PRODUCT INFORMATION – *Galafold*®

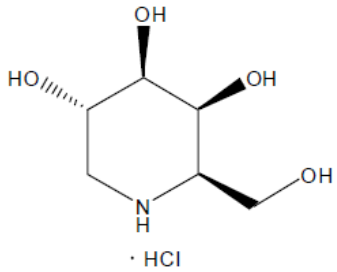
NAME OF THE MEDICINE

Galafold® (123 mg Migalastat Hard Capsules equivalent to 150 mg Migalastat hydrochloride Hard Capsules)

Australian Approved Name (AAN): Migalastat hydrochloride

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

Chemical structure:



Molecular formula: $C_6H_{13}NO_4.HCl$

Molecular weight: 199.63 (hydrochloride salt)
163.17 (free base)

CAS number: Migalastat hydrochloride: 75172-81-5

DESCRIPTION

Migalastat hydrochloride is a white to pale brown powder, freely soluble between pH 1.2 and pH 7.5 in aqueous media. The pKa is 7.47±0.01.

The capsule is a Size 2 hard capsule (6.4x18.0 mm) with an opaque blue cap and opaque white body with "A1001" printed in black.

Each Galafold capsule contains 123 mg migalastat equivalent to 150 mg migalastat hydrochloride.

Galafold hard capsules (108872) also contain the following inactive ingredients: pregelatinised maize starch and magnesium stearate. The capsule shells are made of gelatin and contain the following colouring agents: titanium dioxide (E171) and indigo carmine (E132). The capsules are marked with printing ink (2328), containing shellac (E904), iron oxide black (E172) and potassium hydroxide.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Various alimentary tract and metabolism products.
ATC Code: A16AX14.

PRODUCT INFORMATION – *Galafold*®

Fabry disease is a progressive X-linked lysosomal storage disorder that affects males and females. Fabry disease-causing mutations in the *GLA* gene result in a deficiency of the lysosomal enzyme a-galactosidase A (a-Gal A) that is required for glycosphingolipid substrate (e.g., GL-3, lyso-Gb_3) metabolism. Reduced a-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 α-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 a-Gal A, the genotypes of which are referred to as amenable mutations. Migalastat binding stabilizes these mutant forms of a-Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes where dissociation of migalastat restores a-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 1 and Table 2, respectively, below.

Table 1: 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.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>G	c.A100G	N34D
c.101A>C	c.A101C	N34T
c.101 A>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.108 G>C or c.108G>T	c.G108C or c.G108T	L36F
c.109G>A	c.G109A	A37T

PRODUCT INFORMATION – *Galafold*®

Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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
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>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>G	c.A164G	D55G
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.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.247G>A	c.G247A	D83N
c.253G>A	c.G253A	G85S
c.254G>A	c.G254A	G85D
c.[253G>A; 254G>A]	c.G253A/G254A	G85N
c.[253G>A; 254G>T; 255T>G]	c.G253A/G254T/T255G	G85M
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.G288A or c.G288T or	M96I

PRODUCT INFORMATION – *Galafold*®

Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
c.288G>C	c.G288C	
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.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
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.455A>G	c.A455G	Y152C
c.466G>A	c.G466A	A156T
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.[496C>G; 497T>G]	c. C496G/T497G	L166G
c.496C>G	c.C496G	L166V
c.496_497delinsTC	c.496_497delinsTC	L166S
c.499C>G	c.C499G	L167V
c.506T>C	c.T506C	F169S
c.511G>A	c.G511A	G171S
c.520T>C	c.T520C	C174R

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Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
c.520T>G	c.T520G	C174G
c.525 C>G or c.525C>A	c.C525G or c.C525A	D175E
c.539T>G	c.T539G	L180W
c.540G>C	c.G540C	L180F
c.548G>C	c.G548C	G183A
c.548G>A	c.G548A	G183D
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.559_564 dup	c.559_564dup	p. M187_S188 dup
c.560T>C	c.T560C	M187T
c.561G>T or c.561G>A or c.561G>C	c.G561T or c.G561A or c.G561C	M187I
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>T	c.C602T	S201F
c.602C>A	c.C602A	S201Y
c.608A>T	c.A608T	E203V
c.609 G>C or c.609G>T	c.G609C or c.G609T	E203D
c.613 C>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>G	c.A638G	K213R
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>T	c.A644T	N215I
c.[644 A>G; 937 G>T]	c. A644G/G937T	N215S/D313Y
c.646T>G	c.T646G	Y216D
c.647A>G	c.A647G	Y216C
c.655A>C	c.A655C	I219L
c.656T>A	c.T656A	I219N

PRODUCT INFORMATION – *Galafold*®

Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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.687 T>A or c.687T>G	c.T687A or c.T687G	F229L
c.695T>C	c.T695C	I232T
c.713G>A	c.G713A	S238N
c.716T>C	c.T716C	I239T
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.729 G>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.760-762del GTT	c.760_762delGTT	p.V254del
c.769G>C	c.G769C	A257P
c.770C>G	c.C770G	A257G
c.772 G>C or c.772G>A	c.G772C or c.G772A	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.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

PRODUCT INFORMATION – *Galafold*®

Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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
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.870 G>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.897 C>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>C	c.G902C	R301P
c.902G>A	c.G902A	R301Q
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

PRODUCT INFORMATION – *Galafold*®

Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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.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; 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
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 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.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.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

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Table 1: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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
c.1124G>A	c.G1124A	G375E
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>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

NP GAL0719

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 1 (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 1.

The mutations not amenable to treatment with Galafold are listed in Table 2 below.

Table 2: 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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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 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
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.71 G>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>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 or c.132G>A	c.G131A or c.G132A	W44X
c.132G>T or c.132G>C	c.G132T or c.G132C	W44C
c.134 T>C	c.T134C	L45P
c.134 T>G	c.T134G	L45R
c.134_138delTGCACinsGCTCG	c.134_138delTGCACinsGCTCG	L45R/H46S
c.136 C>T	c.C136T	H46Y
c.137 A>T	c.A137T	H46L
c.137 A>G	c.A137G	H46R
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.140 G>A or 141G>A	c.G140A or G141A	W47X

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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>T	c.C145T	R49C
c.145C>A	c.C145A	R49S
c.145C>G	c.C145G	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.154T>A or c.155 G>C	T154A or 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.166T>A or c.16 G>C	c.T166A or c.G167C	C56S
c.168C>A	c.C168A	C56X
c.187T>C	c.T187C	C63R
c.188G>A	c.G188A	C63Y
c.187T>A or c.188G>C	c.T187A or 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.[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.233 C>G or c.233C>A	c.C233G or c.C233A	S78X
c.235G>T	c.G235T	E79X
c.241 T>C or c.241T>A	c.T241C or c.T241A	W81R
c.242 G>A or c.243G>A	c.G242A or c.G243A	W81X
c.242 G>C	c.G242C	W81S
c.243 G>T or c.243G>C	c.G243T or c.G243C	W81C
c.244A>T	c.A244T	K82X
c.256T>G	c.T256G	Y86D
c.256T>C	c.T256C	Y86H

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.257A>G	c.A257G	Y86C
c.258 T>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>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 or c.279C>A	c.C279G or c.C279A	D93E
c.280T>G	c.T280G	C94G
c.280T>A or c.281 G>C	c.T280A or c.G281C	C94S
c.[280T>A; 281G>C]	c.T280A/G281C	C94T
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
c.284G>T	c.G284T	W95L
c.284G>C	c.G284C	W95S
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>T	c.C334T	R112C
c.334C>A	c.C334A	R112S
c.338T>C	c.T338C	F113S
c.347G>T	c.G347T	G116V
c.350T>G	c.T350G	I117S
c.355C>T	c.C355T	Q119X

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.354_368del15	c.354_368del15	Q119_Y123del5
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.361 G>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.379A>T	c.A379T	K127X
c.386T>C	c.T386C	L129P
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
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.443G>A	c.G443A	S148N
c.442A>C or c.444T>A or c.444T>G	c.A442C or c.T444A or c.T444G	S148R
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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.500T>A	c.T500A	L167Q
c.500T>C	c.T500C	L167P
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>G	c.T514G	C172G
c.514T>C	c.T514C	C172R
c.514T>A or c.515 G>C	c.T514A or c.G515C	C172S
c.515G>T	c.G515T	C172F
c.515G>A	c.G515A	C172Y
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.552T>A or c.552T>G	c.T552A or c.T552G	Y184X
c.553A>T	c.A553T	K185X
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.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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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>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 or c.676T>A	c.T676C or c.T676A	W226R
c.677G>A or c.678G>A	c.G677A or c.G678A	W226X
c.678 G>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.707G>A or c.708G>A	c.G707A or c.G708A	W236X
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 735G>A	c.G734A or G735A	W245X
c.734G>T	c.G734T	W245L
c.739T>C	c.T739C	S247P

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.785 G>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; c.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>C	c.G796C	D266H
c.796G>T	c.G796T	D266Y
c.796G>A	c.G796A	D266N
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.816 C>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.820 G>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
c.826A>T	c.A826T	S276C
c.830G>A or c.831G>A	c.G830A or c.G831A	W277X

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.835C>T	c.C835T	Q279X
c.835C>A	c.C835A	Q279K
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 861G>A	c.G860A or 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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.960T>G or c.960T>A	c.T960G or c.T960A	N320K
c.961C>G	c.C961G	Q321E
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.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>C	c.G1019C	W340S
c.1019G>A c.1020 G>A	c.G1019A or c.G1020A	W340X
c.1021G>A	c.G1021A	E341K
c.1021G>T	c.G1021T	E341X
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.1034 C>G or c.1034C>A	c.C1034G or c.C1034A	S345X
c.1042 G>C	c.G1042C	A348P
c.1045 T>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.1069C>T	c.C1069T	Q357X
c.1072 G>A	c.G1072A	E358K
c.1081G>T	c.G1081T	G361X
c.1081G>A or c.1081G>C	c.G1081A or c.G1081C	G361R
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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.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.1163T>C	c.T1163C	L388P
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.1193A>C	c.A1193C	E398A
c.1196G>A or1197 G>A	c.G1196A or 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.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
c.1250T>C	c.T1250C	L417P
c.1288T>C	c.T1288C	X430Q
g.941_5845del	c.1-179_369+577del	p.?(Exon1_2del)

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
g.?_?del	c.?_?	UNKNOWN (del Exon1_2?)
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
c.89delG	c.89delG	p.R30Kfs*89
c.123delC	c.123delC	p.T41fs*79
c.123_126dupCATG	c.123_126dupCATG	p.G43Hfs*13
c.124_125del	c.124_125del	p.M42Gfs*12
c.125_137del	c.125_137del	p.M42Tfs*74
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
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.210insT	c.210insT	p.E71X
c.214delA	c.214delA	p.M72Wfs*47
c.256delT	c.256delT	p.Y88Mfs*42
g.5052_5079del28	g.5052_5079del28	UNKNOWN
g.5106_5919delins231	c.207_369+651del814ins231	UNKNOWN (del Exon2?)

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.336 Del18	c.336 Del18	p.113del6aa
c.354_368del	c.354_368del	p.Q119_Y123del
c.358 Del6	c.358 Del6	p.120del2aa/L120H
c.363delT	c.363delT	p.A121fs*8
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?)
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.>5.5 kb del to 3UTR	c.?_?del	UNKNOWN (del Exon3_3'UTR?)
c.[374 A>T;383 G>A]	c.A374T/G383A	H125L/G128E
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.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.568delG	c.568delG	p.A190Pfs*1
c.590delG	c.590delG	p.S197Tfs*42
c.[604 T>C;644 A>G]	c.T604C/A644G	p. C202R/N215S
c.606delT	c.606delT	p.C202Wfs*37
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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.Y216Lfs*15
c.646delT	c.646delT	p.Y216Ifs*23
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_717 del	c.715_717 del	p.del I239
c.716dupT	c.716dupT	p.I239fs*10
c.718_719del	c.718_719del	p.K240Efs*8
c.719dupA	c.719dupA	p.K240fs*9
c.722delG	c.722delG	p.S241Ifs*27
c.723dupT	c.723dupT	p. I242Yfs*8
c.736_739delinsCAA	c.736_739delinsCAA	p.T246Qfs*21
c.732delC	c.732delC	p.D244fs*24
c.741ins9	c.741ins9	p.247ins3
c.744delT	c.744delT	p.F248Lfs*20
c.744_745del	c.744_745del	p.F248Lfs*6
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.833dupA	c.833dupA	p.N278Kfs*20
c.833delA	c.833delA	p.N278Ifs*3
c.833_845del	c.833_845del	p.W277fs*34
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.V281AdelT282
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.N298I*1

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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
c.931delC	c.931delC	p.L311Ffs*5
c.941_961del	c.941_961del	p.D315_Q321del
c.946delG	c.946delG	p.V316X
c.946_954dup	c.946_954dup	p.V316_A318dup
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.946_966del	c.946_966del	p.V316_D322del
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

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.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.1168 Ins T	c.1168 Ins T	p. V390fs*9
c.1176_1179del	c.1176_1179del	p.R392Sfs*1
c.1177_1178del	c.1177_1178del	p.K393Afs*4
c.1181_1192del	c.1181_1192del	p.L394_E398delinsQ
c.1187dupT	c.1187dupT	p.F396fs*2
c.1187delT	c.1187delT	p.F396Sfs*7
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.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
IVS1+2 T>C	c.194+2 T>C	UNKNOWN
IVS1+39delAT	c.194+39delAT	UNKNOWN
IVS1-1 G>A	c.195-1 G>A	UNKNOWN
IVS1-1 G>T	c.195-1 G>T	UNKNOWN
IVS1-2 A>G	c.195-2 A>G	UNKNOWN
IVS1-2 A>G;IVS1-49 T>C	c.[195-2 A>G;195-49 T>C]	UNKNOWN
IVS2+1 G>A	c.369+1 G>A	UNKNOWN
IVS2+1G>T	c.369+1G>T	UNKNOWN
IVS2+2 T>G	c.369+2 T>G	UNKNOWN
IVS2-2 A>G	c.370-2A>G	UNKNOWN
IVS3+1 G>A	c.547+1 G>A	UNKNOWN
IVS3+1 G>C	c.547+1 G>C	UNKNOWN
IVS3-162A>T	c.548-162A>T	UNKNOWN
IVS3-2 A>G	c.548-2 A>G	UNKNOWN
IVS3-1 G>A	c.548-1 G>A	UNKNOWN

Table 2: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
IVS3-1 G>C	c.548-1 G>C	UNKNOWN
IVS3-1 G>T	c.548-1 G>T	UNKNOWN
IVS4+1 G>A	c.639+1 G>A	UNKNOWN
IVS4+1 G>C	c.639+1 G>C	UNKNOWN
IVS4+4 A>T	c.639+4 A>T	UNKNOWN
IVS4+861 C>T	c.639+861 C>T	UNKNOWN
IVS4+919 G>A	c.639+919G>A	UNKNOWN
IVS4-859C>T	c.640-859C>T	UNKNOWN
IVS4-11 T>A	c.640-11 T>A	UNKNOWN
IVS4-3 C>G	c.640-3 C>G	UNKNOWN
IVS4-2 A>T	c.640-2 A>T	UNKNOWN
IVS4-1 G>A	c.640-1 G>A	UNKNOWN
IVS4-1 G>T	c.640-1G>T	UNKNOWN
IVS5+2 T>C	c.801+2 T>C	UNKNOWN
IVS5+3 A>G	c.801+3 A>G	UNKNOWN
IVS5+3A>T	c.801+3A>T	UNKNOWN
IVS5+4 A>G	c.801+4 A>G	UNKNOWN
IVS5-2 A>G	c.802-2 A>G	UNKNOWN
IVS6+1 G>T	c.999+1 G>T	UNKNOWN
IVS6+2 T>C	c.999+2 T>C	UNKNOWN
IVS6-2 A>G	c.1000-2 A>G	UNKNOWN
IVS6-2 A>T	c.1000-2 A>T	UNKNOWN
IVS6-1 G>A	c.1000-1 G>A	UNKNOWN
IVS6-1 G>C	c.1000-1 G>C	UNKNOWN
IVS6-10G>A; IVS6-22C>T	c.[1000-10G>A; 1000-22C>T]	UNKNOWN

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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.

Not all mutations have been tested.

Pharmacodynamic effects

Treatment with Galafold in Phase 2 pharmacodynamic trials generally resulted in increases in endogenous α-Gal A activity in white blood cells (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.

Pharmacokinetic properties

Absorption

The absolute bioavailability (AUC) for a single oral 150 mg migalastat hydrochloride dose 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 mean peak migalastat plasma concentration (C_{max}) demonstrated dose-proportional increases at migalastat oral doses from 50 mg to 1,250 mg.

Migalastat hydrochloride 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 plasma concentration (C_{max}) compared with the fasting state.

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 it is well distributed into tissues and greater than total body water (42 L). There was no detectable plasma protein binding following administration of [^{14}C]-migalastat hydrochloride in the concentration range between 1 and 100 mM.

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 hydrochloride revealed that 99% of the radiolabelled 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 radiolabelled dose was recovered in urine 55% of the dose was excreted as unchanged migalastat, 4% as M1 to M3 and 5% was from unassigned components, for a total of 64%. The remaining 5% represents metabolites below quantifiable concentrations. Approximately 20% of the total radiolabelled 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^2. 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^2).

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.

CLINICAL TRIALS

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

The first Phase 3 trial (ATTRACT) was an 18-month, 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 migalastat or continue with ERT. The second period was an optional 12-month open-label extension in which all subjects received migalastat.

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).

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 $eGFR_{CKD-EPI}$ was -0.40 mL/min/1.73 m^2 (95% CI: -2.272, 1.478) in the Galafold group compared to -1.03 mL/min/1.73 m^2 (95% CI: -3.636, 1.575) in the ERT group.

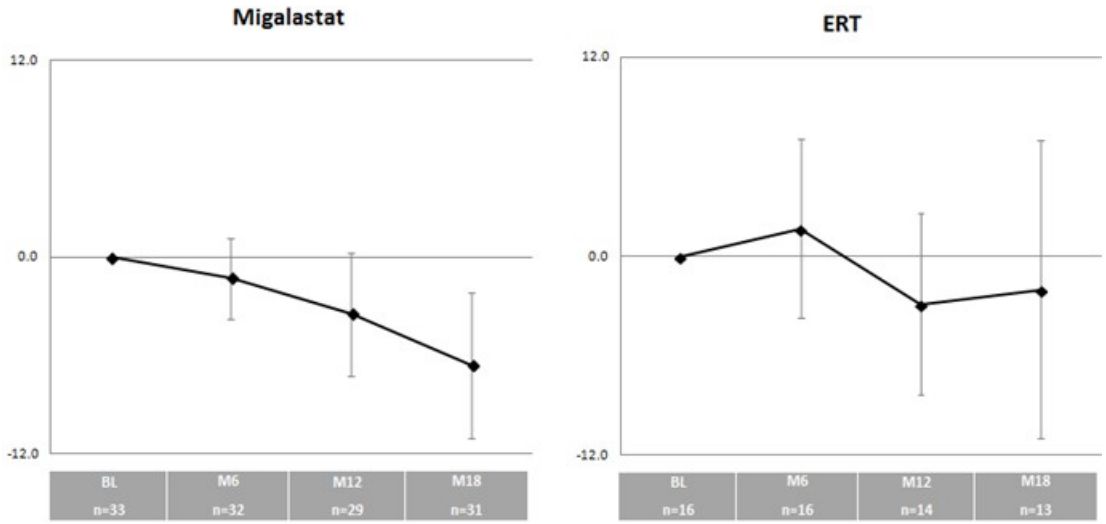
In the ERT-naïve trial and open label extension, renal function remained stable for 3 years of treatment with Galafold. After an average of 36 months of treatment, the mean annualised

rate of change in $eGFR_{CKD-EPI}$ was -0.81 mL/min/1.73 m^2 (95% CI: -2.00, 0.37). 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 migalastat there was a statistically *significant decrease in LVMi (p< 0.05).* The baseline values were 95.3 g/m^2 for the Galafold arm and 92.9 g/m^2 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 migalastat and -2.0 (95% CI: [-11.0, 7.0 n=13) for ERT (Figure 1).

Figure 1: ATTRACT Study: LVMi Change (Mean and 95% CI) over 18 Months with Migalastat and ERT



In the ERT-naïve trial, Galafold resulted in a statistically significant decrease in LVMi for all patients with amenable mutations (p< 0.05); the mean change from baseline in LVMi from Month 18 to 24 was -7.7 (95% CI: -15.4, -0.01; n=27). After follow up in the open label extension, the mean change from baseline in LVMi from Month 30 to 36 was -17.0 (95% CI: -26.2, -7.9; n=15). The mean change from baseline in LVMi from Month 18 to 24 in patients with left ventricular hypertrophy at baseline (females with baseline LVMi > 95 g/m^2 or males with baseline LVMi > 115 g/m^2) was -18.6 (95% CI: -38.2, 1.0; n=8). After follow up in the open label extension, the mean change from baseline in LVMi in patients with left ventricular hypertrophy at baseline from Month 30 to 36 was -30.0 (95% CI: -57.9, -2.2; n=4). No clinically significant differences in LVMi were observed during the initial 6-month placebo-controlled period.

These results demonstrate that Galafold leads to improvements in cardiac hypertrophy, which is a major risk factor for cardiac complications in Fabry disease.

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 randomised to Galafold in Stage 1 demonstrated statistically significant greater reduction (±SEM) in mean interstitial capillary GL-3 deposition (-0.25±0.10; -39%) at Month 6 compared to placebo (+0.07 ± 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±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.

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, 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 3).

Table 3: Number (%) of Patients Who Experienced the Composite Clinical Outcome

Component	Galafold™ (n=34)	ERT (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%)

* 2 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.

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.

Patient-Reported Outcome – Short Form-36 (SF-36v2)

After 24 months of treatment with migalastat in the ERT naïve patients study and 18 months of treatment in ERT experienced patients study, no significant changes from baseline were observed in SF-36v2.

Patient-Reported Outcome – Brief Pain Inventory (BPI)
Patient's pain scales remained stable when switched from ERT to Galafold.

INDICATION

Galafold is indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in the section on ***Mechanism of Action***).

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients

PRECAUTIONS

It is advised to periodically monitor (6 months, or at the usual regular intervals according to national practices) renal function, echocardiographic parameters, and biochemical markers 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 ***Pharmacodynamic properties***).

Galafold is not recommended for use in patients with severe renal insufficiency, defined as estimated GFR less than 30 mL/min/1.73m^2.

Limited data suggest that co-administration of a single dose of Galafold and a standard ERT infusion results in increased exposure to agalsidase 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.

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

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

Effects on fertility

The effects of Galafold on fertility in humans have not been studied. Non-clinical studies suggest no specific hazard for humans on the basis of single- and repeat-dose studies, with the exception of transient but fully reversible infertility in male rats associated with migalastat treatment at ≥ 2.5 mg/kg/day (≥ 0.2 times the clinical exposure based on AUC). The infertility associated with migalastat treatment was reported at subclinical relative exposures. Complete reversibility was seen after 4 weeks off-dose. Similar findings have been noted pre-clinically following treatment with other iminosugars. Galafold did not affect fertility in female rats.

PRODUCT INFORMATION – *Galafold*®

Use in pregnancy – Pregnancy Category B3

There are limited data from the use of Galafold in pregnant women. 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 of ≥ 300 mg/kg/day (≥ 240 times the clinical exposure based on AUC), which were associated with maternal toxicity. No Galafold-related embryofetal development issues were reported up to 1500 mg/kg/day in rats (>50 times the clinical exposure) or 120 mg/kg/day in rabbits (74 times clinical exposure). Galafold is not recommended during pregnancy.

Use in lactation

It is not known whether Galafold is secreted in human milk. However, migalastat has been shown to be secreted 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.

Paediatric use

Galafold has not been studied in paediatric subjects below the age of 16 years.

Genotoxicity

Migalastat hydrochloride was not genotoxic in a bacterial mutation assay, a forward mutation test and a rat micronucleus test.

Carcinogenicity

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 studies or in the carcinogenicity study with Tg.rasH2 mice (at 27 times the AUC exposure expected clinically), 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.

INTERACTIONS WITH OTHER MEDICINES

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.

ADVERSE 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 4: Study AT1001-011 and AT1001-012 Combined, Treatment-Related Treatment-Emergent Adverse Events for Migalastat

	Frequency of adverse reaction (%)		
System Organ Class Preferred Term	**Very common (>=1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Cardiac Disorders			
Palpitations		1.7%	
Ear And Labyrinth Disorders			
Vertigo		2.6%	
Eye Disorders			
Eye Pruritus			0.9%
Visual Acuity Reduced			0.9%
Gastrointestinal Disorders			
Diarrhoea		7.8%	
Nausea		5.2%	
Abdominal Pain		2.6%	
Constipation		2.6%	
Dry Mouth		2.6%	
Defaecation Urgency		1.7%	
Dyspepsia		1.7%	
Abdominal Pain Upper			0.9%
Change Of Bowel Habit			0.9%

PRODUCT INFORMATION – *Galafold*®

	Frequency of adverse reaction (%)		
System Organ Class **Preferred Term**	**Very common (>=1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Faecal Incontinence			0.9%
Irritable Bowel Syndrome			0.9%
Vomiting			0.9%
General Disorders And Administration Site Conditions			
Fatigue		2.6%	
Pain		1.7%	
Inflammation			0.9%
Influenza Like Illness			0.9%
Local Swelling			0.9%
Oedema Peripheral			0.9%
Pyrexia			0.9%
Hepatobiliary Disorders			
Hepatocellular Injury			0.9%
Injury, Poisoning And Procedural Complications			
Incorrect Dose Administered		2.6%	
Overdose			0.9%
Radiation Skin Injury			0.9%
Investigations			
Blood Creatine Phosphokinase Increased		2.6%	
Weight Increased		2.6%	
Blood Bilirubin Increased			0.9%
Blood Calcium Decreased			0.9%
Blood Cholesterol Increased			0.9%
Blood Pressure Increased			0.9%
Body Temperature Increased			0.9%
Liver Function Test Abnormal			0.9%
Weight Decreased			0.9%
White Blood Cell Count Decreased			0.9%
Metabolism And Nutrition Disorders			
Decreased Appetite			0.9%
Hypoglycaemia			0.9%
Musculoskeletal And Connective Tissue Disorders			

PRODUCT INFORMATION – *Galafold*®

	Frequency of adverse reaction (%)		
System Organ Class **Preferred Term**	**Very common (>=1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Muscle Spasms		3.5%	
Myalgia		1.7%	
Pain In Extremity		1.7%	
Torticollis		1.7%	
Flank Pain			0.9%
Muscle Twitching			0.9%
Musculoskeletal Chest Pain			0.9%
Nervous System Disorders			
Headache	10.4%		
Dizziness		5.2%	
Paraesthesia		5.2%	
Hypoaesthesia		1.7%	
Ataxia			0.9%
Balance Disorder			0.9%
Hyperaesthesia			0.9%
Memory Impairment			0.9%
Migraine			0.9%
Neuralgia			0.9%
Somnolence			0.9%
Tremor			0.9%
Psychiatric Disorders			
Depression		1.7%	
Insomnia			0.9%
Sleep Disorder			0.9%
Renal And Urinary Disorders			
Proteinuria		1.7%	
Pollakiuria			0.9%
Respiratory, Thoracic And Mediastinal Disorders			
Dyspnoea		1.7%	
Epistaxis		1.7%	
Rhinorrhoea			0.9%
Skin And Subcutaneous Tissue Disorders			

	Frequency of adverse reaction (%)		
System Organ Class **Preferred Term**	**Very common (>=1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Rash		2.6%	
Pruritus		1.7%	
Erythema			0.9%
Hyperhidrosis			0.9%
Night Sweats			0.9%
Psoriasis			0.9%
Vascular Disorders			
Systolic Hypertension			0.9%

Note: Pooled database from all patients who received at least one dose of migalastat in AT1001-011 (0 – 24 months) and AT1001-012 (0 – 30 months). Source: Table 2 Tintext-1112-Smpc-TEAE.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after approval of the medicine 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.

DOSAGE AND 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 ERT.

The recommended dosage regimen in adults and adolescents 16 years and older is 123 mg migalastat (1 capsule) orally once every other day at the same time of day. Capsules must be swallowed whole. The capsules must not be cut, crushed, or chewed.

Missed dose

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

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.

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^2. See ***Pharmacokinetic properties.***

Hepatic impairment

No dosage adjustment of Galafold is required in patients with hepatic impairment. See ***Pharmacokinetic properties.***

Method of administration

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.

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.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

PVC / PCTFE / PVC/Al blister.

Pack size of 14 capsules.

Store in the original package in order to protect from moisture. Store below 30ºC.

NAME AND ADDRESS OF THE SPONSOR

ERA Consulting (Australia) Pty Ltd
Level 3, 88 Jephson Street
Toowong, QLD 4066
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

DD Month YYYY

The prescriber must ensure that consent and treatment of the patient is in accordance with the appropriate state or territory legislation.