PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGALAFOLD™

Migalastat Capsules

123 mg migalastat (as migalastat hydrochloride)

Various alimentary tract and metabolism products

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PrGALAFOLD™

migalastat capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	capsule / 123 mg migalastat (as migalastat hydrochloride)	black printing ink, gelatin, indigotine (FD&C blue 2), magnesium stearate, pregelatinized maize starch, and titanium dioxide

INDICATIONS AND CLINICAL USE

GALAFOLD™ (migalastat) is indicated for long-term treatment of adults with a confirmed diagnosis of Fabry disease [deficiency of α-galactosidase (α-Gal A)] and who have an α-Gal A mutation determined to be amenable by an *in vitro* assay (see **ACTION AND CLINICAL PHARMACOLOGY - Mechanism of Action, Table 4**).

Treatment with GALAFOLD™ should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease.

Clinical data supporting the effectiveness of GALAFOLD™ for the treatment of Fabry disease patients with amenable mutations are limited (see **CLINICAL TRIALS**).

In clinical trials, individual response to GALAFOLD™ treatment varied considerably among patients with amenable mutations. Patients should be assessed for treatment response or failure when initiating GALAFOLD™, and monitored periodically thereafter (every 6 months or more frequently) throughout the treatment (see **WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests**).

Important Limitations of Use:
GALAFOLD™ is not indicated and should not be used in patients with non-amenable mutations (see **ACTION AND CLINICAL PHARMACOLOGY - Mechanism of Action**). Efficacy was not demonstrated in these patients. GALAFOLD™ may result in a net loss of α-Gal A activity in patients with non-amenable mutations, potentially worsening the disease condition.

GALAFOLD™ should not be used concomitantly with enzyme replacement therapy

(see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Geriatrics (> 65 years of age):
Clinical studies of GALAFOLD™ included a small number of patients aged 65 and over. Dosage adjustment is not expected in this population (see **DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age):
The safety and efficacy of GALAFOLD™ in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

CONTRAINDICATIONS

GALAFOLD™ is contraindicated for use in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. (For a complete listing of ingredients, see **DOSAGE FORMS, COMPOSITION and PACKAGING).**

WARNINGS AND PRECAUTIONS

General
GALAFOLD™ is not indicated and should not be used in patients with non-amenable mutations (see **ACTION AND CLINICAL PHARMACOLOGY - Mechanism of Action**).
GALAFOLD™ may result in a net loss of α-Gal A activity in patients with non-amenable mutations, potentially worsening the disease condition.

The patient should be advised to carefully adhere to the recommended dosing regimen of GALAFOLD™ [one 123 mg migalastat capsule every other day (QOD)]. A higher dose or shorter dosing interval may result in a loss of efficacy, potentially worsening the disease condition (see **DOSAGE AND ADMINISTRATION**).

GALAFOLD™ should not be used concomitantly with enzyme replacement therapy (see **DRUG INTERACTIONS – Drug-Drug Interactions**). Limited data suggest that co-administration of a single dose of GALAFOLD™ and a standard enzyme replacement therapy infusion results in increased exposure to agalsidase of up to 5-fold (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Hepatic/Biliary/Pancreatic
The safety and efficacy of GALAFOLD™ have not been studied in subjects with impaired hepatic function. No dosing adjustment of GALAFOLD™ is expected in this population (see **DOSAGE AND ADMINISTRATION - Recommended Dose and Dosage Adjustment - *Patients with Hepatic Impairment*, ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics – *Special Populations and Conditions* – Hepatic Insufficiency**).

Renal
GALAFOLD™ should not be used in patients with severe renal insufficiency, defined as having an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, due to a significant

increase in the exposure to and prolonged half-life of migalastat. This may result in a net loss of α-Gal A activity, potentially worsening the disease condition (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment –** ***Patients with Renal Impairment;*** **ACTION AND CLINICAL PHARMACOLOGY- Pharmacokinetics-*****Special Populations and Conditions*** **- Renal Insufficiency**).

In clinical studies, no reduction in proteinuria was observed in patients treated with GALAFOLD™.

Sexual Health

Fertility:
The effects of GALAFOLD™ on fertility in humans have not been studied. Infertility in male rats was associated with migalastat treatment at exposures below clinically relevant exposures. Complete reversibility was seen after a 4-week non-dosing recovery period (see **TOXICOLOGY**). GALAFOLD™ did not affect fertility in female rats.

Special Populations

Pregnant Women:
GALAFOLD™ should not be used by pregnant women and is not recommended in women of childbearing potential not using contraception.

In nonclinical studies in pregnant rats, it has been shown that migalastat can penetrate the placental:blood barrier.

In pregnant rabbits, developmental toxicity was observed at maternally toxic doses and was evidenced as a dose-related increase in embryo-fetal death, a reduction in mean fetal weights, retarded ossification and slightly increased incidences of other minor skeletal abnormalities (see **TOXICOLOGY**).

Breastfeeding:
GALAFOLD™ should not be used in breast-feeding women. It is not known whether GALAFOLD™ is excreted in human milk. In nonclinical studies, migalastat has been shown to be excreted into the milk of lactating rats. Accordingly, a risk of migalastat exposure to the breast-feeding infant cannot be excluded.

Pediatrics (< 18 years of age):
The safety and efficacy of GALAFOLD™ in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (> 65 years of age):
Clinical studies of GALAFOLD™ included a small number of patients aged 65 and over. Dosage adjustment is not expected in this population (see **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests
Assessment of renal function is recommended prior to the initiation of GALAFOLD™ treatment. GALAFOLD™ should not be used in patients with severe renal insufficiency, defined as an eGFR less than 30 mL/min/1.73 m^2.

In clinical trials, individual response to GALAFOLD™ varied considerably among patients with amenable mutations. Therefore, it is recommended to monitor renal function, echocardiographic parameters, and biochemical markers (plasma Lyso-Gb_3 or urine GL-3) prior to and periodically (every 6 months or more frequently) following the initiation of GALAFOLD™. An increase in plasma lyso-Gb_3 or urine GL-3 during treatment with GALAFOLD™ may be a sign of treatment failure. In case of meaningful clinical deterioration, GALAFOLD™ treatment should be stopped, further clinical assessment initiated and other treatment options should be considered.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most common adverse reaction reported from clinical trials of migalastat was headache, which was experienced by ≥10% of patients who received GALAFOLD™.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile of GALAFOLD™ was assessed in two Phase 3 clinical trials:

- A double-blind, randomized, placebo-controlled study in patients with Fabry disease and predicted to have migalastat-responsive *GLA* mutations (based on a preliminary *in vitro* assay) and who were naïve to enzyme replacement therapy (ERT-naïve trial) (Table 1)
- A randomized, open-label study in patients with Fabry disease predicted to have migalastat-responsive *GLA* mutations and who were previously treated with enzyme replacement therapy (ERT-experienced trial) (Table 2)

Table 1: Incidence of Adverse Drug Reactions Reported in ≥1% of Patients Treated with GALAFOLD™ Versus Placebo for up to 6 Months in a Double-Blind Study (Enzyme Replacement Therapy-Naïve Trial)

System Organ Class/ Preferred Term	GALAFOLD™ 123 mg QOD† N=34 n (%)‡	Placebo† N=33 n (%)‡
Ear and labyrinth disorders	**1 (2.9%)**	**1 (3.0%)**
Vertigo	1 (2.9%)	1 (3.0%)
Gastrointestinal disorders	**6 (17.6%)**	**4 (12.1%)**
Diarrhoea	2 (5.9%)	0
Dry mouth	2 (5.9%)	1 (3.0%)
Nausea	2 (5.9%)	0
Constipation	1 (2.9%)	1 (3.0%)
Defaecation urgency	1 (2.9%)	0
General disorders and administration site conditions	**1 (2.9%)**	**4 (12.1%)**
Inflammation	1 (2.9%)	0
Injury, poisoning, and procedural complications	**1 (2.9%)**	**1 (3.0%)**
Overdose	1 (2.9%)	0
Investigations	**3 (8.8%)**	**0**
Weight increased	2 (5.9%)	0
Blood pressure increased	1 (2.9%)	0
Musculoskeletal and connective tissue disorders	**3 (8.8%)**	**1 (3.0%)**
Torticollis	2 (5.9%)	0
Muscle spasms	1 (2.9%)	1 (3.0%)
Myalgia	1 (2.9%)	0
Nervous system disorders	**4 (11.8%)**	**3 (9.1%)**
Paraesthesia	2 (5.9%)	0
Dizziness	1 (2.9%)	0
Headache	1 (2.9%)	3 (9.1%)
Hyperaesthesia	1 (2.9%)	0
Hypoaesthesia	1 (2.9%)	0
Psychiatric disorders	**2 (5.9%)**	**1 (3.0%)**
Depression	1 (2.9%)	0

System Organ Class/ Preferred Term	GALAFOLD™ 123 mg QOD† N=34 n (%)‡	Placebo† N=33 n (%)‡
Insomnia	1 (2.9%)	1 (3.0%)
Respiratory, thoracic, and mediastinal disorders	**2 (5.9%)**	**2 (6.1%)**
Epistaxis	2 (5.9%)	1 (3.0%)
Skin and subcutaneous tissue disorders	**1 (2.9%)**	**0**
Rash	1 (2.9%)	0

†Once every other day
‡Percentages are calculated based on the total number of patients treated with the same dose/regimen

Table 2: Incidence of Adverse Drug Reactions Reported in ≥1% of Patients Treated with GALAFOLD™ Versus Enzyme-Replacement Therapy (ERT) for up to 18 Months in an Open-Label Study (Enzyme Replacement Therapy - Experienced Trial)

System Organ Class/ Preferred Term	GALAFOLD™ 123 mg QOD† N=36 n (%)‡	Enzyme Replacement Therapy N=21 n (%)‡
Cardiac disorders	**1 (2.8%)**	**0**
Palpitations	1 (2.8%)	0
Eye disorders	**1 (2.8%)**	**0**
Eye pruritus	1 (2.8%)	0
Gastrointestinal disorders	**10 (27.8%)**	**1 (4.8%)**
Diarrhoea	3 (8.3%)	0
Abdominal pain	2 (5.6%)	0
Dyspepsia	2 (5.6%)	0
Nausea	2 (5.6%)	0
Change of bowel habit	1 (2.8%)	0
Dry mouth	1 (2.8%)	1 (4.8%)
Irritable bowel syndrome	1 (2.8%)	0
General disorders and administration site conditions	**4 (11.1%)**	**2 (9.5%)**
Fatigue	1 (2.8%)	1 (4.8%)
Influenza like illness	1 (2.8%)	0

System Organ Class/ Preferred Term	GALAFOLD™ 123 mg QOD† N=36 n (%)‡	Enzyme Replacement Therapy N=21 n (%)‡
Local swelling	1 (2.8%)	0
Oedema peripheral	1 (2.8%)	0
Pyrexia	1 (2.8%)	0
Investigations	**5 (13.9%)**	**1 (4.8%)**
Blood creatinine phosphokinase increased	2 (5.6%)	0
Blood bilirubin increased	1 (2.8%)	0
Body temperature increased	1 (2.8%)	0
Liver function test abnormal	1 (2.8%)	0
Weight decreased	1 (2.8%)	0
Weight increased	1 (2.8%)	0
White blood cell count decreased	1 (2.8%)	0
Metabolism and nutrition disorders	**1 (2.8%)**	**0**
Hypoglycaemia	1 (2.8%)	0
Musculoskeletal and connective tissue disorders	**3 (8.3%)**	**0**
Flank pain	1 (2.8%)	0
Musculoskeletal chest pain	1 (2.8%)	0
Myalgia	1 (2.8%)	0
Pain in extremity	1 (2.8%)	0
Nervous system disorders	**8 (22.2%)**	**0**
Headache	6 (16.7%)	0
Dizziness	2 (5.6%)	0
Ataxia	1 (2.8%)	0
Paraesthesia	1 (2.8%)	0
Psychiatric disorders	**1 (2.8%)**	**0**
Sleep disorder	1 (2.8%)	0
Respiratory, thoracic, and mediastinal disorders	**2 (5.6%)**	**1 (4.8%)**
Dyspnoea	1 (2.8%)	0
Rhinorrhoea	1 (2.8%)	0
Skin and subcutaneous tissue disorders	**3 (8.3%)**	**0**

System Organ Class/ Preferred Term	GALAFOLD™ 123 mg QOD† N=36 n (%)‡	Enzyme Replacement Therapy N=21 n (%)‡
Hyperhidrosis	1 (2.8%)	0
Night sweats	1 (2.8%)	0
Pruritus	1 (2.8%)	0
Psoriasis	1 (2.8%)	0
Rash	1 (2.8%)	0

†Once every other day
‡Percentages are calculated based on the total number of patients treated with the same dose/regimen

Adverse drug reactions reported during long-term treatment with GALAFOLD™ (mean duration of treatment of approximately 43 months, n=85) were generally in line with those reported during short-term treatment. In addition to the adverse drug reactions listed in Table 1 and Table 2, the following adverse drug reactions were reported: Glomerular filtration rate decreased, urinary tract infection, vitamin D deficiency (2% each), abdominal pain upper, arthralgia, atrial fibrillation, back pain, bile duct stone, biliary dilatation, chest discomfort, hematochezia, hot flush, movement disorder, mucosal dryness, muscular weakness, myocardial ischemia, proteinuria (1% each).

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Clinical trial adverse drug reactions reported in less than 1% of patients in a combined analysis of patients treated with GALAFOLD™ from the two Phase 3 clinical trials (the ERT-naïve trial and the ERT-experienced) for up to 24 months and not reported in either Table 1 or Table 2 were:

Eye disorders: Eye pruritus, visual acuity reduced

Gastrointestinal disorders: Abdominal discomfort, abdominal pain upper, faecal incontinence, vomiting

General disorders and administration site conditions: Feeling hot, hunger, pain

Hepatobiliary disorders: Hepatocellular injury

Investigations: Blood calcium decreased, blood cholesterol increased

Metabolism and nutrition disorders: Decreased appetite

Musculoskeletal and connective tissue disorders: Muscle twitching

Nervous system disorders: Balance disorder, memory impairment, migraine, neuralgia, somnolence, tremor

Renal and urinary disorders: Pollakiuria

Skin and subcutaneous tissue disorders: Erythema

Vascular disorders: Systolic hypertension

Abnormal Hematologic and Clinical Chemistry Findings
Blood Creatinine Phosphokinase Increased, Liver Function Test Abnormal, Blood Bilirubin Increased, Blood Cholesterol Increased, Blood Calcium Decreased, White Blood Cell Count Decreased, all occurred with a frequency of ≥ 1%.

Post-Market Adverse Drug Reactions
Not applicable

DRUG INTERACTIONS

Overview
GALAFOLD™ is not intended for concomitant use with enzyme replacement therapy. GALAFOLD™ increased exposure to agalsidase by up to 5-fold.

Drug-Drug Interactions

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
agalsidase	CT	Single dose of GALAFOLD™ increased exposure to agalsidase by up to 5-fold. Agalsidase had no effect on the pharmacokinetics of migalastat.	GALAFOLD™ is not intended for concomitant use with enzyme replacement therapy.

CT = Clinical Trial

Based upon *in vitro* data, migalastat is not an inducer of CYPIA2, 2B6, or 3A4. Furthermore, migalastat is not an inhibitor or a substrate of CYPIA2, 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, OCT2, MATE1, or MATE2-K human uptake transporters.

Drug-Food Interactions
There are no identified specific drug-food interactions.

Drug-Herb Interactions
The effects of herbal products on the pharmacokinetics of migalastat have not been studied.

Drug-Lifestyle Interactions
The effect of GALAFOLD™ on the ability to drive and use machines has not been established.

The effects of smoking, diet, and alcohol use on the pharmacokinetics of GALAFOLD™ have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Treatment with GALAFOLD™ should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease.

Recommended Dose and Dosage Adjustment
The recommended dosage regimen of GALAFOLD™ in adults 18 years and older is 123 mg migalastat (1 capsule) once every other day at the same time of day. A higher dose or shorter dosing interval may result in a loss of efficacy, potentially worsening the disease condition (see **DETAILED PHARMACOLOGY** – **Pharmacodynamics-*Clinical Studies***).

Elderly population (> 65 years of age)
No dosage adjustment is expected in this population (see **ACTION AND CLINICAL PHARMACOLOGY** – **Pharmacokinetics – *Special Populations and Conditions*- Geriatrics*)***

Patients with Renal Impairment
GALAFOLD™ should not be used in patients with severe renal insufficiency defined as an eGFR less than 30 mL/min/1.73 m^2 (see **WARNINGS AND PRECAUTIONS** – **Renal**, **ACTION AND CLINICAL PHARMACOLOGY** – **Pharmacokinetics – *Special Populations and Conditions* – Renal Insufficiency**).

Patients with Hepatic Impairment
No dosing adjustment of GALAFOLD™ is expected in these patients (see **WARNINGS AND PRECAUTIONS** – **Hepatic/Biliary/Pancreatic, ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics – *Special Populations and Conditions* – Hepatic Insufficiency**).

Missed Dose

GALAFOLD™ should not be taken on 2 consecutive days. If a dose is missed, patients should resume taking GALAFOLD™ at the next dosing day and time.

Administration
For oral use. GALAFOLD™ exposure is decreased by approximately 40% when taken with food, therefore it should not be taken within 2 hours before and after food (see **DRUG INTERACTIONS - Drug-Food Interactions**). 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.

OVERDOSAGE
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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the gene encoding lysosomal hydrolase α-galactosidase A (α-Gal A). More than 800 different mutations in the α-Gal A gene have been reported in Fabry disease patients. Of these, more than 60% are missense mutations that result in a single amino acid substitution. Many of the mutated proteins are fully or partially catalytically competent but are structurally unstable, resulting in reduced levels in the lysosomes for breaking down GL-3 and other lipid substrates. Protein instability varies significantly among different mutant forms of α-Gal A proteins.

Migalastat, an analog of the terminal galactose of GL-3, is a specific potent reversible competitive inhibitor of human α-Gal A. It is also a specific structural stabilizer for the wild-type and many mutant forms of α-Gal A. The net biochemical and clinical effects of migalastat in Fabry disease patients initially involves intracellular accumulation of migalastat-stabilized *and* inhibited α-Gal A enzyme, followed by the recovery of activity of accumulated α-Gal A after migalastat drops to a sub-inhibitory level due to pharmacokinetic elimination. The efficacy of migalastat depends on a net increase of α-Gal A activity resulting from a sufficiently high level of accumulation of the migalastat-inhibited enzyme *and* an adequate duration for recovery of enzyme activity during the dosing interval.

The genotype of α-Gal A determines the nature and extent of the clinical response to GALAFOLD™ in Fabry disease patients. For amenable genotypes, the extent of the migalastat-induced accumulation of the α-Gal A protein can vary significantly. Therefore, response to GALAFOLD™ can differ according to the specific amenable mutation. For non-amenable genotypes, GALAFOLD™ may result in a net loss of α-Gal A activity, potentially

worsening the disease condition.

GALAFOLD™ is only indicated in patients with Fabry disease who have an amenable mutation as listed in Table 4. A mutation is determined to be amenable by a Good Laboratory Practice (GLP)-validated *in vitro* assay (see **DETAILED PHARMACOLOGY – Pharmacodynamics – GALAFOLD™ *Amenability***). The *GLA* mutations not amenable to treatment with GALAFOLD™ are listed in Table 5. The *GLA* mutations are also accessible by health care providers at www.galafoldamenabilitytable.com.

Phase 3 clinical studies were conducted in patients with Fabry disease having 43 (approximately 16%) of the amenable mutations listed in Table 4. Predictability of the extent of clinical-outcome in amenable patients is limited.

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 4 (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 4.

Table 4: GALAFOLD™ (migalastat) Amenability Table

Nucleotide Change	Nucleotide Change	Protein Sequence Change
c.8T>C	c.T8C	L3P
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.58G>C	c.G58C	A20P
c.59C>A	c.C59A	A20D
c.70T>C	c.T70C	W24R
c.70T>G	c.T70G	W24G
c.72G>C	c.G72C	W24C
c.95T>C	c.T95C	L32P
c.97G>T	c.G97T	D33Y
c.98A>G	c.A98G	D33G
c.101A>G	c.A101G	N34S
c.102T>G	c.T102G	N34K
c.103G>C	c.G103C	G35R
c.107T>C	c.T107C	L36S
c.107T>G	c.T107G	L36W
c.108G>C	c.G108C	L36F
c.109G>A	c.G109A	A37T
c.110C>T	c.C110T	A37V
c.122C>T	c.C122T	T41I
c.124A>C	c.A124C	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.137A>C	c.A137C	H46P
c.142G>C	c.G142C	E48Q
c.152T>A	c.T152A	M51K
c.153G>A	c.G153A	M51I
c.157A>G	c.A157G	N53D
c.[157A>C; 158A>T]	c.A157C/A158T	N53L
c.160C>T	c.C160T	L54F
c.161T>C	c.T161C	L54P
c.164A>T	c.A164T	D55V
c.[164A>T; 170A>T]	c.A164T/A170T	D55V/Q57L
c.167G>T	c.G167T	C56F
c.167G>A	c.G167A	C56Y
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.214A>G	c.A214G	M72V

Table 4: GALAFOLD™ (migalastat) Amenability Table

Nucleotide Change	Nucleotide Change	Protein Sequence Change
c.216G>A	c.G216A	M72I
c.218C>T	c.C218T	A73V
c.227T>C	c.T227C	M76T
c.247G>A	c.G247A	D83N
c.253G>A	c.G253A	G85S
c.254G>A	c.G254A	G85D
c.[253G>A; 254G>T; 255T>G]	c.G253A/G254T/T255G	G85M
c.265C>T	c.C265T	L89F
c.272T>C	c.T272C	I91T
c.288G>A	c.G288A	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.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>C	c.T337C	F113L
c.352C>T	c.C352T	R118C
c.361G>A	c.G361A	A121T
c.368A>G	c.A368G	Y123C
c.374A>T	c.A374T	H125L
c.376A>G	c.A376G	S126G
c.383G>A	c.G383A	G128E
c.404C>T	c.C404T	A135V
c.408T>A	c.T408A	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.436C>T	c.C436T	P146S
c.455A>G	c.A455G	Y152C
c.466G>A	c.G466A	A156T
c.467C>T	c.C467T	A156V
c.484T>G	c.T484G	W162G
c.493G>C	c.G493C	D165H
c.494A>G	c.A494G	D165G
c.[496C>G; 497T>G]	c.C496G/T497G	L166G
c.496C>G	c.C496G	L166V
c.506T>C	c.T506C	F169S
c.520T>C	c.T520C	C174R
c.520T>G	c.T520G	C174G
c.525C>G	c.C525G	D175E
c.548G>C	c.G548C	G183A
c.548G>A	c.G548A	G183D

Table 4: GALAFOLD™ (migalastat) Amenability Table

Nucleotide Change	Nucleotide Change	Protein Sequence Change
c.550T>A	c.T550A	Y184N
c.551A>G	c.A551G	Y184C
c.553A>G	c.A553G	K185E
c.559A>G	c.A559G	M187V
c.560T>C	c.T560C	M187T
c.561G>T	c.G561T	M187I
c.559_564dup	c.559_564dup	p.M187_S188dup
c.572T>A	c.T572A	L191Q
c.581C>T	c.C581T	T194I
c.584G>T	c.G584T	G195V
c.593T>C	c.T593C	I198T
c.595G>A	c.G595A	V199M
c.596T>G	c.T596G	V199G
c.599A>G	c.A599G	Y200C
c.602C>T	c.C602T	S201F
c.602C>A	c.C602A	S201Y
c.608A>T	c.A608T	E203V
c.609G>C	c.G609C	E203D
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.628C>T	c.C628T	P210S
c.629C>T	c.C629T	P210L
c.638A>T	c.A638T	K213M
c.640C>T	c.C640T	P214S
c.641C>T	c.641T	P214L
c.643A>G	c.A643G	N215D
c.644A>G	c.A644G	N215S
c.[644A>G; 937G>T]	c.A644G/G937T	N215S/D313Y
c.646T>G	c.T646G	Y216D
c.647A>G	c.A647G	Y216C
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.671A>G	c.A671G	N224S
c.673C>G	c.C673G	H225D
c.683A>G	c.A683G	N228S
c.687T>A	c.T687A	F229L
c.695T>C	c.T695C	I232T
c.713G>A	c.G713A	S238N
c.716T>C	c.T716C	I239T
c.724A>T	c.A724T	I242F
c.725T>A	c.T725A	I242N
c.729G>C	c.G729C	L243F

Table 4: GALAFOLD™ (migalastat) Amenability Table

Nucleotide Change	Nucleotide Change	Protein Sequence Change
c.728T>G	c.T728G	L243W
c.730G>A	c.G730A	D244N
c.730G>C	c.G730C	D244H
c.735T>G	c.T735G	W245G
c.740C>G	c.C740G	S247C
c.747C>G	c.C747G	N249K
c.749A>C	c.A749C	Q250P
c.758T>C	c.T758C	I253T
c.758T>G	c.T758G	I253S
c.760_762delGTT	c.760_762delGTT	p.V254del
c.769G>C	c.G769C	A257P
c.770C>G	c.C770G	A257G
c.772G>C	c.G772C	G258R
c.773G>T	c.G773T	G258V
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.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.811G>A	c.G811A	G271S
c.[811G>A; 937G>T]	c.G811A/G937T	G271S/D313Y
c.812G>A	c.G812A	G271D
c.827G>A	c.G827A	S276N
c.829T>G	c.T829G	W277G
c.831G>T	c.G831T	W277C
c.835C>G	c.C835G	Q279E
c.838C>A	c.C838A	Q280K
c.840A>T	c.A840T	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.862G>C	c.G862C	A288P
c.866T>G	c.T866G	I289S
c.868A>C	c.A868C	M290L
c.870G>A	c.G870A	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

Table 4: GALAFOLD™ (migalastat) Amenability Table

Nucleotide Change	Nucleotide Change	Protein Sequence Change
c.886A>T	c.A886T	M296L
c.887T>C	c.T887C	M296T
c.888G>A	c.G888A	M296I
c.893A>G	c.A893G	N298S
c.897C>G	c.C897G	D299E
c.898C>T	c.C898T	L300F
c.899T>C	c.T899C	L300P
c.901C>G	c.C901G	R301G
c.902G>C	c.G902C	R301P
c.902G>A	c.G902A	R301Q
c.902G>T	c.G902T	R301L
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.924A>T	c.A924T	K308N
c.925G>C	c.G925C	A309P
c.928C>T	c.C928T	L310F
c.931C>G	c.C931G	L311V
c.935A>G	c.A935G	Q312R
c.936G>T	c.G936T	Q312H
c.937G>T	c.G937T	D313Y
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
c.956T>C	c.T956C	I319T
c.959A>T	c.A959T	N320I
c.962A>G	c.A962G	Q321R
c.962A>T	c.A962T	Q321L
c.963G>C	c.G963C	Q321H
c.964G>A	c.G964A	D322N
c.966C>A	c.C966A	D322E
c.973G>A	c.G973A	G325S
c.973G>C	c.G973C	G325R
c.979C>G	c.C979G	Q327E
c.983G>C	c.G983C	G328A
c.1001G>A	c.G1001A	G334E
c.1012G>A	c.G1012A	E338K
c.1016T>A	c.T1016A	V339E
c.1028C>T	c.C1028T	P343L
c.1033T>C	c.T1033C	S345P
c.1046G>C	c.G1046C	W349S
c.1055C>T	c.C1055T	A352V
c.1061T>A	c.T1061A	I354K
c.1066C>G	c.C1066G	R356G

Table 4: GALAFOLD™ (migalastat) Amenability Table		
Nucleotide Change	Nucleotide Change	Protein Sequence Change
c.1066C>T	c.C1066T	R356W
c.1067G>A	c.G1067A	R356Q
c.1067G>C	c.G1067C	R356P
c.1073A>C	c.A1073C	E358A
c.1073A>G	c.A1073G	E358G
c.1074G>T	c.G1074T	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
c.1153A>G	c.A1153G	T385A
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>G	c.C1225G	P409A
c.1225C>T	c.C1225T	P409S
c.1225C>A	c.C1225A	P409T
c.1228A>G	c.A1228G	T410A
c.1229C>T	c.C1229T	T410I
c.1232G>A	c.G1232A	G411D
c.1235C>A	c.C1235A	T412N
c.1253A>G	c.A1253G	E418G
c.1261A>G	c.A1261G	M421V

The mutations not amenable to treatment with GALAFOLD™ are listed in Table 5 below.

UNKNOWN in the column of ‘protein sequence change’ indicates 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 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.1A>C	*c.A1C*	*M1L*
c.1A>G	*c.A1G*	*M1V*
c.2T>G	*c.T2G*	*M1R*
c.2T>C	*c.T2C*	*M1T*
c.2T>A	*c.T2A*	*M1K*
c.3G>A	*c.G3A*	*M1I*
c.19G>T	*c.G19T*	*E7X*
c.41T>C	*c.T41C*	*L14P*
c.43G>C	*c.G43C*	*A15P*
c.47T>A	*c.T47A*	*L16H*
c.47T>C	*c.T47C*	*L16P*
c.53T>C	*c.T53C*	*F18S*
c.56T>A	*c.T56A*	*L19Q*
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	*c.G71A*	*W24X*
c.92C>T	*c.C92T*	*A31V*
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>C	*c.G127C*	*G43R*
c.127G>A	*c.G127A*	*G43S*
c.128G>A	*c.G128A*	*G43D*
c.128G>T	*c.G128T*	*G43V*
c.131G>A	*c.G131A*	*W44X*
c.132G>T	*c.G132T*	*W44C*
c.134T>C	*c.T134C*	*L45P*
c.134T>G	*c.T134G*	*L45R*
c.134_138delTGCACinsGCTCG	*c.134_138delTGCACinsGCTCG*	*L45R/H46S*
c.136C>T	*c.C136T*	*H46Y*
c.137A>T	*c.A137T*	*H46L*
c.137A>G	*c.A137G*	*H46R*
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	*c.G141C*	*W47C*
c.139T>C	*c.T139C*	*W47R*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.142G>A	*c.G142A*	*E48K*
c.144G>T	*c.G144T*	*E48D*
c.145C>T	*c.C145T*	*R49C*
c.145C>A	*c.C145A*	*R49S*
c.146G>T	*c.G146T*	*R49G*
c.146G>C	*c.G146C*	*R49P*
c.146G>T	*c.G146T*	*R49L*
c.149T>G	*c.T149G*	*F50C*
c.154T>G	*c.T154G*	*C52G*
c.154T>C	*c.T154C*	*C52R*
c.155G>C	*c.G155C*	*C52S*
c.155G>A	*c.G155A*	*C52Y*
c.156C>A	*c.C156A*	*C52X*
c.156C>G	*c.C156G*	*C52W*
c.166T>G	*c.T166G*	*C56G*
c.167G>C	*c.G167C*	*C56S*
c.168C>A	*c.C168A*	*C56X*
c.187T>C	*c.T187C*	*C63R*
c.188G>A	*c.G188A*	*C63Y*
c.188G>C	*c.G188C*	*C63S*
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.202C>T	*c.C202T*	*L68F*
c.215T>G	*c.T215G*	*M72R*
c.218C>A	*c.C218A*	*A73E*
c.227T>G	*c.T227G*	*M76R*
c.233C>G	*c.C233G*	*S78X*
c.235G>T	*c.G235T*	*E79X*
c.241T>C	*c.T241C*	*W81R*
c.242G>A	*c.G242A*	*W81X*
c.242G>C	*c.G242C*	*W81S*
c.243G>T	*c.G243T*	*W81C*
c.244A>T	*c.A244T*	*K82X*
c.256T>G	*c.T256G*	*Y86D*
c.256T>C	*c.T256C*	*Y86H*
c.257A>G	*c.A257G*	*Y86C*
c.258T>G	*c.T258G*	*Y86X*
c.262T>G	*c.T262G*	*Y88D*
c.266T>C	*c.T266C*	*L89P*
c.266T>G	*c.T266G*	*L89R*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.268T>C	*c.T268C*	*C90R*
c.269G>A	*c.G269A*	*C90Y*
c.270C>A	*c.C270A*	*C90X*
c.274G>C	*c.G274C*	*D92H*
c.274G>A	*c.G274A*	*D92N*
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	*c.C279G*	*D93E*
c.280T>G	*c.T280G*	*C94G*
c.281G>C	*c.G281C*	*C94S*
c.281G>A	*c.G281A*	*C94Y*
c.284G>A	*c.G284A*	*W95X*
c.284G>T	*c.G284T*	*W95L*
c.284G>C	*c.G284C*	*W95S*
c.295C>T	*c.C295T*	*Q99X*
c.299G>A	*c.G299A*	*R100K*
c.299G>C	*c.G299C*	*R100T*
c.305C>G	*c.C305G*	*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.334C>T	*c.C334T*	*R112C*
c.334C>A	*c.C334A*	*R112S*
c.338T>C	*c.T338C*	*F113S*
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.361G>C	*c.G361C*	*A121P*
c.371T>A	*c.T371A*	*V124D*
c.374A>C	*c.A374C*	*H125P*
c.379A>T	*c.A379T*	*K127X*
c.386T>C	*c.T386C*	*L129P*
c.389A>G	*c.A389G*	*K130R*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.392T>C	*c.T392C*	*L131P*
c.394G>A	*c.G394A*	*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	*c.T402G*	*Y134X*
c.406G>C	*c.G406C*	*D136H*
c.406G>T	*c.G406T*	*D136Y*
c.412G>A	*c.G412A*	*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*
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	*c.G439A*	*G147R*
c.440G>A	*c.G440A*	*G147E*
c.443G>A	*c.G443A*	*S148N*
c.444T>G	*c.T444G*	*S148R*
c.453C>G	*c.C453G*	*Y151X*
c.456C>A	*c.C456A*	*Y152X*
c.463G>C	*c.G463C*	*D155H*
c.467C>A	*c.C467A*	*A156D*
c.469C>T	*c.C469T*	*Q157X*
c.484T>C	*c.T484C*	*W162R*
c.485G>A	*c.G485A*	*W162X*
c.485G>T	*c.G485T*	*W162L*
c.486G>C	*c.G486C*	*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.500T>A	*c.T500A*	*L167Q*
c.500T>C	*c.T500C*	*L167P*
c.503A>G	*c.A503G*	*K168R*
c.504A>C	*c.A504C*	*K168N*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
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>G	*c.T514G*	*C172G*
c.514T>C	*c.T514C*	*C172R*
c.515G>C	*c.G515C*	*C172S*
c.515G>T	*c.G515T*	*C172F*
c.515G>A	*c.G515A*	*C172Y*
c.516T>G	*c.T516G*	*C172W*
c.519C>A	*c.C519A*	*Y173X*
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.557A>C	*c.A557C*	*H186P*
c.560T>G	*c.T560G*	*M187R*
c.572T>C	*c.T572C*	*L191P*
c.605G>A	*c.G605A*	*C202Y*
c.604T>C	*c.T604C*	*C202R*
c.606T>G	*c.T606G*	*C202W*
c.607G>A	*c.G607A*	*E203K*
c.611G>A or 612G>A	*c.G611A or G612A*	*W204X*
c.612G>T	*c.G612T*	*W204C*
c.614C>G	*c.C614G*	*P205R*
c.617T>C	*c.T617C*	*L206P*
c.620A>G	*c.A620G*	*Y207C*
c.634C>T	*c.C634T*	*Q212X*
c.658C>T	*c.C658T*	*R220X*
c.661C>T	*c.C661T*	*Q221X*
c.666C>A	*c.C666A*	*Y222X*
c.667T>G	*c.T667G*	*C223G*
c.667T>C	*c.T667C*	*C223R*
c.668G>A	*c.G668A*	*C223Y*
c.670A>G	*c.A670G*	*N224D*
c.674A>G	*c.A674G*	*H225R*
c.676T>C	*c.T676C*	*W226R*
c.677G>A	*c.G677A*	*W226X*
c.678G>T	*c.G678T*	*W226C*
c.679C>T	*c.C679T*	*R227X*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
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.700G>T	*c.G700T*	*D234Y*
c.702T>G	*c.T702G*	*D234E*
c.704C>A	*c.C704A*	*S235Y*
c.704C>G	*c.C704G*	*S235C*
c.704C>T	*c.C704T*	*S235F*
c.706T>C	*c.T706C*	*W236R*
c.707G>A	*c.G707A*	*W236X*
c.707G>T	*c.G707T*	*W236L*
c.708G>C	*c.G708C*	*W236C*
c.712A>C	*c.A712C*	*S238R*
c.718A>T	*c.A718T*	*K240X*
c.734G>A or 735G>A	*c.G734A or G735A*	*W245X*
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.782G>A	*c.G782A*	*G261D*
c.782G>T	*c.G782T*	*G261V*
c.785G>A	*c.G785A*	*W262X*
c.785G>T	*c.G785T*	*W262L*
c.786G>C	*c.G786C*	*W262C*
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>C	*c.G796C*	*D266H*
c.796G>T	*c.G796T*	*D266Y*
c.796G>A	*c.G796A*	*D266N*
c.797A>C	*c.A797C*	*D266A*
c.797A>T	*c.A797T*	*D266V*
c.798T>A	*c.T798A*	*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*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.[806T>G,937G>T]	*c.T806G/G937T*	*V269G/D313Y*
c.811G>T	*c.G811T*	*G271C*
c.812G>T	*c.G812T*	*G271V*
c.815A>G	*c.A815G*	*N272S*
c.816C>A	*c.C816A*	*N272K*
c.819T>G	*c.T819G*	*F273L*
c.820G>A	*c.G820A*	*G274S*
c.821G>T	*c.G821T*	*G274V*
c.823C>T	*c.C823T*	*L275F*
c.826A>G	*c.A826G*	*S276G*
c.830G>A	*c.G830A*	*W277X*
c.835C>A	*c.C835A*	*Q279K*
c.836A>G	*c.A836G*	*Q279R*
c.837G>C	*c.G837C*	*Q279H*
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>G	*c.T859G*	*W287G*
c.860G>A or 861G>A	*c.G860A or G861A*	*W287X*
c.861G>C	*c.G861C*	*W287C*
c.863C>A	*c.C863A*	*A288D*
c.865A>T	*c.A865T*	*I289F*
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	*c.T881G*	*L294X*[#]
c.890C>G	*c.C890G*	*S297C*
c.890C>T	*c.C890T*	*S297F*
c.892A>C	*c.A892C*	*N298H*
c.894T>G	*c.T894G*	*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*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.931C>T	*c.C931T*	*L311F*
c.932T>C	*c.T932C*	*L311P*
c.932T>G	*c.T932G*	*L311R*
c.947T>A	*c.T947A*	*V316E*
c.950T>A	*c.T950A*	*I317N*
c.950T>G	*c.T950G*	*I317S*
c.958A>T	*c.A958T*	*N320Y*
c.960T>G	*c.T960G*	*N320K*
c.961C>G	*c.C961G*	*Q321E*
c.961C>T	*c.C961T*	*Q321X*
c.974G>A	*c.G974A*	*G325D*
c.979C>A	*c.C979A*	*Q327K*
c.982G>A	*c.G982A*	*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	*c.T1018C*	*W340R*
c.1020G>A	*c.G1020A*	*W340X*
c.1021G>A	*c.G1021A*	*E341K*
c.1023A >C	*c.A1023C*	*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	*c.C1034G*	*S345X*
c.1042G>C	*c.G1042C*	*A348P*
c.1045T>C	*c.T1045C*	*W349R*
c.1046G>A	*c.G1046A*	*W349X*
c.1048G>C	*c.G1048C*	*A350P*
c.1054G>C	*c.G1054C*	*A352P*
c.1055C>A	*c.C1055A*	*A352D*
c.1065C>A	*c.C1065A*	*N355K*
c.1069C>T	*c.C1069T*	*Q357X*
c.1072G>A	*c.G1072A*	*E358K*
c.1081G>A	*c.G1081A*	*G361R*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.1088G>C	*c.G1088C*	*R363P*
c.1095T>A	*c.T1095A*	*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.1124_1129del	*c.1124_1129del*	*G375_V376del*
c.1129_1140dup	*c.1129_1140dup*	*A377_P380dup*
c.1130C>A	*c.C1130A*	*A377D*
c.1132T>C	*c.T1132C*	*C378R*
c.1133G>A	*c.G1133A*	*C378Y*
c.1144T>C	*c.T1144C*	*C382R*
c.1145G>A	*c.G1145A*	*C382Y*
c.1146C>G	*c.C1146G*	*C382W*
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.1165C>G	*c.C1165G*	*P389A*
c.1166C>G	*c.C1166G*	*P389R*
c.1166C>T	*c.C1166T*	*P389L*
c.1181_1183dup	*c.1181_1183dup*	*L394_G395InsV*
c.1187T>A	*c.T1187A*	*F396Y*
c.1192G>T	*c.G1192T*	*E398X*
c.1196G>A or 1197G>A	*c.G1196A or G1197A*	*W399X*
c.1202C>G	*c.C1202G*	*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.1226_1231del	*c.1226_1231del*	*p.409_410delinsR*
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.1247A>C	*c.A1247C*	*Q416P*
c.1247_1248CT>AA	*c.C1247A/T1248A*	*L417K*
c.1250T>G	*c.T1250G*	*L417R*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
g.941_5845del	*c.1-179_369+577del*	*p.?(Exon1_2del)*
g.?_?del	*c.?_?*	*UNKNOWN (del Exon1_2?)*
c.18delA	*c.18delA*	*p.P6fs114*
c.26delA	*c.26delA*	*p.H9Lfs111*
c.32delG	*c.32delG*	*p.G11Afs109*
c.33delC	*c.33delC*	*p.G11fs109*
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.C12Ffs104*
c.147_148InsCCC	*c.147_148 InsCCC*	*p.49InsP*
c.58_83del	*c.58_83del*	*p.A20_G28delfs2*
c.58_72del	*c.58_72del*	*p.A20_W24del*
c.85dupG	*c.85dupG*	*p.A29Gfs1*
c.123delC	*c.123delC*	*p.T41fs79*
c.123_126dupCATG	*c.123_126dupCATG*	*p.G43Hfs13*
c.124_125del	*c.124_125del*	*p.M42Gfs12*
c.125_137del	*c.125_137del*	*p.M42Tfs74*
c.154delT	*c.154delT*	*p.C52Afs68*
c.162delT	*c.162delT*	*p.L54fs66*
c.181_182dupA	*c.181_182dupA*	*p.D61Efs5*
c.184delT	*c.184delT*	*p.S62Pfs58*
g.2594_10904dup	*c.195-2500_999+197dup*	*UNKNOWN*
g.3422_6041delinsCG	*c.194+2049_369+773del2620insCG*	*UNKNOWN*
g.?_?del	*c.195-?_547+?del*	*UNKNOWN (del Exon2_3?)*
g.?_?dup	*c.?_?dup*	*UNKNOWN (Exon2_4dup?)*
g.2934_6378del	*c.194+1561_370-891del*	*UNKNOWN (E66_Y123del; del Exon2?)*
g.3396_6012del	*c.194+2023_370-1257del*	*UNKNOWN (E66_Y123del; del Exon2?)*
g.3260_6410del	*c.194+1887_370-859del*	*UNKNOWN (E66_Y123del; del Exon2?)*
g.2979_6442del	*c.194+1606_369+1174del*	*UNKNOWN (E66_Y123del; del Exon2)*
c.256delT	*c.256delT*	*p.Y88Mfs42*
g.5106_5919delins231	*c.207_369+651del814ins231*	*UNKNOWN (del Exon2?)*
c.259_276del	*c.259_276del*	*p.87_92del*
c.267_268dupCT	*c.267_268dupCT*	*p.C90Sfs31*
c.270delC	*c.270delC*	*p.C90X*
c.281_286delinsT	*c.281_286delinsT*	*p.C94Ffs26*
c.297_298del	*c.297_298del*	*p.Q99fs22*
c.305delC	*c.305delC*	*p.S102X*
c.317_327del	*c.317_327del*	*p.S102fs16*
c.323_324insCAGA	*c.323_324insCAGA*	*p.D109Rfs14*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.336 del18	*c.336del18*	*p.113del6aa*
c.358del6	*c.358del6*	*p.120del2aa/L120H*
c.363delT	*c.363delT*	*p.A121fs8*
g.5271_9366del4096insT	*c.369+3_639+954del3129insT*	*UNKNOWN (del Exon3 and 4?)*
g.7086_7487del	*c.370-183_547+41del*	*UNKNOWN (del Exon3?)*
g.6736_11545del	*c.370-533_c.1290+277del*	*UNKNOWN (del Exon3_7?)*
g.6009_9741del	*c.369+741_640-390del*	*UNKNOWN (del Exon3 and 4?)*
g.6547_9783del	*c.369+1279_640-348del*	*UNKNOWN (del Exon3 and 4?)*
g.>5.5kb del to 3UTR	*c.?_?del*	*UNKNOWN (del Exon3_3'UTR)*
c.[374A>T;383G>A]	*c.A374T/G383A*	*H125L/G128E*
c.402delT	*c.402delT*	*p.Y134X*
c.409delG	*c.409delG*	*p.V137Lfs27*
c.413dupG	*c.413dupG*	*p.G138fs2*
c.421delA	*c.421delA*	*p.T141Pfs23*
c.426dupC	*c.426dupC*	*p.A143Rfs13*
c.452delA	*c.452delA*	*p.Y151Sfs13*
c.457_459del	*c.457_459del*	*p.153delD*
c.477delT	*c.477delT*	*p.F159Lfs5*
c.486_498del	*c.486_498del*	*p.W162Cfs1*
c.516insGAC	*c.516insGAC*	*p.152 Ins D*
c.520delT	*c.520delT*	*p.C174Vfs17*
c.[604T>C;644A>G]	*c.T604C/A644G*	*p.C202R/N215S*
c.568delG	*c.568delG*	*p.A190Pfs1*
c.590delG	*c.590delG*	*p.S197Tfs42*
c.606delT	*c.606delT*	*p.C202Wfs37*
c.613_621del	*c.613_621del*	*p.205_207del*
c.614delC	*c.614delC*	*p.P205Lfs34*
c.618_619del	*c.618_619del*	*p.L206fs24*
c.621dupT	*c.621dupT*	*p.M208Yfs24*
g.?_?del	*c.?_?del*	*UNKNOWN (del Exon5_7?)*
g.[10237_11932del; 11933_12083inv; 12084_12097del]	*g.[10237_11932del; 11933_12083inv; 12084_12097del]*	*UNKNOWN*
c.646dupT	*c.646dupT*	*p.Y216Lfs15*
c.646delT	*c.646delT*	*p.Y216Ifs23*
c.650_663dup14	*c.650_663dup14*	*p.Q221fs23*
c.672_673ins37	*c.672_673ins37*	*p.H225Tfs18*
c.674_732del	*c.674_732del*	*p.H225Lfs5*
c.678delG	*c.678delG*	*p.A230Lfs9*
c.715_717 del	*c.715_717 del*	*p.I239del*
c.716dupT	*c.716dupT*	*p.I239fs10*
c.718_719del	*c.718_719del*	*p.K240Efs8*
c.719dupA	*c.719dupA*	*p.K240fs9*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.722delG	*c.722delG*	*p.S241Ifs27*
c.723dupT	*c.723dupT*	*p.S238fs8*
c.732delC	*c.732delC*	*p.D244fs24*
c.741ins9	*c.741ins9*	*p.247ins3*
c.744delT	*c.744delT*	*p.F248Lfs20*
c.744_745del	*c.744_745del*	*p.F248Lfs6*
c.746_747del	*c.746_747del*	*p.N249Tfs5*
c.759delT	*c.759delT*	*p.I253Mfs15*
c.760dupG	*c.760dupG*	*p.V254Gfs1*
c.761_762del	*c.761_762del*	*p.V254Gfs9*
c.774_775del	*c.774_775del*	*p.G258fx5*
c.777delA	*c.777delA*	*p.P259fs9*
c.782dupG	*c.782dupG*	*p.G261fs3*
c.807delG	*c.807delG*	*p.V269fs12*
c.833dupA	*c.833dupA*	*p.N278Kfs20*
c.833delA	*c.833delA*	*p.N278Ifs3*
c.842_844del	*c.842_844del*	*p.V281AdelT282*
c.881delT	*c.881delT*	*p.L294Yfs22*
c.892_893insT	*c.892_893insT*	*p.N298I1*
c.893_894insG	*c.893_894insG*	*p.N298Kfs1*
c.902dupG	*c.902dupG*	*p.R301fs13*
c.909_918del	*c.909_918del*	*p.I303Mfx10*
c.914delC	*c.914delC*	*p.P305Lfs11*
c.931delC	*c.931delC*	*p.L311Ffs5*
c.941_961del	*c.941_961del*	*p.D315_Q321del*
c.946delG	*c.946delG*	*p.V316X*
c.950_954dupTTGCC	*c.950_954dupTTGCC*	*p.A318fs31*
c.974dupG	*c.974dupG*	*p.G325fs7*
c.986delA	*c.986delA*	*p.Y329Sfs18*
c.988delC	*c.988delC*	*p.Q330Sfs17*
c.946_966del	*c.946_966del*	*p.V316_D322del*
c.994delA	*c.994delA*	*p.R332Dfs15*
c.996_999del	*c.996_999del*	*p.R332fs14*
c.997dupC	*c.997dupC*	*p.Q333Pfs5*
c.1011_1029del	*c.1011_1029del*	*p.F337fs4*
c.1017_1020delins24	*c.1017_1020delins24*	*p.V339fs7*
c.1017_1027del	*c.1017_1027del*	*p.V339fs5*
c.1021delG	*c.1021delG*	*p.E341Nfs6*
c.1025delG	*c.1025delG*	*p.R342Hfs5*
c.1030_1031insT	*c.1030_1031insT*	*p.L344fs30*
c.1033_1034del	*c.1033_1034del*	*p.S345Rfs28*
c.1037delG	*c.1037delG*	*p.G346Afs1*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.1040dupT	*c.1040dupT*	*p.L347Ffs27*
c.1041dupA	*c.1041dupA*	*p.L347fs27*
c.1042dupG	*c.1042dupG*	*p.A348Gfs26*
c.1043_1044insG	*c.1043_1044insG*	*p.A348fs26*
c.1049delC	*c.1049delC*	*p.A350Vfs1*
c.1151_1152delinsAT	*c.1151_1152delinsAT*	*p.I384N*
c.1055_1057dup	*c.1055_1057dup*	*p.353InsT*
c.1057_1058del	*c.1057_1058del*	*p.M353Dfs20*
c.1072_1074del	*c.1072_1074del*	*p.358delE*
c.1074_1075del	*c.1074_1075del*	*p.E358Dfs15*
c.1077delT	*c.1077delT*	*p.I359Mfs31*
c.1081_1100del	*c.1081_1100del*	*p.G360fs7*
c.1086_1098del	*c.1086_1098del*	*p.P362fs24*
c.1088delG	*c.1088delG*	*p.R363Pfs27*
c.1091_1092del	*c.1091_1092del*	*p.S364Lfs9*
c.1093dupT	*c.1093dupT*	*p.Y365Lfs9*
c.1095delT	*c.1095delT*	*p.Y365X*
c.1096_1100del	*c.1096_1100del*	*p.Y365fs7*
c.1102_1103delinsTTATAC	*c.1102_1103delinsTTATAC*	*p.A368delinsFYfs23*
c.1122_1125del	*c.1122_1125del*	*p.K374fs15*
c.1123_1175del	*c.1123_1175del*	*p.G375_R392del*
c.1139delC	*c.1139delC*	*p.380Lfs10*
c.1145_1149del	*c.1145_1149del*	*p.C382Yfs14*
c.1146_1148del	*c.1146_1148del*	*p.383delF*
c.1156_1157del	*c.1156_1157del*	*p.Q386Afs10*
c.1167dupT	*c.1167dupT*	*p.P389fs9*
c.1168insT	*c.1168insT*	*p.V390fs9*
c.1176_1179del	*c.1176_1179del*	*p.R392Sfs1*
c.1177_1178del	*c.1177_1178del*	*p.K393Afs4*
c.1187dupT	*c.1187dupT*	*p.F396fs2*
c.1187delT	*c.1187delT*	*p.F396Sfs7*
c.1188delC	*c.1188delC*	*p.F396fs7*
c.1201dupT	*c.1201dupT*	*p.S401Ffs49*
c.1208delT	*c.1208delT*	*p.L403X*
c.1208ins21	*c.1208ins21*	*UNKNOWN*
c.1209_1211del	*c.1209_1211del*	*p.404delR*
c.1223delA	*c.1223delA*	*p.N408Ifs9*
c.1235_1236del	*c.1235_1236del*	*p.T412Sfs37*
c.1277_1278del	*c.1277_1278del*	*p.K426Rfs23*
c.1284_1287del	*c.1284_1287del*	*p.L428Ffs23*
c.[359T>C; 361G>A]	*c.T359C/G361A*	*L120P/A121T*
c.[644A>G; 811G>A]	*c.A644G; c.G811A*	*N215S/G271S*

Table 5: Mutations Not Amenable to GALAFOLD™ (migalastat)

Nucleotide Change		*Protein Sequence Change*
c.[644A>G; 811G>A; 937G>T]	*c.A644G/G811A/G937T*	*N215S/G271S/D313Y*
c.790G>T; c.805G>A	*c.G790T/G805A*	*D264Y/V269M*
c.963_964GG>CA	*c.G963C/G964A*	*Q321H/D322N*
c.1288T>C	*c. T1288C*	*X430Q*
IVS1+2T>C	*c.194+2T>C*	*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+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*
IVS3-2A>G	*c.548-2A>G*	*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*
IVS4-1G>T	*c.639-1G>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*
IVS4-11T>A	*c.640-11T>A*	*UNKNOWN*
IVS4-3C>G	*c.640-3C>G*	*UNKNOWN*
IVS4-2A>T	*c.640-2A>T*	*UNKNOWN*
IVS4-1G>A	*c.640-1G>A*	*UNKNOWN*
IVS5+2T>C	*c.801+2T>C*	*UNKNOWN*
IVS5+3A>G	*c.801+3A>G*	*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*
IVS6-2A>G	*c.1000-2A>G*	*UNKNOWN*
IVS6-2A>T	*c.1000-2A>T*	*UNKNOWN*
IVS6-1G>A	*c.1000-1G>A*	*UNKNOWN*
IVS6-1G>C	*c.1000-1G>C*	*UNKNOWN*

Pharmacodynamics
Migalastat is a specific potent reversible competitive inhibitor of human α-Gal A and also a specific structural stabilizer for wild-type and many mutant forms of α-Gal A. Incubation of cells derived from Fabry patients with an amenable mutation or of cells transiently expressing an amenable mutation results in an accumulation of migalastat-inhibited α-Gal A protein in lysosomes. When the concentration of migalastat drops to a sub-inhibitory level, the accumulated α-Gal A regains enzymatic function, resulting in increased enzymatic activity compared to that without migalastat treatment. For non-amenable mutations, migalastat treatment resulted in a limited or no increase in the cellular α-Gal A activity decreased enzymatic activity (see **DETAILED PHARMACOLOGY**-**Pharmacodynamics**).

In Phase 2 pharmacodynamic trials in Fabry patients with amenable mutations, oral treatment with various doses and dosing intervals of migalastat hydrochloride (HCl), including 150 mg QOD, resulted in apparent increases in α-Gal A activity in peripheral blood mononuclear cells (PBMCs), skin, and kidney when assayed in a system where the concentration of migalastat was significantly diluted (see **DETAILED PHARMACOLOGY**-**Pharmacodynamics**). Migalastat HCl dosed at 25 mg to 250 mg BID resulted in a dose-dependent and significant increase in urine GL-3 in most of the patients. However, migalastat HCl 150 mg QOD decreased GL-3 in most patients. Increases in PBMC α-Gal A activity and decreases in GL-3 observed with migalastat HCl 150 mg QOD were not further enhanced when patients switched to higher, less frequent doses (250 and 500 mg, 3 days on/4 days off).

In the Phase 2 and Phase 3 clinical trials, in non-amenable patients, GALAFOLD™ (150 mg migalastat HCl, QOD) resulted in a significant increase from baseline in the levels of plasma lyso-Gb_3 and urine GL-3 in all male patients and 80% of the female patients (see **DETAILED PHARMACOLOGY**-**Pharmacodynamics – *Clinical Studies***).

Cardiac Electrophysiology:
In a randomized, double-blind, double-dummy, positive- and placebo-controlled, four-arm crossover ECG assessment study in healthy subjects (N=52), single 150 mg and 1250 mg doses of migalastat HCl were not observed to have any clinically relevant effect on the QTc interval, the QRS duration, the PR interval, or heart rate.

Pharmacokinetics

The pharmacokinetic parameters obtained following single and multiple dose studies of GALAFOLD™ are presented in Table 6.

Table 6: Summary of Plasma Pharmacokinetic Parameters of Migalastat in Healthy Subjects Following a Single Oral Dose (150 mg) of Migalastat HCl

	C_{max} [a]	t_{max} [b] (h)	$t_{½}$ [c] (h)	$AUC_{0-\infty}$ [a] (ng·hr/mL)	CL/F [c] (L/h)	V_z/F [c] (L)
Mean	1500 to 1600 ng/mL or about 10 µM	3	4	10000 to 13000	4 to 6	77 to 133

[a]Approximate range of means across Phase 1 studies following single 150 mg migalastat HCl dose
[b]Approximate median across Phase 1 studies
[c]Approximate range of means across Phase 1 studies

Absorption: The absolute bioavailability (AUC) for a single oral 150 mg migalastat HCl dose was approximately 75%. Following a single oral dose of 150 mg migalastat HCl 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 HCl oral doses from 50 mg to 1,250 mg.

Migalastat HCl 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. GALAFOLD™ exposure is decreased by approximately 40% when taken with food, therefore it should not be taken within 2 hours before and after food. GALAFOLD™ should be taken every other day at the same time of day to ensure optimal benefits to the patient.

Distribution: In healthy volunteers, the volume of distribution (Vz/F) of migalastat following ascending single oral doses (25-675 mg migalastat HCl) ranged from 77 to 133 L, indicating that it is well distributed into tissues. There was no appreciable plasma protein binding *in vitro* with [^{14}C]-migalastat HCl over the concentration range of 1 to 100 µM (200 to 19,900 ng/mL).

In nonclinical tissue distribution studies in mice and rats, migalastat was shown to penetrate the blood:brain barrier.

Metabolism: Based upon *in vivo* data, migalastat is a substrate for UGT, being a minor elimination pathway. A pharmacokinetic trial in healthy male volunteers with 150 mg [^{14}C]-migalastat HCl revealed that 99% of the radio-labeled dose recovered in plasma was comprised of unchanged migalastat (77%) and 3 dehydrogenated O-glucuronide-conjugated metabolites, M1to M3 (13%). Approximately 9% of the total radioactivity was unassigned.

Excretion: A pharmacokinetic trial in healthy male volunteers with 150 mg [^{14}C]-migalastat HCl revealed that approximately 77% of the radio-labeled dose was recovered in urine of which 55% 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 radio-labeled dose was excreted in feces, with unchanged migalastat being the only measured component.

Following ascending single oral doses (25-675 mg migalastat HCl), 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 and Conditions

Pediatrics (< 18 years of age): The safety and efficacy of GALAFOLD™ in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics: Clinical studies of GALAFOLD™ included a 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.

Race: Data generated from a study in subjects of Japanese ethnicity indicated that there are no differences in the pharmacokinetic profile of migalastat due to race.

Hepatic Insufficiency: 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 would affect the pharmacokinetics of migalastat.

Renal Insufficiency: GALAFOLD™ has not been studied in patients with Fabry disease who have an eGFR less than 30 mL/min/1.73 m^2. In a single-dose study with GALAFOLD™ in non-Fabry subjects with varying degrees of renal insufficiency, exposures (AUC) were increased by 4.3-fold in subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Mean plasma T1/2 in these patients was about 32 hours.

The exposures (AUC) were increased 1.8-fold in subjects with moderate renal impairment (eGFR between 60 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2). Mean plasma T1/2 in these patients was about 22 hours.

STORAGE AND STABILITY

Store at room temperature (15-30°C) in the original package in order to protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

Store in a safe place and out of the reach of children. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

GALAFOLD™ is an oral immediate release, size 2 hard capsule with an opaque blue cap and opaque white body with the identifying code “A1001” printed in black.

GALAFOLD™ is provided in a quantity of 14 capsules packaged in a blister strip comprised of polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) and an aluminium foil lidding with a vinyl acrylic heat seal coating. Blister strips are encased in a paperboard secondary pack forming a blister card.

Composition

GALAFOLD™ is available as a hard capsule containing 123 mg of migalastat (equivalent to 150 mg migalastat HCl).

Each hard gelatin capsule contains within it the following non-medicinal ingredients: black printing ink, gelatin, indigotine (FD&C blue 2), magnesium stearate, pregelatinized maize starch, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: migalastat hydrochloride (USAN); migalastat (INN)

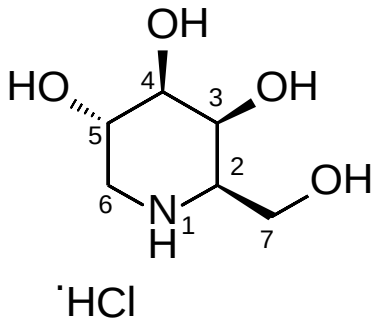
Chemical name:

CAS: 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, hydrochloride (1:1), (2R,3S,4R,5S)-

IUPAC: (+)- (2R,3S,4R,5S)-2-(hydroxymethyl)piperidine-3,4,5-triol, hydrochloride

Molecular formula and molecular mass: $C_6H_{13}NO_4 \bullet HCl$
199.63 g/mol (hydrochloride salt)
163.17 g/mol (free base)

Structural formula:



Physiochemical properties

Physical form: White to almost white solid

Solubility: Freely soluble between pH 1.2 and 7.5 in aqueous media

Solvent	Solution pH	Solubility (mg/mL)	Temperature (°C)
Hydrochloric Acid	1.2	>500	15 to 25
Phthalate Buffer	4.6	>500	15 to 25
Phosphate Buffer	6.8	>500	15 to 25

Solvent	Solution pH	Solubility (mg/mL)	Temperature (°C)
Phosphate Buffer	7.5	>500	15 to 25
Methanol	n/a	6	20
Ethanol	n/a	<1	20
Acetonitrile	n/a	<1	20

pH: 4.7 (1% aqueous solution at room temperature)

pKa: 7.47 ± 0.01

CLINICAL TRIALS

The clinical efficacy and safety of GALAFOLD™ have been evaluated in two completed Phase 3 pivotal trials and an ongoing open-label extension trial. All patients received the recommended dosage of 123 mg GALAFOLD™ every other day. Phase 3 clinical studies were conducted in patients with Fabry disease having 43 (approximately 16%) of the amenable mutations listed in Table 4.

Study Demographics and Trial Design

Table 7: Summary of Patient Demographics for Clinical Trials in Fabry Disease

Study #	Trial design	Dosage, route of administration, and duration	Study subjects (n = number)[1]	Mean age (Range)	Gender (M/F)
AT1001-012 (enzyme replacement therapy-experienced)	Phase 3 randomized open-label, active-controlled	GALAFOLD™ 123 mg QOD oral, or enzyme replacement therapy (agalsidase alfa or agalsidase beta) IV infusion every 14 days (as per approved prescribing information) 18 months (Followed by a 12-month open-label period)	57	48.9 years (18 to 72 years)	25/32
AT1001-011 (enzyme replacement therapy-naïve)	Phase 3 randomized double-blind placebo-controlled trial	GALAFOLD™ 123 mg or placebo QOD, oral 6 months (followed by an 18-month open-label period)	67	42.2 years (16 to 68 years)	24/43

[1] Number of randomized patients with Fabry disease who were predicted to have migalastat response *GLA* mutations

based on preliminary *in vitro* assay

The first Phase 3 trial (ERT - experienced trial) was an 18-month randomized open-label active comparator trial that evaluated the efficacy and safety of GALAFOLD™ compared to enzyme replacement therapy (ERT (agalsidase beta or agalsidase alfa)) in male and female patients (84% Caucasian) with Fabry disease who were receiving ERT prior to trial entry and who have amenable mutations (identified based on a GLP-validated *in vitro* assay, n=52). At baseline, 53% of patients had neurologic disorders, 72% had cardiac disorders, and 75% of patients had renal disorders. Patients were randomized in a ratio of 1.5:1 to switch to GALAFOLD™ (150 mg migalastat HCl, QOD) or continue with ERT. After 18 months of treatment, patients in the ERT treatment arm switched to GALAFOLD™ (150 mg migalastat HCl, QOD) and patients in the GALAFOLD™ treatment arm continued on the same treatment for a 12-month extension period.

The second Phase 3 trial (ERT-naïve trial) was a 6-month randomized double-blind placebo-controlled trial (through month 6) with an 18-month open-label period that evaluated the efficacy and safety of GALAFOLD™ in male and female patients (97% Caucasian) with Fabry disease who were naïve to ERT or had previously been on ERT and had stopped for at least 6 months prior to trial entry and who have amenable mutations (identified based on a GLP-validated *in vitro* assay, n=50). Patients were randomized in a ratio of 1:1 to receive either GALAFOLD™ (150 mg migalastat HCl, QOD) or placebo for 6 months (Stage 1), followed by Stage 2 in which patients in the GALAFOLD™ arm continued to receive GALAFOLD™ (150 mg migalastat HCl, QOD) and patients in the placebo arm switched to GALAFOLD™ (150 mg migalastat HCl, QOD) for 6 months, followed by an open-label extension phase in which all patients from Stage 2 continued to receive GALAFOLD™ treatment for 12 months.

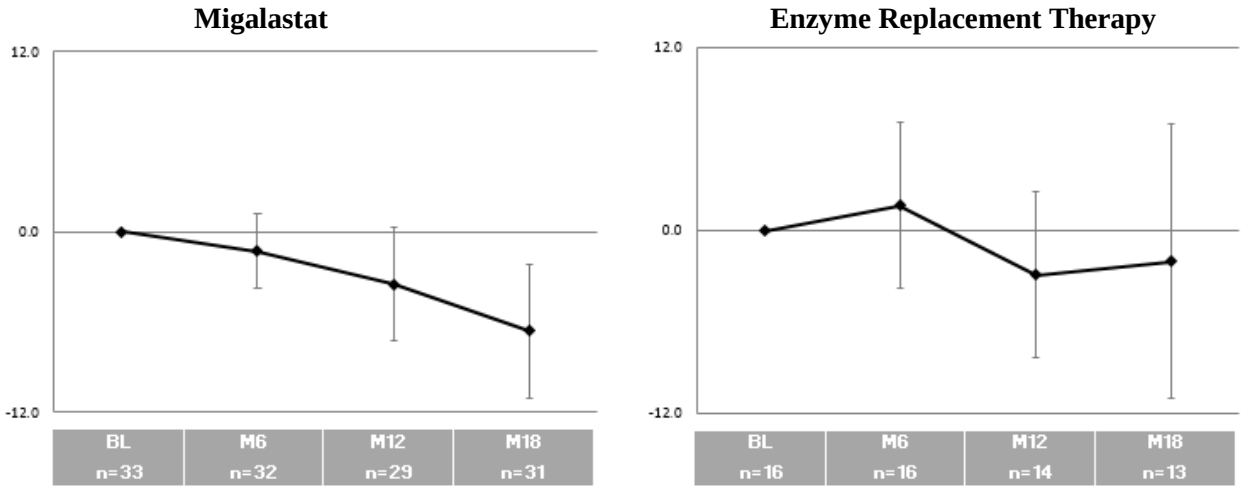
Study results

Renal Function
In the ERT-experienced trial, renal function remained stable for up to 18 months of treatment with GALAFOLD™. Mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ was -0.40 mL/min/1.73 m^2 (95% CI: -2.272, 1.478; n=34) in the GALAFOLD™ group compared to -1.03 mL/min/1.73 m^2 (95% CI: -3.636, 1.575; n=18) in the ERT group.

In the ERT-naïve trial, no clinically significant differences in renal function were observed during the initial 6-month placebo-controlled period. In the open-label period, renal function remained stable over 18-24 months of GALAFOLD™ treatment (18 months for patients administered placebo in Stage 1 and 24 months for patients treated with GALAFOLD™ in Stage 1). After 18/24 months of GALAFOLD™ treatment, the mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ was -0.30 mL/min/1.73 m^2 (95% CI: -1.65, 1.04; n=41).

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 change from baseline to Month 18 in LVMi (g/m^2) in patients with left ventricular hypertrophy (females with baseline LVMi > 95 g/m^2 and males with baseline LVMi > 115 g/m^2) was -8.4 g/m^2 (95% CI: -15.7, 2.6; n=13) for migalastat and 4.5 g/m^2 (95% CI: -10.7, 18.4; n=5) for ERT.

Figure 1 ERT – Experienced Trial: LVMi Change (Mean and 95% CI) Over 18 Months with Migalastat and Enzyme Replacement Therapy (ERT)



The y-axes present change in LVMi and units are g/m^2
BL-baseline; ERT=enzyme replacement therapy; LVMi=left ventricular mass index; M=Month

In the ERT-naïve trial, no clinically significant differences in LVMi were observed during the initial 6-month placebo-controlled period. The mean change from baseline in LVMi at Months 18/24 was -7.7 g/m^2 (95% CI: -15.4, -0.01; n=27). The mean change from baseline in LVMi at Months 18/24 in patients with left ventricular hypertrophy at baseline (females with baseline LVMi > 95 g/m^2 or males with baseline LVMi > 115 g/m2) was -18.6 g/m^2 (95% CI: -38.2, 1.0; n=8).

Disease Substrate
In the ERT-naïve trial, GALAFOLD™ showed statistically significant reductions in plasma lyso-Gb_3 concentrations and kidney interstitial capillary GL-3 inclusions in patients with amenable mutations. Patients with amenable mutations randomized to GALAFOLD™ in Stage 1 demonstrated a statistically significant greater reduction (±SEM) in mean interstitial capillary GL-3 inclusions (-0.25 ± 0.10; -39%, n=25) at Month 6 compared to placebo (+0.07 ± 0.13; +14%, n=20) (p=0.008). Patients with amenable mutations randomized 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 ± 0.15; -58%, n=17) (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™.

In the ERT-experienced trial, plasma lyso-Gb_3 levels remained low and stable for up to 18 months in patients with amenable mutations switched from ERT to GALAFOLD™, and in patients remaining on ERT.

Composite Clinical Outcomes
In the ERT-experienced trial an analysis of a composite clinical outcome composed of renal, cardiac, and cerebrovascular events, or death, the frequency of events observed in the GALAFOLD™ treatment group was 29% and was 44% in the ERT group.

Table 8: Number (%) of Patients in the Modified Intent to Treat Population Who Experienced the Composite Clinical Outcome

Component	GALAFOLD™ (n=34)	Enzyme Replacement Therapy (n=18)
Renal	8 (24%)	6 (33%)
Cardiac	2 (6%)	3 (17%)
Cerebrovascular	0 (0%)	1 (6%)
Death	0 (0%)	0 (0%)
Any	10 (29%)	8* (44%)

* Two ERT-experienced patients each had 1 cardiac and 1 renal event.
Renal events included increased proteinuria and decreased GFR (GALAFOLD™ and ERT treatment groups); cardiac events included arrhythmia (GALAFOLD™ and ERT treatment groups) and cardiac failure (ERT treatment group only); cerebrovascular event was transient ischemic attack.

DETAILED PHARMACOLOGY

Pharmacodynamics

In vitro Studies

Migalastat is a potent specific competitive reversible inhibitor of human α-Gal A with a K_i value in the low nanomolar range, and also specifically increases the physical stability of recombinant human α-Gal A (rhα-Gal A) *in vitro* at pH 7.4 or at lysosomal pH (about pH 5.2).

In cells derived from Fabry patients with amenable mutations or transiently transfected with a *GLA* construct with an amenable mutation, migalastat incubation increased the cellular α-Gal A activity, which is detected only after the cells had been thoroughly washed to remove migalastat. The increase in α-Gal A activity was associated with increased cellular levels of α-Gal A protein. The sensitivity and the maximum extent of the response to migalastat differed significantly among different mutations.

For non-amenable mutations, migalastat resulted in a limited or no increase in the cellular α-Gal A activity. Normal (wild-type) α-Gal A responded to migalastat similarly to non-amenable α-Gal A mutations. Therefore, α-Gal A response to GALAFOLD™ in heterozygous female Fabry patients with the same amenable mutation may differ. Moreover, the response in females may be lower than that of male Fabry patients with the same mutation due to suppression of the activity of the wild-type α-Gal A protein in heterozygous females.

Migalastat-induced α-Gal A activity can only be realized after the intracellular migalastat concentration drops below a sub-inhibitory level. For example, fibroblasts derived from male Fabry patients significantly accumulate GL-3. A 7-day incubation with migalastat followed by 3-day incubation without migalastat resulted in a significant reduction in cellular GL-3. However 10-day incubation with migalastat and no off period did not change the level of cellular GL-3.

GALAFOLD™ Amenability

To identify Fabry disease mutations likely to have a clinically relevant response to GALAFOLD™, more than 530 mutations were tested using a HEK-293 cell system transiently transfected with a mutant GLA construct. The criteria for identifying migalastat amenability is: HEK-293 cells transiently expressing the mutant protein showing an absolute increase in α-Gal A activity that is≥ 3.0% of wild-type α-Gal A activity AND a relative increase in α-Gal A activity that is ≥1.20-fold above baseline after the cells are treated with 10 μM migalastat for 5 days. The migalastat concentration of 10 μM used in the assay is close to the mean plasma C_{max} of migalastat following a single oral dose of migalastat 123 mg in healthy individuals (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics –** Table 6). Mutations with an *in vitro* response to migalastat that do not meet the amenability criteria are classified as non-amenable.

The extent of the *in vitro* response to 10 μM migalastat differs across amenable mutations. Across amenable mutations listed in Table 4, the absolute increase in α-Gal A activity ranged from 3.0% to 75.9% of wild-type; the relative increase in α-Gal A activity ranged from 1.2-fold to 37.34-fold above baseline; and mean baseline activity ranged from BLD (below the limit of detection) to 124.5% of wild-type.

Phase 3 clinical studies were conducted in patients with Fabry disease having 43 (approximately 16%) of the amenable mutations listed in Table 4. Predictability of the extent of clinical-outcome in amenable patients is limited.

Clinical Studies

A Phase 2 study was conducted in Fabry patients with amenable mutations. Migalastat treatment in each patient included dose-escalation from 25, to 100, to 250 mg migalastat HCl BID with each dose level for two weeks, then 25 mg migalastat HCL BID for 6 weeks, and finally 50 mg migalastat HCl QD for 6 weeks. Urine GL-3 was significantly increased from baseline in a dose-dependent manner in most patients dosed at 25, 100, and 250 mg BID. About half of the patients dosed at 50 mg QD had a moderate increase in urine GL-3.

Decreases in GL-3 were observed in most male and female patients with amenable mutations treated with150 mg migalastat HCl QOD. These decreases were not further enhanced when patients were switched to higher and less frequent doses (250 and 500 mg, 3 days on/4 days off).

There were 9 male patients with 5 different non-amenable mutations and 10 female patients with 7 different non-amenable mutations in clinical trials. GALAFOLD™ 123 mg QOD resulted in a

significant increase from baseline in the levels of plasma lyso-Gb_3 and urine GL-3 in all the male patients and 80% of the female patients.

TOXICOLOGY

Repeat-Dose Toxicology

Repeat-dose toxicity studies were conducted for up to 6 months duration in rats, for up to 14 days duration in dogs, and for up to 9 months duration in monkeys. In rats, dogs, and monkeys, migalastat was generally well tolerated with no evidence of systemic toxicity.

In chronic studies in rats and monkeys, the highest doses on study were established as the no-observed-adverse-effect-level (NOAEL). End-of-study systemic exposure to migalastat at the NOAEL dose greatly exceeded the exposure in humans at a clinically relevant dose of 150 mg migalastat HCl once every other day (≥55-fold based on AUC in the chronic toxicity studies).

Genotoxicity and Carcinogenicity

Migalastat was non-mutagenic *in vitro* in a 5-strain bacterial mutagenicity study and in the mouse lymphoma L5178Y cell Tk gene mutation assay in the presence and absence of metabolic activation. *In vivo*, migalastat did not induce micronuclei in bone marrow erythrocytes upon migalastat dosing at 2,000 mg/kg/day for 2 days.

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.

Reproductive and Developmental Toxicity

In male rats, migalastat treatment impaired fertility at systemic exposures that were less than that in humans at a clinically relevant dose (<0.2-fold, based on AUC). Effects on male fertility were reversible following a 4-week non-dosing recovery period. At doses which impaired male fertility, there were no macroscopic changes or histological changes in the male reproductive system or changes in sperm parameters that could account for the reduction in fertility.

In the rabbit embryo-fetal toxicity study, findings including embryo-fetal death, a reduction in mean fetal weight, retarded ossification, and slightly increased incidences of minor skeletal abnormalities were observed at doses associated with maternal toxicity (≥300 mg/kg/day; ≥240-fold, based on AUC).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrGALAFOLD™

migalastat capsules

Read this carefully before you start taking **GALAFOLD** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **GALAFOLD**.

What is GALAFOLD used for?

GALAFOLD is used for the long-term treatment of Fabry disease in adults who have certain genetic mutations (changes) in an enzyme called alpha-galactosidase A (α–Gal A). GALAFOLD is not to be used in patients with Fabry disease who have other genetic mutations. Your doctor will perform a genetic test to determine if you can take GALFOLD.

How does GALAFOLD work?

Fabry disease is caused by a defect in the α–Gal A enzyme. This 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.

GALAFOLD works by fixing a defect in the α–Gal A enzyme so that it can work better to reduce the amount of GL-3 that has built up in your cells and tissues. This helps the organs affected by Fabry disease work better.

What are the ingredients in GALAFOLD?

Medicinal ingredient: migalastat hydrochloride
Non-medicinal ingredients: black printing ink, gelatin, indigotine (FD&C Blue 2), magnesium stearate, pregelatinized maize starch, and titanium dioxide.

GALAFOLD comes in the following dosage forms:

As a capsule containing 123 mg migalastat (as migalastat hydrochloride)

Do not use GALAFOLD if you:

- are allergic to migalastat or any of the other ingredients in GALAFOLD
- are allergic to any component of the GALAFOLD container
- are also receiving another medicine used to treat Fabry disease called Enzyme Replacement Therapy (ERT)
- have severe kidney problems

- are pregnant
- are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GALAFOLD. Talk about any health conditions or problems you may have, including if:

- you have problems with your kidneys
- you have problems with your liver
- you or your partner are planning a pregnancy

Other warnings you should know about:

Pregnancy:
Do not take GALAFOLD if you are pregnant. GALAFOLD may harm an unborn baby. You must tell your doctor if you are or think you may be pregnant before taking GALAFOLD. You must use an effective birth control method while taking GALAFOLD. Talk to your healthcare professional for advice on effective methods of birth control.

Breast-feeding:
You should not breastfeed if you are taking GALAFOLD since it may get into your breast milk and harm your baby. Talk to your healthcare professional if you are planning on breastfeeding in the future.

Fertility:
It is not known if GALAFOLD affects fertility in men and women. Talk to your healthcare professional if you and your partner are planning to have a baby in the future.

Driving and using machines:
Before doing tasks which require special attention, wait until you know how you respond to GALAFOLD.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with GALAFOLD:

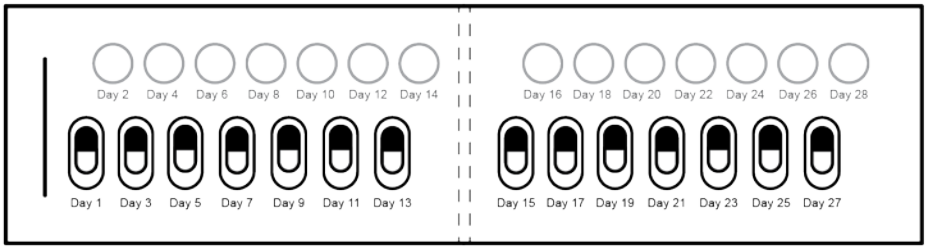
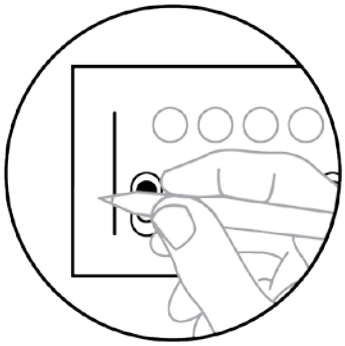
- Other medicines used to treat Fabry disease called enzyme replacement therapy (ERT) like agalsidase.

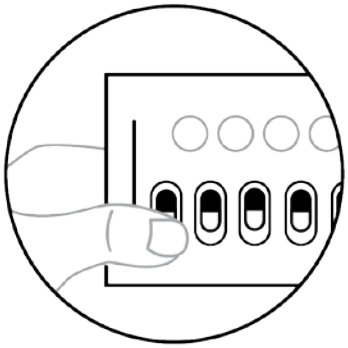
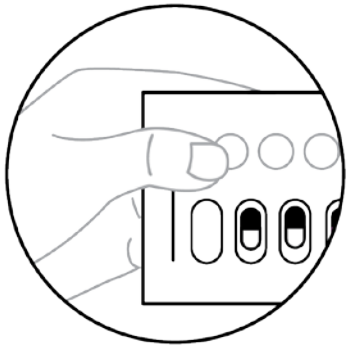
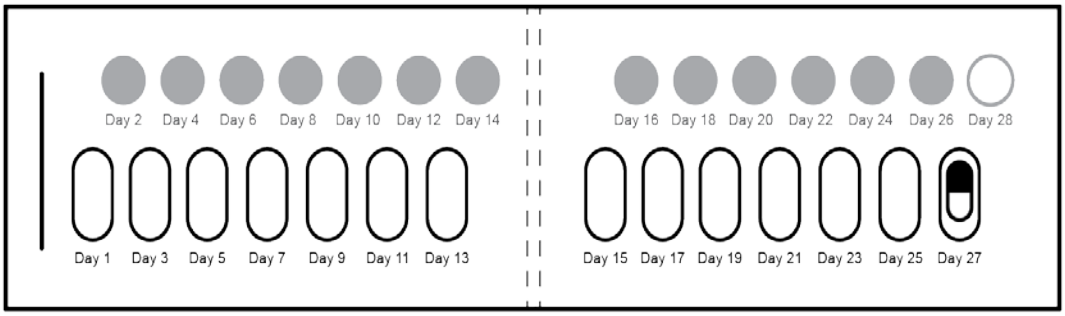
How to take GALAFOLD:

- Take one capsule every other day at the same time of the day.

- Do not take GALAFOLD two days in a row.

- Take GALAFOLD on an empty stomach. Do not eat at least two hours before and two hours after you take GALAFOLD.This is because your body may not absorb the medicine completely if taken with food.
- Swallow the capsule whole. Do not cut, crush or chew the capsule.
- Do not stop taking this medicine without talking to your doctor.
- GALAFOLD will be given to you by a healthcare professional who has experience in the diagnosis and treatment of Fabry disease.
- Always take GALAFOLD exactly as your healthcare professional has told you.
- If you are not sure how to take GALAFOLD, talk to your healthcare professional.

<table>
<tr><td colspan="2"> 
</td></tr>
<tr><td colspan="2">One GALAFOLD blister sleeve = 14 hard capsules = 28 days of treatment</td></tr>
<tr><td>  </td><td>On your first day of taking GALAFOLD from a new blister sleeve, record the starting date on the blister sleeve.</td></tr>
</table>

<table>
<tr><td>  </td><td>Then, punch out the capsule labeled “Day 1” that is furthest to the left on the blister sleeve.</td></tr>
<tr><td>  </td><td>On the next day, punch out the perforated white circle labeled “Day 2”. This will help you remember which day you did not take the medicine. You should only take GALAFOLD™ once every other day.</td></tr>
<tr><td colspan="2"> 
</td></tr>
<tr><td colspan="2">After Day 2, continue moving towards the right on the blister sleeve.
Take GALAFOLD on odd numbered days (e.g. Day 1, Day 3, Day 5).
Punch out the perforated white circles on even numbered days (e.g. Day 2, Day 4, Day 6).</td></tr>
</table>

Usual dose:

One 123 mg capsule every other day

Overdose:

If you think you have taken too much GALAFOLD, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take your capsule at the usual time but remember later that day, take the capsule when you remember on the same day.
- If you miss a dose of this medicine for an entire day, do not take the missed capsule. Wait and take a capsule on the next day when you would usually take this medicine.
- Never take GALAFOLD two days in a row.
- Never take two capsules to make up for a missed dose.

What are possible side effects from using GALAFOLD?

These are not all the possible side effects you may feel when taking GALAFOLD. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- headache
- abdominal pain or discomfort, including upper abdominal pain
- back pain
- change in vision
- change in typical or normal bowel movements
- constipation
- dizziness or a sensation of spinning
- dry mouth
- excessive sweating
- feeling hot
- feeling tired
- fever
- flank pain (pain in the side)
- flu (body aches, feeling tired, fever)
- frequent urination
- increase or decrease in appetite
- increase or decrease in weight
- increased or decreased sense of touch or sensation
- indigestion
- inflammation (pain, redness and swelling)
- itching
- itching of the eye
- joint pain
- local swelling

- memory problems
- migraine (intense headaches, usually on one side of the head)
- muscle pain in the chest
- muscle pain, twitching, spasms or weakness
- nausea and vomiting
- night sweats (excessive sweating during the night)
- nose bleed
- pain in arms or legs
- painful and twisted neck
- runny nose
- skin rash or redness
- sleep disorder, including somnolence (sleepiness or drowsiness) and insomnia (difficulty falling asleep or staying asleep)
- sudden urge to pass stools or inability to control bowel movements
- tremor (unintentional trembling or shaking movements)

GALAFOLD may cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON:			
Ataxia (lack of muscle coordination): difficulty walking or difficulty with fine motor tasks, lack of coordination.	✓		
Atrial fibrillation (abnormal heart rhythm which is rapid and irregular): occasional chest pain, heart palpitations, fainting, lightheadedness, rapid heartbeat, shortness of breath		✓	
Bile duct stone, biliary dilation (presence of a gallstone in the bile duct, widening of the bile duct): sudden severe pain on the upper right side of the abdomen,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
fever or chills, jaundice (yellowing of the eyes or skin), dark urine, itching, light-colored stools, nausea and vomiting			
Blood in stools		✓	
Chest discomfort	✓		
Depression		✓	
Diarrhea: loose or watery stools	✓		
Difficult or labored breathing		✓	
High blood pressure	✓		
Hypoglycemia (low blood sugar): change in mood or vision, feeling faint or fainting, headache, hunger, rapid heartbeat, shaking, sweating	✓		
Irritable bowel syndrome (bouts of pain or cramping of stomach, bloating, diarrhea and/or constipation): swelling, excessive gas		✓	
Movement disorders: involuntary muscle movements, lack of coordination, tremor	✓		
Myocardial ischemia (lack of blood flow to the heart which can lead to heart attack): sudden chest pain, pressure or discomfort, feeling faint, feeling anxious, shortness of breath, irregular heartbeat, nausea, sudden heavy sweating			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Palpitations: awareness of heartbeat, fluttering of heart, rapid or strong heartbeats		✓	
Paresthesia (tingling in extremities): feeling of tingling or pins and needles in hands or feet	✓		
Peripheral edema (buildup of fluid in the arms / legs which causes the affected tissue to become swollen and stiff, and may cause weight gain)		✓	
Proteinuria (protein in the urine): cloudiness of the urine, foaming of the urine, and in severe cases swelling of the feet and legs and weight gain		✓	
Psoriasis (chronic skin disease): red, itchy, scaly patches of the skin	✓		
Urinary tract infection: difficulty or increased need to urinate, pain or burning sensation when passing urine, pain in the pelvis or mid-back, urine that appears cloudy		✓	
UNCOMMON:			
Balance problems	✓		
Liver injury (damage to the liver): abdominal pain, dark urine, fatigue, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice)		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Neuralgia (pain that follows the path of the nerve): sudden attacks of severe sharp shooting pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature between 15°C-30°C in the original package to protect from moisture.

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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away unused capsules.

If you want more information about GALAFOLD™:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:

https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website: www.almacgroup.com, or by calling + 44 (0) 28 3833 2200

This leaflet was prepared by:

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