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: C₆H13NO₄.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.

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 α‑galactosidase A (α-Gal A) that is required for glycosphingolipid substrate (e.g., GL-3, lyso-Gb3) metabolism. Reduced α-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 α-Gal A, the genotypes of which are referred to as amenable mutations. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes where dissociation of migalastat restores α-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](http://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 |
| 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.288G>C  | c.G288A or c.G288T or c.G288C  | M96I |
| c.289G>C | c.G289C | A97P |
| c.290C>T | c.C290T | A97V |
| c.305C>T | c.C305T | S102L |
| c.311G>T | c.G311T | G104V |
| c.316C>T  | c.C316T  | L106F  |
| c.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 |
| 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 |
| 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 |
| 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 |
| 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  |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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.T706Cor 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 |
| 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 |
| 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 |
| 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 |
| 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) |
| 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?) |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
|  |  | NP GAL 0719 |

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 (AUC0-∞) and mean peak migalastat plasma concentration (Cmax) 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 (AUC0-∞) and reductions of 15% to 40% in mean peak migalastat plasma concentration (Cmax) 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 [14C]-migalastat hydrochloride in the concentration range between 1 and 100 μM.

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 [14C]-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 [14C]-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 (t1/2) 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 m2. 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 m2).

*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 eGFRCKD-EPI was ‑0.40 mL/min/1.73 m2 (95% CI: -2.272, 1.478) in the Galafold group compared to ‑1.03 mL/min/1.73 m2 (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 eGFRCKD-EPI was -0.81 mL/min/1.73 m2 (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/m2 for the Galafold arm and 92.9 g/m2 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/m2 or males with baseline LVMi > 115 g/m2) 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-Gb3 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-Gb3 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/1.73m2.

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.

**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 | Very common(>=1/10) | Common(≥1/100 to <1/10) | Uncommon(≥1/1,000 to <1/100) |
| Preferred Term |
| 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% |
| 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 |  |  |  |
| 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 |  |  |  |
| 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 m2. 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.