y216Ifs*23                   |
| c.646dupT                | c.646dupT                | p.Y216Lfs*15                   |
| c.650_663dup14           | c.650_663dup14           | p.Q221fs*23                    |
| c.672_673ins37           | c.672_673ins37           | p.H225Tfs*18                   |
| c.674_732del             | c.674_732del             | p.H225Lfs*5                    |
| c.678delG                | c.678delG                | p.A230Lfs*9                    |
| c.700_702del             | c.700_702del             | p.D234del                      |
| c.715_717del             | c.715_717del             | p.delI239                      |
| c.716dupT                | c.716dupT                | p.I239fs*10                    |
| c.718_719del             | c.718_719del             | p.K240Efs*8                    |
| c.719delA                | c.719delA                | p.K240Rfs*29                   |
| c.719dupA                | c.719dupA                | p.K240fs*9                     |
| c.722delG                | c.722delG                | p.S241Ifs*27                   |
| c.723dupT                | c.723dupT                | p.I242Yfs*8                    |
| c.732delC                | c.732delC                | p.D244fs*24                    |
| c.736_739delinsCAA       | c.736_739delinsCAA       | p.T246Qfs*21                   |
| c.741ins9                | c.741ins9                | p.247ins3                      |
| c.744_745del             | c.744_745del             | p.F248Lfs*6                    |
| c.744delT                | c.744delT                | p.F248Lfs*20                   |
| c.746_747del             | c.746_747del             | p.N249Tfs*5                    |
| c.756delA                | c.756delA                | p.I253Vfs*14                   |
| c.759delT                | c.759delT                | p.I253Mfs*15                   |
| c.760dupG                | c.760dupG                | p.V254Gfs*1                    |
| c.761_762del             | c.761_762del             | p.V254Gfs*9                    |
| c.774_775del             | c.774_775del             | p.G258fx*5                     |
| c.777delA                | c.777delA                | p.P259fs*9                     |
| c.782dupG                | c.782dupG                | p.G261fs*3                     |
| c.802-2_802-3delCA       | c.802-2_802-3delCA       | UNKNOWN                        |
| c.803_806delTAGT         | c.803_806delTAGT         | p.L268X                        |
| c.807delG                | c.807delG                | p.V269fs*12                    |
| c.833_845del             | c.833_845del             | p.W277fs*34                    |
| c.833delA                | c.833delA                | p.N278Ifs*3                    |
| c.833dupA                | c.833dupA                | p.N278Kfs*20                   |
| c.838_849del             | c.838_849del             | p.Q280_283del                  |
| c.841_844delGTAA         | c.841_844delGTAA         | p.Q280fs*34                    |
| c.842_844del             | c.842_844del             | p.V281A delI282                |
| c.848_851delAGAT         | c.848_851delAGAT         | Q283Rfs*33                     |
| c.858_863delinsTTGG      | c.858_863delinsTTGG      | p.W287fs*9                     |
| c.863delC                | c.863delC                | p.A288Vfs*29                   |
| c.881delT                | c.881delT                | p.L294Yfs*22                   |
| c.891dupT                | c.891dupT                | p.N298X                        |
| c.892_893insT            | c.892_893insT            | p.N298Ifs*1                    |
| c.893_894insG            | c.893_894insG            | p.N298Kfs*1                    |
| c.902dupG                | c.902dupG                | p.R301fs*13                    |
| c.909_918del             | c.909_918del             | p.I303Mfx*10                   |
| c.914delC                | c.914delC                | p.P305Lfs*11                   |



**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b> | <b>Nucleotide change</b> | <b>Protein Sequence change</b> |
|--------------------------|--------------------------|--------------------------------|
| c.931delC                | c.931delC                | p.L311Ffs*5                    |
| c.931dupC                | c.931dupC                | p.L311Pfs*4                    |
| c.941_961del             | c.941_961del             | p.D315_Q321del                 |
| c.946_954dup             | c.946_954dup             | p.V316_A318dup                 |
| c.946_966del             | c.946_966del             | p.V316_D322del                 |
| c.946delG                | c.946delG                | p.V316X                        |
| c.950_954dupTTGCC        | c.950_954dupTTGCC        | p.A318fs*31                    |
| c.972delG                | c.972delG                | p.G325Afs*21                   |
| c.974dupG                | c.974dupG                | p.G325fs*7                     |
| c.986delA                | c.986delA                | p.Y329Sfs*18                   |
| c.988delC                | c.988delC                | p.Q330Sfs*17                   |
| c.994delA                | c.994delA                | p.R332Dfs*15                   |
| c.994dupA                | c.994dupA                | p.R332Kfs*5                    |
| c.996_999del             | c.996_999del             | p.R332fs*14                    |
| c.997dupC                | c.997dupC                | p.Q333Pfs*5                    |
| c.1011_1029del           | c.1011_1029del           | p.F337fs*4                     |
| c.1017_1020delins24      | c.1017_1020delins24      | p.V339fs*7                     |
| c.1017_1027del           | c.1017_1027del           | p.V339fs*5                     |
| c.1021delG               | c.1021delG               | p.E341Nfs*6                    |
| c.1025delG               | c.1025delG               | p.R342Hfs*5                    |
| c.1028delC               | c.1028delC               | p.343Lfs*3                     |
| c.1029_1030delTC         | c.1029_1030delTC         | p.P343fs*29                    |
| c.1030_1031insT          | c.1030_1031insT          | p.L344fs*30                    |
| c.1033_1034del           | c.1033_1034del           | p.S345Rfs*28                   |
| c.1037delG               | c.1037delG               | p.G346Afs*1                    |
| c.1040dupT               | c.1040dupT               | p.L347Ffs*27                   |
| c.1041dupA               | c.1041dupA               | p.L347fs*27                    |
| c.1042dupG               | c.1042dupG               | p.A348Gfs*26                   |
| c.1043_1044insG          | c.1043_1044insG          | p.A348fs*26                    |
| c.1049delC               | c.1049delC               | p.A350Vfs*1                    |
| c.1055_1056delCT         | c.1055_1056delCT         | p.A352Dfs*20                   |
| c.1055_1057dup           | c.1055_1057dup           | p.353insT                      |
| c.1057_1058del           | c.1057_1058del           | p.M353Dfs*20                   |
| c.1072_1074del           | c.1072_1074del           | p.358delE                      |
| c.1074_1075del           | c.1074_1075del           | p.E358Dfs*15                   |
| c.1077delT               | c.1077delT               | p.I359Mfs*31                   |
| c.1081_1100del           | c.1081_1100del           | p.G360fs*7                     |
| c.1086_1098del           | c.1086_1098del           | p.P362fs*24                    |
| c.1088delG               | c.1088delG               | p.R363Pfs*27                   |
| c.1091_1092del           | c.1091_1092del           | p.S364Lfs*9                    |
| c.1093dupT               | c.1093dupT               | p.Y365Lfs*9                    |
| c.1095delT               | c.1095delT               | p.Y365X                        |
| c.1096_1100del           | c.1096_1100del           | p.Y365fs*7                     |
| c.1102delG               | c.1102delG               | p.A368Qfs*21                   |
| c.1102delGinsTTATAC      | c.1102delGinsTTATAC      | p.A368delinsFYfs*23            |
| c.1114_1115insTCCC       | c.1114_1115insTCCC       | p.G373Pfs*1                    |
| c.1122_1125del           | c.1122_1125del           | p.K374fs*15                    |
| c.1123_1175del           | c.1123_1175del           | p.G375_R392del                 |
| c.1124_1129del           | c.1124_1129del           | G375_V376del                   |
| c.1129_1140dup           | c.1129_1140dup           | A377_P380dup                   |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b> | <b>Nucleotide change</b>       | <b>Protein Sequence change</b>       |
|--------------------------|--------------------------------|--------------------------------------|
| c.1139delC               | c.1139delC                     | p.380Lfs*10                          |
| c.1145_1149del           | c.1145_1149del                 | p.C382Yfs*14                         |
| c.1146_1148del           | c.1146_1148del                 | p.383delF                            |
| c.1151_1152delinsAT      | c.1151_1152delinsAT            | p.I384N                              |
| c.1156_1157del           | c.1156_1157del                 | p.Q386Afs*10                         |
| c.1167dupT               | c.1167dupT                     | p.P389fs*9                           |
| c.1168insT               | c.1168insT                     | p.V390fs*9                           |
| c.1176_1179del           | c.1176_1179del                 | p.R392Sfs*1                          |
| c.1177_1178del           | c.1177_1178del                 | p.K393Afs*4                          |
| c.1181_1183dup           | c.1181_1183dup                 | L394_G395insV                        |
| c.1181_1192del           | c.1181_1192del                 | p.L394_E398delinsQ                   |
| c.1187delT               | c.1187delT                     | p.F396Sfs*7                          |
| c.1187dupT               | c.1187dupT                     | p.F396fs*2                           |
| c.1188delC               | c.1188delC                     | p.F396fs*7                           |
| c.1193_1196delAATG       | c.1193_1196delAATG             | p.E398Gfs*3                          |
| c.1201dupT               | c.1201dupT                     | p.S401Ffs*49                         |
| c.1202dupC               | c.1202dupC                     | p.R402Kfs*48                         |
| c.1208delT               | c.1208delT                     | p.L403X                              |
| c.1208ins21              | c.1208ins21                    | UNKNOWN                              |
| c.1209_1211del           | c.1209_1211del                 | p.404delR                            |
| c.1223delA               | c.1223delA                     | p.N408Ifs*9                          |
| c.1226_1231del           | c.1226_1231del                 | p.409_410delinsR                     |
| c.1235_1236del           | c.1235_1236del                 | p.T412Sfs*37                         |
| c.1277_1278del           | c.1277_1278del                 | p.K426Rfs*23                         |
| c.1281_1282insCTTA       | c.1281_1282insCTTA             | p.L429Ifs*21                         |
| c.1284_1287del           | c.1284_1287del                 | p.L428Ffs*23                         |
| g.941_5845del            | c.1-179_369+577del             | p.?(Exon1_2del)                      |
| g.2594_10904dup          | c.195-2500_999+197dup          | UNKNOWN                              |
| g.2934_6378del           | c.194+1561_370-891del          | UNKNOWN<br>(E66_Y123del; del Exon2?) |
| g.2979_6442del           | c.194+1606_369+1174del         | UNKNOWN<br>(E66_Y123del; del Exon2)  |
| g.3260_6410del           | c.194+1887_370-859del          | UNKNOWN<br>(E66_Y123del; del Exon2?) |
| g.3396_6012del           | c.194+2023_370-1257del         | UNKNOWN<br>(E66_Y123del; del Exon2?) |
| g.3422_6041delinsCG      | c.194+2049_369+773del2620insCG | UNKNOWN                              |
| g.5052_5079del28         | g.5052_5079del28               | UNKNOWN                              |
| g.5106_5919delins231     | c.207_369+651del814ins231      | UNKNOWN (del Exon2?)                 |
| g.5271_9366del4096insT   | c.369+3_639+954del3129insT     | UNKNOWN (del Exon3 and 4?)           |
| g.6009_9741del           | c.369+741_640-390del           | UNKNOWN (del Exon3 and 4?)           |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| <b>Nucleotide change</b>                           | <b>Nucleotide change</b>                       | <b>Protein Sequence change</b> |
|--|--|--------------------------------|
| g.6547_9783del                                     | c.369+1279_640-348del                          | UNKNOWN (del Exon3 and 4?)     |
| g.6736_11545del                                    | c.370-533_c.1290+277del                        | UNKNOWN (del Exon3_7?)         |
| g.7086_7487del                                     | c.370-183_547+41del                            | UNKNOWN (del Exon3?)           |
| g.[10237_11932del; 11933_12083inv; 12084_12097del] | g.10237_11932del/11933_12083inv/12084_12097del | UNKNOWN                        |
| g.>5.5kdel to 3UTR                                 | c.?_?del                                       | UNKNOWN (delExon3_3'UTR?)      |
| g.?_?del   | c.?_?  | UNKNOWN (del Exon1_2?)         |
| g.?_?del   | c.195-?_547+?del                               | UNKNOWN (del Exon2_3?)         |
| g.?_?del   | c.?_?del                                       | UNKNOWN (del Exon5_7?)         |
| g.?_?dup   | c.?_?dup                                       | UNKNOWN (Exon2_4dup?)          |
| IVS1+2T>C  | c.194+2T>C                                     | UNKNOWN                        |
| IVS1+39delAT                                       | c.194+39delAT                                  | UNKNOWN                        |
| IVS1-1G>A  | c.195-1G>A                                     | UNKNOWN                        |
| IVS1-1G>T  | c.195-1G>T                                     | UNKNOWN                        |
| IVS1-2A>G  | c.195-2A>G                                     | UNKNOWN                        |
| IVS1-2A>G; IVS1-49T>C                              | c.195-2A>G/195-49T>C                           | UNKNOWN                        |
| IVS2+1G>A  | c.369+1G>A                                     | UNKNOWN                        |
| IVS2+1G>T  | c.369+1G>T                                     | UNKNOWN                        |
| IVS2+2T>G  | c.369+2T>G                                     | UNKNOWN                        |
| IVS2-2A>G  | c.370-2A>G                                     | UNKNOWN                        |
| IVS3+1G>A  | c.547+1G>A                                     | UNKNOWN                        |
| IVS3+1G>C  | c.547+1G>C                                     | UNKNOWN                        |
| IVS3+1G>T  | c.547+1G>T                                     | UNKNOWN                        |
| IVS3-1G>A  | c.548-1G>A                                     | UNKNOWN                        |
| IVS3-1G>C  | c.548-1G>C                                     | UNKNOWN                        |
| IVS3-1G>T  | c.548-1G>T                                     | UNKNOWN                        |
| IVS3-2A>G  | c.548-2A>G                                     | UNKNOWN                        |
| IVS3-162A>T  | c.548-162A>T                                   | UNKNOWN                        |
| IVS4+1G>A  | c.639+1G>A                                     | UNKNOWN                        |
| IVS4+1G>C  | c.639+1G>C                                     | UNKNOWN                        |
| IVS4+4A>T  | c.639+4A>T                                     | UNKNOWN                        |
| IVS4+861C>T  | c.639+861C>T                                   | UNKNOWN                        |
| IVS4+919G>A  | c.639+919G>A                                   | UNKNOWN                        |
| IVS4-1G>A  | c.640-1G>A                                     | UNKNOWN                        |
| IVS4-1G>T  | c.640-1G>T                                     | UNKNOWN                        |
| IVS4-2A>T  | c.640-2A>T                                     | UNKNOWN                        |
| IVS4-3C>G  | c.640-3C>G                                     | UNKNOWN                        |
| IVS4-4A>C  | c.640-4A>C                                     | UNKNOWN                        |
| IVS4-11T>A   | c.640-11T>A                                    | UNKNOWN                        |
| IVS4-859C>T  | c.640-859C>T                                   | UNKNOWN                        |
| IVS5+1G>T  | c.801+1G>T                                     | UNKNOWN                        |

**Table 3: Mutations not amenable to Galafold (migalastat)**

| Nucleotide change      | Nucleotide change       | Protein Sequence change |
|------------------------|-------------------------|-------------------------|
| IVS5+2T>C              | c.801+2T>C              | UNKNOWN                 |
| IVS5+3A>G              | c.801+3A>G              | UNKNOWN                 |
| IVS5+3A>T              | c.801+3A>T              | UNKNOWN                 |
| IVS5+4A>G              | c.801+4A>G              | UNKNOWN                 |
| IVS5-2A>G              | c.802-2A>G              | UNKNOWN                 |
| IVS6+1G>T              | c.999+1G>T              | UNKNOWN                 |
| IVS6+2T>C              | c.999+2T>C              | UNKNOWN                 |
| IVS6-1G>A              | c.1000-1G>A             | UNKNOWN                 |
| IVS6-1G>C              | c.1000-1G>C             | UNKNOWN                 |
| IVS6-2A>G              | c.1000-2A>G             | UNKNOWN                 |
| IVS6-2A>T              | c.1000-2A>T             | UNKNOWN                 |
| IVS6-10G>A; IVS6-22C>T | c.1000-10G>A/1000-22C>T | UNKNOWN                 |

NP GAL 0719

Not all mutations have been tested.

#### Pharmacodynamic effects

Treatment with Galafold in Phase 2 pharmacodynamic trials generally resulted in increases in endogenous  $\alpha$ -Gal A activity in WBCs, as well as in skin and kidney for the majority of patients. In patients with amenable mutations, GL-3 levels tended to decrease in urine and in kidney interstitial capillaries.

#### Clinical efficacy and safety

The clinical efficacy and safety of Galafold have been evaluated in two Phase 3 pivotal trials and two open-label extension (OLE) trials. All patients received the recommended dosage of 123 mg Galafold every other day.

The first Phase 3 trial (ATTRACT) was a randomised open-label active comparator trial that evaluated the efficacy and safety of Galafold compared to enzyme replacement therapy (ERT) (agalsidase beta, agalsidase alfa) in 52 male and female patients with Fabry disease who were receiving ERT prior to trial entry and who have amenable mutations (ERT-experienced trial). The study was structured in two periods. During the first period (18-months) ERT-experienced patients were randomised to switch from ERT to Galafold or continue with ERT. The second period was an optional 12-month open-label extension in which all subjects received Galafold.

The second Phase 3 trial (FACETS) was a 6-month randomised double-blind placebo-controlled trial (through month 6) with an 18-month open-label period to evaluate the efficacy and safety of Galafold in 50 male and female patients with Fabry disease who were naïve to ERT, or had previously been on ERT and had stopped for at least 6 months and who have amenable mutations (ERT-naïve trial). The first OLE trial (AT1001-041) included patients from Phase 2 and Phase 3 studies and has completed. The mean extent of exposure to the marketed dose of Galafold 123 mg QOD in patients completing study AT1001-041 was 3.57 ( $\pm$ 1.23) years (n=85). The maximum exposure was 5.6 years.

The second OLE trial (AT1001-042) included patients that both transferred from OLE study AT1001-041 and directly from Phase 3 study ATTRACT, and is ongoing. *Renal Function*  
In the ERT-experienced trial, renal function remained stable for up to 18 months of treatment with Galafold. Mean annualised rate of change in eGFR<sub>CKD-EPI</sub> was -0.40 mL/min/1.73 m<sup>2</sup> (95% CI: -2.272, 1.478; n=34) in the Galafold group compared to -1.03 mL/min/1.73 m<sup>2</sup> (95% CI: -3.636, 1.575; n=18)

in the ERT group. The mean annualised rate of change from baseline in eGFR<sub>CKD-EPI</sub> in patients treated for 30 months with Galafold was -1.72 mL/min/1.73 m<sup>2</sup> (95% CI: -2.653, -0.782; n=31).

In the ERT- naïve trial and open-label extension, renal function remained stable for up to 5 years of treatment with Galafold. After an average of 3.4 years of treatment, the mean annualised rate of change in eGFR<sub>CKD-EPI</sub> was -0.74 mL/min/1.73 m<sup>2</sup> (95% CI: -1.89, 0.40; n=41). No clinically significant differences were observed during the initial 6-month placebo-controlled period.

#### *Left Ventricular Mass Index (LVMI)*

In the ERT-experienced trial, following 18 months of treatment with Galafold there was a statistically significant decrease in LVMI (p< 0.05). The baseline values were 95.3 g/m<sup>2</sup> for the Galafold arm and 92.9 g/m<sup>2</sup> for the ERT arm and the mean change from baseline in LVMI at Month 18 was -6.6 (95% CI: -11.0, -2.1; n=31) for Galafold and -2.0 (95% CI: -11.0, 7.0; n=13) for ERT. The change from baseline to Month 18 in LVMI (g/m<sup>2</sup>) in patients with left ventricular hypertrophy (females with baseline LVMI > 95 g/m<sup>2</sup> and males with baseline LVMI > 115 g/m<sup>2</sup>) was -8.4 (95% CI: -15.7, 2.6; n=13) for migalastat and 4.5 (95% CI: -10.7, 18.4; n=5) for ERT. After 30 months treatment with Galafold, the mean change from baseline in LVMI was -3.8 (95% CI: -8.9, 1.3; n=28) and the mean change from baseline in LVMI in patients with left ventricular hypertrophy at baseline was -10.0 (95% CI: -16.6, -3.3; n=10).

In the ERT-naïve trial, Galafold resulted in a statistically significant decrease in LVMI (p< 0.05); the mean change from baseline in LVMI at Month 18 to 24 was -7.7 (95% CI: -15.4, -0.01; n=27). After follow up in the OLE, the mean change from baseline in LVMI at Month 36 was -8.3 (95% CI: -17.1, 0.4; n=25) and at Month 48 was -9.1 (95% CI: -20.3, 2.0; n=18). The mean change from baseline in LVMI at Month 18 to 24 in patients with left ventricular hypertrophy at baseline (females with baseline LVMI > 95 g/m<sup>2</sup> or males with baseline LVMI > 115 g/m<sup>2</sup>) was -18.6 (95% CI: -38.2, 1.0; n=8). After follow up in the OLE, the mean change from baseline in LVMI in patients with left ventricular hypertrophy at baseline at Month 36 was -30.0 (95% CI: -57.9, -2.2; n=4) and at Month 48 was -33.1 (CI: -60.9, -5.4; n=4). No clinically significant differences in LVMI were observed during the initial 6-month placebo-controlled period.

#### *Disease Substrate*

In the ERT-experienced trial, plasma lyso-Gb<sub>3</sub> levels slightly increased but remained low in patients with amenable mutations treated with Galafold for the 30 month duration of the study. Plasma lyso-Gb<sub>3</sub> levels also remained low in patients on ERT for up to 18 months.

In the ERT- naïve trial, Galafold showed statistically significant reductions in plasma lyso-Gb<sub>3</sub> concentrations and kidney interstitial capillary GL-3 inclusions in patients with amenable mutations. Patients randomised to Galafold in Stage 1 demonstrated statistically significant greater reduction ( $\pm$ SEM) in mean interstitial capillary GL-3 deposition (-0.25 $\pm$ 0.10; -39%) at month 6 compared to placebo (+0.07  $\pm$  0.13; +14%) (p=0.008). Patients randomised to placebo in Stage 1 and switched to Galafold at month 6 (Stage 2) also demonstrated statistically significant decreases in interstitial capillary GL-3 inclusions at month 12 (-0.33 $\pm$ 0.15; -58%) (p=0.014). Qualitative reductions in GL-3 levels were observed in multiple renal cell types: podocytes, mesangial cells, and glomerular endothelial cells, respectively, over 12 months of treatment with Galafold.

#### *Composite Clinical Outcomes*

In the ERT-experienced trial, an analysis of a composite clinical outcome composed of renal, cardiac, and cerebrovascular events, or death, showed that the frequency of events observed in the Galafold treatment group was 29% compared to 44% in the ERT group over 18 months. The frequency of events in patients treated with Galafold over 30 months (32%) was similar to the 18 month period.

#### *Patient-Reported Outcome - Gastrointestinal Symptoms Rating Scale*

In the ERT-naïve trial, analyses of the Gastrointestinal Symptoms Rating Scale demonstrated that treatment with Galafold was associated with statistically significant (p<0.05) improvements versus placebo from baseline to month 6 in the diarrhoea domain, and in the reflux domain for patients with

symptoms at baseline. During the open-label extension, statistically significant ( $p < 0.05$ ) improvements from baseline were observed in the diarrhoea and indigestion domains, with a trend of improvement in the constipation domain.

### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Galafold in one or more subsets of the paediatric population in the treatment of Fabry disease (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

The absolute bioavailability (AUC) for a single oral 150 mg migalastat hydrochloride dose or a single 2-hour 150 mg intravenous infusion was approximately 75%. Following a single oral dose of 150 mg migalastat hydrochloride solution, the time to peak plasma concentration was approximately 3 hours. Plasma migalastat exposure ( $AUC_{0-\infty}$ ) and  $C_{max}$  demonstrated dose-proportional increases at migalastat hydrochloride oral doses from 50 mg to 1,250 mg.

Migalastat administered with a high-fat meal, or 1 hour before a high-fat or light meal, or 1 hour after a light meal, resulted in significant reductions of 37% to 42% in mean total migalastat exposure ( $AUC_{0-\infty}$ ) and reductions of 15% to 40% in mean peak migalastat exposure ( $C_{max}$ ) compared with the fasting state. See section 4.2.

### Distribution

In healthy volunteers, the volume of distribution ( $V_z/F$ ) of migalastat following ascending single oral doses (25-675 mg migalastat HCl) ranged from 77 to 133 L, indicating it is well distributed into tissues and greater than total body water (42 litres). There was no detectable plasma protein binding following administration of [ $^{14}C$ ]-migalastat hydrochloride in the concentration range between 1 and 100  $\mu M$ .

### Biotransformation

Based upon in vivo data, migalastat is a substrate for UGT, being a minor elimination pathway. Migalastat is not a substrate for P-glycoprotein (P-gP) *in vitro* and it is considered unlikely that migalastat would be subject to drug-drug interactions with cytochrome P450s. A pharmacokinetic trial in healthy male volunteers with 150 mg [ $^{14}C$ ]-migalastat HCl revealed that 99% of the radiolabeled dose recovered in plasma was comprised of unchanged migalastat (77%) and 3 dehydrogenated O-glucuronide conjugated metabolites, M1 to M3 (13%). Approximately 9% of the total radioactivity was unassigned.

### Elimination

A pharmacokinetic trial in healthy male volunteers with 150 mg [ $^{14}C$ ]-migalastat hydrochloride revealed that approximately 77% of the radiolabeled dose was recovered in urine of which 55% of was excreted as unchanged migalastat and 4% as combined metabolites M1, M2 and M3. Approximately 5% of the total sample radioactivity was unassigned components. Approximately 20% of the total radiolabeled dose was excreted in faeces, with unchanged migalastat being the only measured component.

Following ascending single oral doses (25-675 mg migalastat hydrochloride), no trends were found for clearance,  $CL/F$ . At the 150 mg dose,  $CL/F$  was approximately 11 to 14 L/hr. Following administration of the same doses, the mean elimination half-life ( $t_{1/2}$ ) ranged from approximately 3 to 5 hours.

## Special populations

### Patients with renal impairment

Galafold has not been studied in patients with Fabry disease who have a GFR less than 30 mL/min/1.73 m<sup>2</sup>. In a single dose study with Galafold in non-Fabry subjects with varying degrees of renal insufficiency, exposures were increased by 4.3-fold in subjects with severe renal impairment (GFR < 30 mL/min/1.73 m<sup>2</sup>).

### Patients with hepatic impairment

No studies have been carried out in subjects with impaired hepatic function. From the metabolism and excretion pathways, it is not expected that a decreased hepatic function may affect the pharmacokinetics of migalastat.

### Elderly (> 65 years)

Clinical studies of Galafold included small number of patients aged 65 and over. The effect of age was evaluated in a population pharmacokinetic analysis on plasma migalastat clearance in the ERT-naïve study population. The difference in clearance between Fabry patients ≥ 65 years and those < 65 years was 20%, which was not considered clinically significant.

## Gender

The pharmacokinetic characteristics of migalastat were not significantly different between females and males in either healthy volunteers or in patients with Fabry disease.

## **5.3 Preclinical safety data**

Non-clinical studies suggest no specific hazard for humans on the basis of single-and repeat-dose studies, with the exception of transient and fully reversible infertility in male rats associated with migalastat treatment. The infertility associated with migalastat treatment was reported at clinically relevant exposures. Complete reversibility was seen after 4 weeks off-dose. Similar findings have been noted pre-clinically following treatment with other iminosugars. In the rabbit embryo-foetal toxicity study, findings including embryo-foetal death, a reduction in mean foetal weight, retarded ossification, and slightly increased incidences of minor skeletal abnormalities were observed only at doses associated with maternal toxicity.

In a rat 104-week carcinogenicity study, there was an increased incidence of pancreatic islet cell adenomas in males at a dose level 19-fold higher than the exposure (AUC) at the clinically efficacious dose. This is a common spontaneous tumour in *ad libitum*-fed male rats. In the absence of similar findings in females, no findings in the genotoxicity battery or in the carcinogenicity study with Tg.rasH2 mice, and no pre-neoplastic pancreatic findings in the rodents or monkeys, this observation in male rats is not considered related to treatment and its relevance to humans is unknown.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule contents

Pregelatinised starch (maize)

Magnesium stearate

#### Capsule shell

Gelatin

Titanium dioxide (E171)

Indigotine (E132)

#### Printing ink

Shellac

Black iron oxide

Potassium hydroxide

#### **6.2 Incompatibilities**

Not applicable.

#### **6.3 Shelf life**

4 years

#### **6.4 Special precautions for storage**

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

#### **6.5 Nature and contents of container**

PVC / PCTFE / PVC/Al blister.

Pack size of 14 capsules.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Amicus Therapeutics UK Ltd

Phoenix House,

Oxford Road,

Tatling End,

Gerrards Cross,

Buckinghamshire

SL9 7AP

United Kingdom

tel +44 1753 888 567

fax +44 1753 437 192

e-mail [info@amicusrx.co.uk](mailto:info@amicusrx.co.uk)

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1082/001

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26 May 2016



## 10. DATE OF REVISION OF THE TEXT

DD month YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services Limited  
Seagoe Industrial Estate  
Portadown, Craigavon  
BT63 5UA  
United Kingdom

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Galafold 123 mg hard capsules  
migalastat

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains migalastat hydrochloride equivalent to 123 mg migalastat

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Do not eat food at least 2 hours before and 2 hours after taking your medicine to give a minimum 4 hours fast. Take at the same time each day.

Swallow the capsule whole. Do not cut, crush, or chew the capsule.

Read the package leaflet before use.

Oral use.

Take Galafold capsule every other day and punch out the perforated circle on the blister sleeve on the days you are not taking Galafold.

Instructions to open

1. PRESS and hold tab at the left
2. PULL out card on the right
3. PUSH capsule through the foil
4. PUSH card back into holder

To access the package leaflet, scan the code below.

QR code to be included + [www.galafoldsmpc.co.uk](http://www.galafoldsmpc.co.uk)

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amicus Therapeutics UK Ltd  
Phoenix House,  
Oxford Road,  
Tatling End,  
Gerrards Cross,  
Buckinghamshire  
SL9 7AP  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1082/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

galafold 123 mg hard capsules

**MINIMUM PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING**

**BLISTER SLEEVE**

**1. NAME OF THE MEDICINAL PRODUCT**

Galafold 123 mg hard capsules  
migalastat

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Amicus Therapeutics UK, Ltd

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

LOT:

**5. OTHER**

See package leaflet for further instructions.

Punch out the perforated circles on days you are not taking Galafold.

Galafold is to be taken every other day.

Starting date:



**MINIMUM PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

**3. EXPIRY DATE**

**4. BATCH NUMBER**

LOT:

**5. OTHER**

## **B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Galafold 123 mg hard capsules

Migalastat

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Galafold is and what it is used for
2. What you need to know before you take Galafold
3. How to take Galafold
4. Possible side effects
5. How to store Galafold
6. Contents of the pack and other information

#### 1. What Galafold is and what it is used for

Galafold contains the active substance migalastat.

This medicine is used for the long-term treatment of Fabry disease in adults and adolescents aged 16 years and older who have certain genetic mutations (changes).

Fabry disease is caused by the lack of or a faulty enzyme called alpha-galactosidase A ( $\alpha$ -Gal A). Depending upon the kind of mutation (change) in the gene that produces  $\alpha$ -Gal A, the enzyme does not work properly or is completely absent. This enzyme defect leads to abnormal deposits of a fatty substance known as globotriaosylceramide (GL-3) in kidneys, heart, and other organs, leading to the symptoms of Fabry disease.

This medicine works by stabilising the enzyme that your body produces naturally, so that it can work better to reduce the amount of GL-3 that has accumulated in your cells and tissues.

#### 2. What you need to know before you take Galafold

##### Do not take Galafold if you:

- are allergic to migalastat or any of the other ingredients of this medicine (listed in section 6)

##### Warnings and precautions

Talk to your doctor before taking Galafold if you are currently taking enzyme replacement therapy. You should not take Galafold if you are also receiving enzyme replacement therapy.

Your doctor will monitor your condition and whether your medicine is working every 6 months while you are taking Galafold. If your condition worsens, your doctor may evaluate you further or may discontinue your treatment with Galafold.

**Children and adolescents**

This medicine has not been studied in children and adolescents under the age of 16 years; therefore, the safety and efficacy in this age group has not been established.

**Other medicines and Galafold**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines because certain other medicines may increase or decrease the amount of Galafold in your body.

**Pregnancy, breast-feeding, and fertility***Pregnancy*

There is very limited experience with the use of this medicine in pregnant women. If you are pregnant, think you may be pregnant, or are planning to have a baby, do not take this medicine until you have checked with your doctor, pharmacist, or nurse. While taking Galafold you should use effective birth control.

*Breast-feeding*

Do not take this medicine if you are breast-feeding, until you have spoken with your doctor, pharmacist, or nurse. It is not yet known whether this medicine passes into breast milk. Your doctor will decide whether you need to stop breast-feeding or temporarily stop your medicine.

*Fertility in men*

It is not yet known if this medicine affects fertility in men. The effects of Galafold on fertility in humans have not been studied.

*Fertility in women*

It is not yet known if this medicine affects fertility in women.

If you are planning to have a baby, ask your doctor, pharmacist, or nurse for advice.

**Driving and using machines**

It is unlikely that this medicine will affect your ability to drive and use machines.

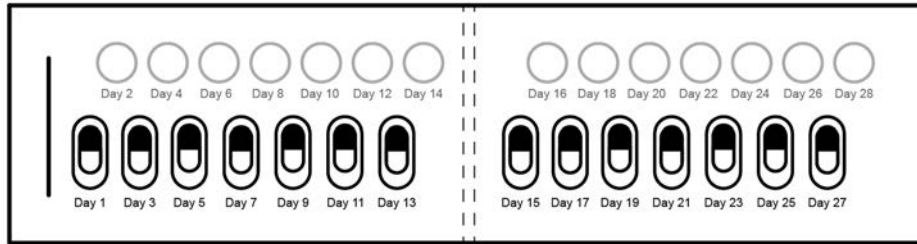
**3. How to take Galafold**

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

Take one capsule every other day at the same time of the day. Do not take Galafold on two consecutive days.

. Do not eat food at least 2 hours before and 2 hours after taking your medicine. This minimum 4 hours fast around taking your medicine is needed to allow your medicine to be fully absorbed. Clear liquids, including carbonated drinks, can be consumed during this period.

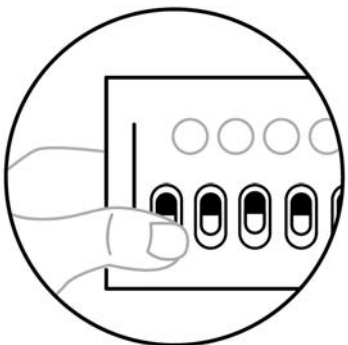
Swallow the capsule whole. Do not cut, crush, or chew the capsule.



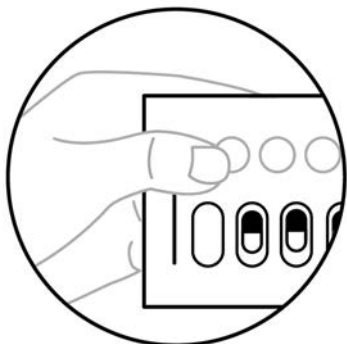
One Galafold blister sleeve = 14 hard capsules = 28 days of therapy



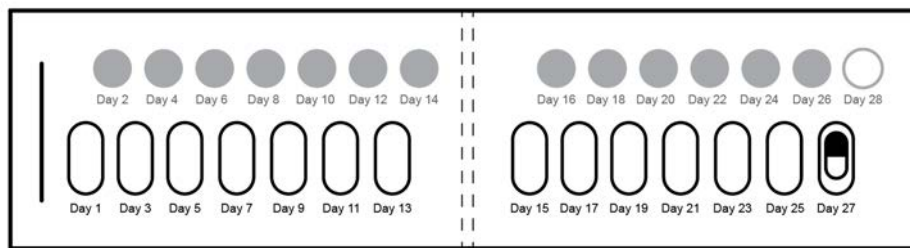
On your first day of taking this medicine from a new blister sleeve, record the date on the blister sleeve.



Then, punch out the left-most capsule labelled Day 1.



On the next day, punch out the perforated white circle labelled Day 2. This will help you remember which day you did not take the medicine. You should only take Galafold once every other day.



After Day 2, continue moving right on the blister sleeve.  
Alternate daily between taking the capsule on odd numbered days and punching out the perforated white circles on even numbered days, up to and including day 28.

### **If you take more Galafold than you should**

If you take more capsules than you should, then you should stop taking the medicine and contact your doctor. You may get a headache and feel dizzy.

### **If you forget to take Galafold**

If you forget to take your capsule at the usual time but remember later, you can take the capsule only if it is within 12 hours of your normal dosing time. If more than 12 hours has passed you should resume taking Galafold at the next planned dosing day and time according to your every other day dosing schedule.. Do not take two capsules to make up for your missed dose.

### **If you stop taking Galafold**

Do not stop taking this medicine without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common:** may affect more than 1 in 10 people

- Headache

**Common:** may affect up to 1 in 10 people

- |  |  |                              |
|--|--|------------------------------|
| • Palpitations (the feeling of a pounding heart)         | • Muscle spasms                                      | • Rash                       |
| • Sensation of spinning (vertigo)                        | • Muscle pain (myalgia)                              | • Persistent itch (pruritus) |
| • Diarrhoea  | • Painful stiff neck (torticollis)                   | • Pain                       |
| • Feeling sick (nausea)                                  | • Tingling in extremities (paraesthesia)             |                              |
| • Stomach ache   | • Dizziness  |                              |
| • Constipation   | • Reduced sense of touch or sensation (hypoesthesia) |                              |
| • Dry mouth  | • Depression   |                              |
| • Sudden need to defecate                                | • Protein in the urine (proteinuria)                 |                              |
| • Indigestion (dyspepsia)                                | • Shortness of breath (dyspnoea)                     |                              |
| • Tiredness  | • Nose bleed (epistaxis)                             |                              |
| • raised levels of creatine phosphokinase in blood tests |  |                              |
| • Weight gain  |  |                              |

## Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Galafold

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Galafold contains

- The active substance is migalastat. Each capsule contains migalastat hydrochloride equivalent to 123 mg migalastat
- The other ingredients are:  
Capsule contents: Pregelatinised maize starch and magnesium stearate  
Capsule shell: Gelatin, titanium dioxide, and indigotine  
Printing ink: Shellac, black iron oxide, and potassium hydroxide

### What Galafold looks like and contents of the pack

Opaque, blue, and white hard capsules, marked with “A1001” in black ink, containing white to pale brown powder.

Galafold is available in a blister pack containing 14 capsules.

### Marketing Authorisation Holder

Amicus Therapeutics UK Ltd  
Phoenix House,  
Oxford Road,  
Tatling End,  
Gerrards Cross,  
Buckinghamshire  
SL9 7AP  
United Kingdom  
tel +44 1753 888 567  
fax +44 1753 437 192  
e-mail [info@amicusrx.co.uk](mailto:info@amicusrx.co.uk)

### Manufacturer

Almac Pharma Services Limited  
Seagoe Industrial Estate  
Portadown, Craigavon

BT63 5UA  
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder (if you cannot reach your Amicus representative by phone please contact via the email address listed below):

**België/Belgique/Belgien**

Amicus Therapeutics, UK Ltd  
Tél/Tel: 080079245  
Email: MedInfo@amicusrx.com

**България**

Amicus Therapeutics, UK Ltd  
Тел.: 008001113214  
Email: MedInfo@amicusrx.com

**Česká republika**

Amicus Therapeutics, UK Ltd  
Tel: 800142207  
Email: MedInfo@amicusrx.com

**Danmark**

Amicus Therapeutics, UK Ltd  
Tlf: 80253262  
Email: MedInfo@amicusrx.com

**Deutschland**

Amicus Therapeutics GmbH  
Tel: + 49 89 2488 798 10 & 0800 000 2038  
Email: MedInfo@amicusrx.com

**Eesti**

Amicus Therapeutics, UK Ltd  
Tel: 8000111911  
Email: MedInfo@amicusrx.com

**Ελλάδα**

Amicus Therapeutics, UK Ltd  
Τηλ: 00800126169  
Email: MedInfo@amicusrx.com

**España**

Amicus Therapeutics S.L.U  
Tel: +34 900 941 616  
Email: MedInfo@amicusrx.com

**France**

Amicus Therapeutics SAS  
Tél: +33 800 906 788  
Email: MedInfo@amicusrx.com

**Hrvatska**

Amicus Therapeutics, UK Ltd  
Tel: 0800222452  
Email: MedInfo@amicusrx.com

**Lietuva**

Amicus Therapeutics, UK Ltd  
Tel: 880033167  
Email: MedInfo@amicusrx.com

**Luxembourg/Luxemburg**

Amicus Therapeutics, UK Ltd  
Tél/Tel: 80027003  
Email: MedInfo@amicusrx.com

**Magyarország**

Amicus Therapeutics, UK Ltd  
Tel.: 0680021202  
Email: MedInfo@amicusrx.com

**Malta**

Amicus Therapeutics, UK Ltd  
Tel: 80062674  
Email: MedInfo@amicusrx.com

**Nederland**

Amicus Therapeutics BV  
Tel: + 31 20 235 8510 & 0800 0228399  
Email: MedInfo@amicusrx.com

**Norge**

Amicus Therapeutics, UK Ltd  
Tlf: 80013837  
Email: MedInfo@amicusrx.com

**Österreich**

Amicus Therapeutics, UK Ltd  
Tel: 0800005475  
Email: MedInfo@amicusrx.com

**Polska**

Amicus Therapeutics, UK Ltd  
Tel.: 008001215475  
Email: MedInfo@amicusrx.com

**Portugal**

Amicus Therapeutics, UK Ltd  
Tel: 800812531  
Email: MedInfo@amicusrx.com

**România**

Amicus Therapeutics, UK Ltd  
Tel: + 0808 03 4288, 877-309-5040  
Email: MedInfo@amicusrx.com



**Ireland**

Amicus Therapeutics, UK Ltd  
Tel: 1800936230  
Email: MedInfo@amicusrx.com

**Ísland**

Amicus Therapeutics, UK Ltd  
Sími: 8007634  
Email: MedInfo@amicusrx.com

**Italia**

Amicus Therapeutics S.r.l.  
Tel: 800795572  
Email: MedInfo@amicusrx.com

**Κύπρος**

Amicus Therapeutics, UK Ltd  
Τηλ: 80097595  
Email: MedInfo@amicusrx.com

**Latvija**

Amicus Therapeutics, UK Ltd  
Tel: 80005391  
Email: MedInfo@amicusrx.com

**Slovenija**

Amicus Therapeutics, UK Ltd  
Tel: 080081794  
Email: MedInfo@amicusrx.com

**Slovenská republika**

Amicus Therapeutics, UK Ltd  
Tel: 0800002437  
Email: MedInfo@amicusrx.com

**Suomi/Finland**

Amicus Therapeutics, UK Ltd  
Puh/Tel: 0800917780  
Email: MedInfo@amicusrx.com

**Sverige**

Amicus Therapeutics, UK Ltd  
Tel: 020795493  
Email: MedInfo@amicusrx.com

**United Kingdom**

Amicus Therapeutics, UK Ltd  
Tel: 08082346864 & +44 175 3888 567  
Email: MedInfo@amicusrx.com

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.