Australian Government

Department of Health and Ageing

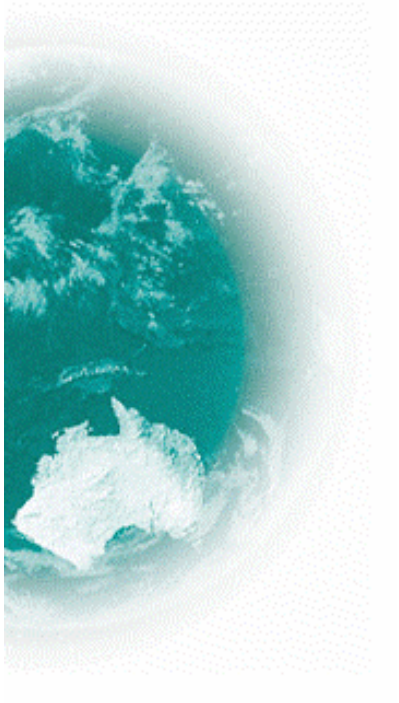
Therapeutic Goods Administration

Australian Public Assessment Report for Agalsidase alfa ghu

Proprietary Product Name: Replagal

Submission No: PM-2009-01140-3-3

Sponsor: Shire Australia Pty Limited



June 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Manufacturing Process
Decision:	Approved
Date of Decision:	7 May 2010
Active ingredient(s):	Agalsidase alfa ghu
Product Name(s):	Replagal
Sponsor's Name and Address:	Shire Australia Pty Ltd PO Box 6240 North Ryde NSW 2113
Dose form(s):	Concentrated solution
Strength(s):	3.5 mg/3.5 mL
Container(s):	Single dose vial closed with a butyl rubber stopper and sealed with an aluminium overseal with a flip off plastic cap.
Pack size(s):	1 single dose vial.
Approved Therapeutic use:	Replagal (agalsidase alfa ghu) is indicated for long-term enzyme replacement therapy of patients with Fabry Disease (α-galactosidase A deficiency).
Route(s) of administration:	Intravenous infusion
Dosage:	0.2 mg/kg every 2 weeks
ARTG Number:	82818

Product Background

Replagal (agalsidase alfa ghu) is a human α-galactosidase A produced by recombinant gene activation techniques in a human cell line (HT-1080) which specifically cleaves the terminal α-linked galactose residues from glycosylated sphingolipid ceramide moieties. The amino acid sequence is that which is encoded by the endogenous human α-galactosidase A gene and the resultant protein has a human glycosylation pattern. Replagal is a homodimeric glycoprotein, with each subunit consisting of 398 amino acids. The protein undergoes post-translational modification by the removal of a 31 residue signal sequence and the addition of 3 N-linked carbohydrate chains. Glycosylation is required for both the activity and stability of the molecule. The unglycosylated or deglycosylated enzyme is inactive. Mannose-6-phosphate (Man6P) is required for its uptake into the target cells and sialylation is required to confer a sufficiently long circulatory half-life to allow the enzyme to reach the target cells.

Fabry disease is a glycosphingolipid storage disorder that is caused by deficient activity of the lysosomal enzyme α-galactosidase A. Globotriaosylceramide (Gb3, also known as ceramide trihexoside, CTH), which is the glycosphingolipid substrate for this enzyme, progressively accumulates within vulnerable cells and tissues of affected patients. Replagal catalyses the hydrolysis of Gb3, cleaving a terminal galactose residue from the molecule. Agalsidase alfa ghu has been produced in a human cell line to provide for a human glycosylation profile that determines biodistribution to allow preferential uptake by target cells. The hydrolysis of Gb3 in affected

individuals causes a reduction in the amount of Gb3 in many cell types in the body, including cells of the liver, heart, kidney and blood vessel endothelial cells as well as in the plasma.

The pharmacodynamic effect (degradation of accumulated globotriaosylceramide, Gb3) of agalsidase alfa occurs in the lysosomes of affected tissues and not in the circulation, where at a neutral pH it is not enzymatically active. For agalsidase alfa, calculations of serum clearance only measure removal from the serum and not whole-body clearance. To produce a consistent pharmacodynamic effect in patients, the critical factors are lysosomal uptake and tissue half-lives of agalsidase alfa. Once transported into the lysosomes, there is no reversibility of tissue uptake and re-release into the circulation.

Fabry disease is a rare X-linked recessive glycosphingolipid storage disorder caused by deficient activity of the lysosomal enzyme, α-galactosidase A. The natural course of the condition is variable, with the first symptoms of acroparaesthesia (burning pain in the extremities associated with numbness and tingling in the hands and feet) usually commencing in childhood. Premature death usually occurs in the fourth or fifth decade of life and results from renal, cardiac or cerebrovascular complications. Heterozygous females have an intermediate level of enzyme activity and are usually asymptomatic or exhibit mild manifestations. Rarely females may be as severely affected as hemizygous males due to skewed X-chromosome inactivation.

Shire Australia Pty Limited has submitted an application to register a new drug substance manufacturing process to replace the current drug substance manufacturing process. In its letter of application, the sponsor states that the new manufacturing process was developed in order to:

1. increase the technology's robustness by implementing a bioreactor (agalAF1) process in place of the previously employed roller bottle (RB) process, and
2. eliminate animal-sourced components.

There were no changes proposed for either the product information (PI) or consumer medicine information (CMI) documents as a result of this particular application. However, the sponsor has appended a late request to remove the gender restriction in the current PI that infusion of Replagal at home may be considered for adult male patients who are tolerating their infusions well. The proposal is that it may be considered for patients who are tolerating their infusions well. The sponsor did supply some data to support this change and these data were reviewed by the Delegate.

There are no changes proposed by the sponsor to the Indications which remain as follows:

Replagal (agalsidase alfa ghu) is indicated for long-term enzyme replacement therapy of patients with Fabry Disease (α-galactosidase A deficiency).

Apart from the text on home infusion, there are no changes proposed to the Dosage and Administration section.

Regulatory Status

Replagal (AUST R 82818) was entered on to the Australian Register of Therapeutics Goods on 17 May 2002.

The new manufacturing process for the drug substance was approved in the European Union (EU) on 28 April 2009 and Switzerland on 27 April 2010.

Replagal is not approved in the USA due to the granting of market exclusivity to a competitor agalsidase product in accordance with the Orphan Drug Act.

A similar application to the current Australian submission is still under review in Canada.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Structure

The mature enzyme is a glycoprotein which consists of a homodimer of two approximately 50,000 dalton molecular weight subunits, each consisting of 398 amino acids. Agalsidase alfa is post-translationally modified by the removal of a signal sequence of 31 residues and by the addition of carbohydrate chains to 3 N-linked glycosylation sites. Newly synthesized agalsidase alfa is targeted to the lysosome via mannose-6-phosphate (M6P) residues on its carbohydrate. Inside the cell there are M6P receptors in the Golgi complex which direct the enzyme to the lysosomes. The M6P moiety is also recognized by specific M6P receptors on the cell surface.

Manufacture

The manufacturing process is summarised as follows:

Cell culture growth in bioreactors and recovery of unpurified bulk intermediate, followed by a purification process consisting of chromatographic and filtration steps, as well as viral inactivation/reduction steps.

Summary of Manufacturing Process Change

The current approved manufacturing process for agalsidase alfa, termed the RB process, uses a roller bottle cell culture platform that involves the use of bovine serum and animal derived proteins. In order to remove animal-derived components from the process and to enhance the operational efficiency, the agalAF1 process has been developed with the following key changes to the manufacturing process, as outlined in the sponsor's letter of application, as follows:

- adaptation of the approved master cell line and cell culture process to culture media devoid of animal derived components without changing the cell substrate
- change from the use of roller bottles to a bioreactor to enhance the operational efficiency and increase the robustness of the drug substance manufacturing process
- modification of the purification process to accommodate the cell culture process changes and to ensure the drug substance quality
- revision to the drug substance and drug product release specifications as a consequence of the above changes

There are no changes to the Replagal drug substance and drug product formulations and manufacturing sites, the drug product manufacturing process, the drug product analytical methods nor the drug product container closure.

Physical and Chemical Properties

The products derived from the agalAF1 process have been demonstrated to be comparable to that derived from the RB process with respect to strength, purity/impurity, potency, safety and quality. The agalAF1 process has been appropriately validated and it has been demonstrated that the manufacturing process is robust, and that the levels of impurities in agalsidase alfa are well controlled.

Specifications

The release specifications for agalAF1 drug substance are the same as for the current commercial roller bottle material, with a few exceptions. The assays to control residual animal-derived components have been removed, because bovine serum is no longer a component of cell culture media. An assay that provided redundant information to the other assay has been removed. The qualitative host cell protein analysis was replaced with a quantitative host cell protein assay. Changes to the acceptance criteria for some assays were modified.

Stability

Stability data for drug substance manufactured by the agalAF1 process confirm that agalsidase alfa is expected to be maintained through 24 months when stored at -65 to -85°C. Therefore the shelf-life is established at 24 months at -65 to -85°C. Stability data will continue to be collected in accordance with the established stability protocol.

Drug Product

The formulation and manufacture are unchanged.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were reviewed. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability studies to date substantiate the proposed shelf-life for agalAF1 process derived drug product is 24 months at 5±3°C. Stability studies will be continued and data collected in accordance with the established stability protocol.

Photostability studies using Replagal agalAF1 process material were also conducted. The results show no evident photo-induced changes following exposure of Replagal in its market package.

The test results for all assays were comparable to the dark control. Earlier in-use stability studies have also shown that Replagal, diluted as it would be for clinical administration, is physically stable for at least 24 hours at room temperature.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. There are no issues of concern.

III. Nonclinical Findings

Introduction

This submission concerns a change in the agalsidase alfa drug substance manufacturing process which aims to increase capacity and to remove animal derived cell culture media: the agalsidase alfa animal component free bioreactor (agalAF1) manufacturing process will replace the current roller bottle (RB) process. The key issue is the comparability of the drug substance derived from the two methods in terms of quality, safety and efficacy.

Evaluation of the comparability of the agalAF1 and RB-derived products based on physicochemical methods did not reveal any major structural differences. However, there appears to be an increase in Man6P residues and less sialic acid residues in the agalAF1 product, which could theoretically result in differences in cellular uptake and plasma pharmacokinetics. Therefore, the aim of the three submitted nonclinical studies was to assess whether these changes altered the biological activity, pharmacokinetics and tissue distribution of agalsidase alfa. These studies appropriately used the intravenous (IV) route of administration, which is the intended route of administration in humans.

Pharmacology

Pharmacodynamic comparability

Pharmacodynamic comparability was assessed in a non-Good Laboratory Practice (GLP) study using the *Gla*^{tm1Kul} knockout mouse, a model for human Fabry disease. The *Gla*^{tm1Kul} mouse is deficient in a-galactosidase A and accumulates high levels of Gb3. A significant reduction of

accumulated Gb_3 levels following agalsidase alfa administration was used as a pharmacodynamic measure of enzyme activity *in vivo.* Administration of material from both processes resulted in a statistically significant reduction in Gb_3 levels in heart and liver compared to vehicle controls, with a similar level of percent reduction in both tissues.

The data broadly demonstrated the pharmacodynamic comparability of the formulations in terms of reducing Gb_3 levels in a relevant animal model. However, the study design was far from optimal as only one time point was used and the lowest doses were already near the top of the dose-response curve, thus decreasing the sensitivity of the experiment to detect any differences.

Pharmacokinetics

Pharmacokinetic comparability

The effects of the manufacturing change on plasma pharmacokinetics (PK) and cellular uptake (tissue distribution) were investigated in GLP-compliant studies in monkeys and rats, respectively.

Absorption

The cynomolgus monkey was an appropriate species to use for this study as the PK of many biotechnology-derived products have been shown to be similar in humans and in non-human primates. The crossover design of this study helped to minimise animal use while increasing comparability within similar sample sizes. Each formulation was well tolerated at a dose of 1 mg/kg IV and did not result in any adverse clinical signs or changes in food consumption or body weight.

The plasma pharmacokinetics of the two products were shown to be comparable, as demonstrated by the fit of the ratios of mean normalized maximal plasma concentration (C_{max}), normalized area under the plasma concentration time curve from zero time to 240 minutes (AUC_{0-240}), and normalized area under the plasma concentration time curve from zero time to infinity ($AUC_{0-\infty}$) values to the standard 90% confidence interval (0.80-1.25), as well as by the similarity of model-dependent pharmacokinetic parameters such as half-life ($t_{1/2}$), clearance (CL) and volume of distribution (V_d) at steady-state. While the mean $t_{1/2}$ for agalsidase alfa from the agalAF1 process was about 25% shorter than that for the RB process product (29.5 vs. 38.4 minutes), as might be expected from decreased sialylation, this difference was not statistically significant due to high individual variability. Moreover, this difference was not observed for $t_{1/2}$ values measure in the rat distribution studies.

Distribution

A GLP-compliant biodistribution study using ^{125}I-agalsidase alfa was performed in Sprague Dawley (SD) rats as this is an accepted rodent species for use in absorption/distribution/metabolism/excretion (ADME) studies, and was also the rodent species utilized in the toxicology program for Replagal.

The biodistribution, pharmacokinetic parameters (90% confidence intervals), excretion and total recovery of radioactivity were shown to be comparable for the two lots following a single IV dose of 0.2 or 1.0 mg/kg agalsidase alfa to male rats.

Nonclinical Summary and Conclusions

Pharmacodynamic comparability of agalAF1- and RB-derived agalsidase alfa was demonstrated in a non-GLP study using the *Gla^{tm1Kul}* knockout mouse, a model for human Fabry disease. The two products showed similar reductions in globotriaosylceramide (Gb_3) levels in both the heart and liver compared to vehicle controls.

In a crossover GLP study in cynomolgus monkeys using 1.0 mg/kg IV agalsidase alfa, the pharmacokinetic comparability of the two test article lots was demonstrated by the fit of the ratios of mean normalized C_{max}, normalized AUC_{0-240}, and normalized $AUC_{0-\infty}$ values to the standard 90%

confidence interval (0.80-1.25), as well as by the similarity of model-dependent pharmacokinetic parameters such as $t_{1/2,}$ CL and volume of distribution at steady-state.

A GLP biodistribution study using ^{125}I-agalsidase alfa in male SD rats showed comparable biodistribution, plasma pharmacokinetics, excretion and total recovery of radioactivity for agalAF1- and RB-derived agalsidase alfa following a single IV dose of 0.2 or 1.0 mg/kg.

Issues addressed by the nonclinical data

The submitted nonclinical data suggest that the observed small differences in C-terminal heterogeneity and glycosylation do not lead to any biologically significant differences in either pharmacodynamic or pharmacokinetic properties, at least in relevant animal models.

Therefore, there are no nonclinical objections to the registration of Replagal produced by the new manufacturing process.

Issues not addressed by the nonclinical data

Nonclinical studies do not address the potential differences in immunogenicity that may arise in humans as a result of the observed differences in physicochemical properties between agalAF1 and RB-derived agalsidase alfa lots. This issue can only be addressed by clinical investigation of antibody formation and immunogenicity.

IV. Clinical Findings

Clinical Summary and Conclusions

There were no clinical data submitted with the original submission.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was a comprehensive evaluation of the quality data, of which only a summary was described in Section II. In the initial glycosylation evaluation report, the evaluator stated that the proposed changes have the potential to significantly change the glycosylation of the protein and concomitantly its action. In his conclusion to this report, the evaluator stated that the charge distribution and glycan profiling demonstrated unequivocally that the change in manufacturing process results in a significantly different glycosylation profile. The product made by the proposed bioreactor process has statistically significantly more Man6P residues and fewer sialic acid residues than the product made by the current registered process. As noted by the evaluator, this would be expected to result in a more efficient cellular uptake and a shorter circulatory half-life. Instead a less efficient cellular uptake was observed. Circulatory half-life data has been evaluated by the quality evaluator. At the end of the report, the evaluator asked three questions. The first related to differing data about the proportions of glycan groups, the second related to two sets of cellular uptake data which appeared to show opposite results for how well the bioreactor-manufactured product was taken up into cells compared with the roller bottle batches and the third commented that the burden of proof of biocomparability, despite the observed differences in glycosylation, was still on the sponsor.

The final glycosylation evaluation report analysed the sponsor's responses to the above three questions. In relation to the difference in data for glycan peak groups, this was explained by the fact that the data were obtained using two different analytical methods, one of which, the

fluorometric method, is not a validated method and was only used during early development of agalsidase alfa manufactured via the roller bottle process. This explanation was considered acceptable by the evaluator. In relation to the two sets of data supplied for cellular uptake, it would appear that, once more, this came about because of the use of two different analytical procedures. The sponsor argued that direct comparison of the data between methods was not appropriate but that both results are considered valid metrics within each assay system. In other words, within the precision of the analytical procedures, materials from the two processes have comparable cell uptake ability by both assay methods. The answer to the third question touched on the glycosylation analysis, cellular uptake, tissue distribution and pharmacokinetics, the last two topics being more specifically within the domain of the quality evaluator. The sponsor argued that the comparability of the roller bottle and agalAF1 methods has been extensively demonstrated both *in vitro* and *in vivo*.

The Delegate quoted from the overall conclusions of the biochemistry evaluator:

"The characterization methods have demonstrated an alternative glycan profile for material produced by the proposed process. The most significant of these differences are the higher level of Man6P found in the bioreactor material and the variation in the relative proportions of sialylated glycans. A number of analytical techniques have been used to fully characterise the glycan profile and to determine the comparability of the material derived from the two processes. The sponsor has sought to explain some of the variation in the detected glycans and post-translational modification seen in the materials as being due to variance in the analytical techniques employed. This may in part be true. The sponsor has further demonstrated through the use of *in vitro* bioassays that the key biological processes[1] of cellular uptake are comparable and that the agal AF1 material is well within the historical range of roller bottle derived material".

The final recommendation of the biochemistry evaluator was that there are no objections to the change in registration of Replagal on the basis of glycosylation properties.

The Delegate expressed some concerns with the above. The first is that there would appear to have been no acknowledgement in the submission originally provided that there were a number of different analytical techniques used to assess various parameters. It was left to the evaluator to ask the relevant questions. It is clear that the two products have very different chemical identities. This problem is compounded by the presentation of data derived using different analytical techniques. The Delegate requested some explanation from the sponsor as to why it was not thought important to point out these differences at the beginning. The Delegate's second concern was that the biochemistry evaluator, despite his final recommendation, still has reservations concerning the differences between the analytical techniques employed. This is reflected in the evaluator's comment that "this may in part be true" which was in reference to the sponsor's attempt to explain the variations in certain parameters on the basis of the different analytical techniques employed. The Delegate had concerns with the cellular uptake data, which, according to the evaluator, has one set of data which shows that the bioreactor-manufactured product is taken up less effectively than the roller bottle batches, despite higher Man6P levels while there is another set of data which indicates the exact opposite. The sponsor's response is that direct comparison of these datasets is not appropriate, yet both results are considered valid metrics within each assay system. If the latter is truly the case, one is apparently left with the situation where there are two equally valid results, within the limitations and specifications of each, but where the two results are in opposite directions. The sponsor was requested to give a detailed commentary on each of the above concerns.

There were no objections on viral and prion safety grounds to the registration of the new drug substance manufacturing process.

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[1] Delegate's amendment – in the original the singular 'process' is used

The ratified recommendation of the 129th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC), held on 23 November 2009, was that there should be no objection on quality and pharmaceutic grounds to approval. However, the PSC did raise concerns about the degree of characterisation of the product subsequent to the change and considered that the sponsor should be asked to provide human pharmacokinetic data if available.

The sponsor's comment in response to the PSC recommendation was as follows:

In regard to human pharmacokinetic data comparing the two manufacturing processes, Shire has not conducted a human pharmacokinetic study for the reasons outlined….

The basis for this statement would appear to be that the sponsor has claimed that the agalAF1 derived material has demonstrated biocomparability to the currently registered material in *in vitro* internalisation assays and *in vivo* non-clinical studies.

Nonclinical

There was also a comprehensive evaluation of the nonclinical data. The nonclinical data package consisted of three intravenous studies that aimed to assess whether the differences in C-terminal and glycosylation patterns between the products of the two manufacturing methods altered the biological activity, pharmacokinetics and tissue distribution of agalsidase alfa *in vivo*.

Pharmacodynamic comparability was assessed in a non-GLP study using the *Gla*^{tm1Kul} knockout mouse, a model for human Fabry disease. This mouse type is deficient in α-galactosidase A and accumulates high levels of Gb3. Administration of material from both processes resulted in a statistically significant reduction in Gb3 levels in heart and liver compared to vehicle controls, with a similar level of percentage reduction in both tissues. As noted by the nonclinical evaluator, the data broadly demonstrated the pharmacodynamic comparability of the formulations in terms of reducing Gb3 levels in a relevant animal model. However, as also noted by the evaluator, the study design was far from optimal as only one time point was used and the lowest doses were already near the top of the dose-response curve, thus decreasing the sensitivity of the experiment to detect any differences.

In a crossover GLP-compliant study in cynomolgus monkeys using 1.0 mg/kg IV agalsidase alfa, the pharmacokinetic absorption/exposure comparability of the two test article lots was demonstrated by the fit of the ratios of mean normalized C_{max}, normalized AUC_{0-240} and normalized $AUC_{0-\infty}$ with respect to the standard 90% confidence interval [0.80, 1.25], as well as by the similarity of model-dependent pharmacokinetic parameters such as $t_{1/2}$, CL and volume of distribution at steady state. The evaluator made the comment that the cynomolgus monkey was an appropriate species to be used for this type of study.

A GLP-compliant biodistribution study using ^{125}I-agalsidase alfa in male SD rats showed comparable biodistribution, plasma pharmacokinetics, excretion and total recovery of radioactivity for agalAF1- and roller bottle-derived agalsidase alfa following a single IV dose of 0.2 or 1.0 mg/kg. SD rats are an accepted rodent species for use in ADME studies and were also the rodent species utilized in the toxicology programme for Replagal.

The nonclinical evaluator concluded that the submitted nonclinical data suggest that, in relevant animal models, the observed small differences in C-terminal heterogeneity and glycosylation do not lead to any biologically significant differences in either pharmacodynamic or pharmacokinetic properties.

However, equally importantly, the nonclinical evaluator concluded that the nonclinical studies do not address the potential differences in immunogenicity that may arise in humans as a result of the observed differences in physicochemical properties between agalAF1 and roller bottle-derived agalsidase alfa lots. The further comment was made that this issue can only be addressed by clinical investigation of antibody formation and immunogenicity.

The sponsor responded to the nonclinical evaluation report, taking up the issue of the potential immunogenicity of agalsidase alfa ghu manufactured using the bioreactor process. The response was a one-page document, previously submitted to the European Medicines Agency (EMEA) which had raised an identical concern. This document will be discussed under the next heading as it actually discusses results in human subjects.

Clinical

There was no collection of clinical data in the original submission.

As commented upon by the nonclinical evaluator, the sponsor submitted a response to the nonclinical evaluator's concern that the issue of potential differences in immunogenicity that may arise in humans as a result of the observed differences in physicochemical properties between agalAF1- and roller bottle-derived agalsidase alfa lots can only be addressed by clinical investigation of antibody formation and immunogenicity. Since the response was only one page in length and was in fact the only clinical commentary submitted, the Delegate reproduced it in full for the meeting of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC). The ACPM was also provided with copies of the EMEA Quality Assessment Report, the EMEA Non-clinical/Clinical Assessment Report and the various EMEA approvals which were supplied by the sponsor. Members of the ACPM were able to observe that similar issues were raised by the corresponding EMEA evaluators.

Post-marketing experience

There was no post-marketing data supplied which related to the agalAF1-derived agalsidase alfa. The sponsor was requested to provide whatever data is now to hand for the new product, particularly as the latter has been approved in the EU since April 2009.

Risk-Benefit Analysis

There are a number of concerns with this application and the submission that accompanied it. As noted above, the Delegate was not completely satisfied that the sponsor has answered all the questions of the biochemistry evaluator satisfactorily. In particular, the Delegate remained unconvinced by the explanation regarding the different results for cellular uptake. It is evident also that the biochemistry evaluator, despite his overall conclusion, still entertained reservations. The Delegate asked three questions to which he requested detailed responses.

The nonclinical evaluator made the comment that the design of the study of reduction of Gb3 levels in *Gla*^{tm1Kul} knockout mice was far from optimal as only one time point was used and the lowest doses were already near the top of the dose-response curve, thus decreasing the sensitivity of the experiment to detect any differences. The sponsor was requested to make a comment on this issue.

However, by far the most important issue raised by the nonclinical evaluator concerns the lack of any clinical trial immunogenicity data. It is extremely difficult to compensate for this lack. There was no clinical trial data submitted with the original submission. The nonclinical studies did not include any immunogenicity comparisons between the new and old products. The only clinical trial data submitted was in fact in response to this concern of the nonclinical evaluator. This was a one-page summary of what is presently known about immunological seroconversion in response to agalsidase alfa. It would appear to be an infrequent event with no neutralizing antibodies identified so far and the clinical consequences of IgG antibodies unclear.

There was some evidence from an ongoing trial in the USA (TKT029) in which both old and new products have been used. This supportive data indicates that after the changeover to agalAF1 material:

- no AEs have been reported in any of the 11 patients who had undergone the maximum treatment duration of 25 weeks

- none of the 11 subjects has developed or increased IgG titres after treatment for 3 months with enzyme manufactured with the agalAF1 process
- Gb3 levels have remained low and stable throughout the treatment period.

The Delegate emphasized that only this summary has been seen. No actual individual patient data has been seen or any clinical study reports, either interim or completed. The Delegate noted that the sponsor intends to revise this ongoing study by increasing the total number of patients to be monitored for immunogenicity from 11 to 25 and to follow these patients for 52 weeks of treatment. It also appears that as well as being tested for antibodies against Replagal at Weeks 13 and 25, the subjects will be tested every 26 weeks thereafter. It was considered curious that even although the 11 patients had undergone the maximum treatment duration of 25 weeks at that time, only IgG titres at 3 months (presumably the Week 13 time point) have been commented on above. No immunogenicity data at the Week 25 time point has been provided. Nor has any information relating to immunoglobulin E (IgE) or neutralizing antibodies been provided.

As part of the EMEA approval process, the sponsor has agreed to provide to the EMEA an interim report after 52 weeks exposure of the 11 patients as a post-approval commitment, as well as the final report after all 25 patients have completed 52 weeks of therapy. The EMEA has also requested that the sponsor should report earlier in case of any irregular, unexpected results and should gather data on 0, 3, 6, 9 and 12 months of therapy.

The Delegate requested that the sponsor provide, as part of its pre-ACPM response, the most up-to-date information available with regard to efficacy, safety and immunogenicity from the ongoing study, including comparisons of whatever immunogenicity results are available for weeks 0, 13, 25 and 51/52. This discussion should include IgE and/or neutralizing antibody results as well as those for IgG antibodies. Much of this data should be available because data on 11 patients treated for 25 weeks was presented to the EMEA's Committee for Medicinal Products for Human Use (CHMP) in time for its approval in April 2009.

Thus there have been doubts raised about the quality of the quality and nonclinical data and the Delegate has asked the sponsor to address the relevant issues. However, by far the most important deficiency of the submission has been the lack of evaluable clinical data, particularly immunogenicity data. Without any such data whatsoever, the Delegate would find it impossible to recommend approval of the application. However, it seems that there is in limited form some clinical data relating to immunogenicity from the ongoing TKT029 study. The sponsor has been requested to provide a much more comprehensive summary of the available data from this study. At this stage, the Delegate was only able to recommend a qualified approval.

The Delegate proposed to approve the application contingent on satisfactory responses to the questions asked of the sponsor by the Delegate (see below).

The particular advice of the ACPM was requested in relation to the following issues:

1. whether it regards the lack of any evaluable human pharmacokinetic and immunogenicity data as an insurmountable barrier to approval or whether the limited clinical data available from the ongoing study TKT029 may be regarded as adequate for the purpose of this submission
2. whether there should there be any reference to the new manufacturing process for the drug substance in the PI
3. the views of the ACPM in relation to the conditions of registration recommended by the Delegate (see below).

The sponsor was asked to comment on the following issues:

1. the Delegate has enumerated concerns relating to the quality data and evaluation and has requested a comment on each

2. the nonclinical evaluator made the comment that the design of the study of reduction of Gb3 levels in *Gla*^{tm1Kul} knockout mice was far from optimal as only one time point was used and the lowest doses were already near the top of the dose-response curve, thus decreasing the sensitivity of the experiment to detect any differences
3. the lack of any evaluable human pharmacokinetic or immunogenicity data
4. how it has met/is meeting its timetable of post-marketing commitments with the EMEA.

The sponsor was also been asked to provide:

1. the most up-to-date information available with regard to efficacy, safety and immunogenicity from the ongoing TKT029 study, including comparisons of whatever immunogenicity results are available for weeks 0, 13, 25 and 51/52. This discussion should include IgE and/or neutralizing antibody results as well as those for IgG antibodies
2. whatever post-marketing data is available in relation to the new agalAF1-derived product.

In its pre-ACPM submission, the sponsor provided the following response:

Immunogenicity

The sponsor did not specifically design or conduct a clinical study to determine the extent of immunogenicity that may result from the agalsidase alfa molecule manufactured using the new animal free (agalAF1) process. However, as described below, it has committed to monitoring 25 paediatric patients in Study TKT029 for development of antibodies using Replagal manufactured via the animal free, bioreactor process.

Study TKT029 is an ongoing Phase 2, open-label, single arm, multi-centre study to assess the safety, including immunogenicity, and pharmacokinetics of Replagal in paediatric patients. It is an extension study of Study TKT023 which has previously been submitted to TGA. A total of 12 patients from TKT023 continued to receive treatment in TKT029 and entered subsequent treatment cycles with RB Replagal. During the third quarter of 2008, the 11 remaining patients (Cohort 1) in the ongoing TKT029 study were transitioned to treatment with Replagal manufactured via the agalAF1 manufacturing process. With the exception of one patient who discontinued due to lack of protocol compliance in June 2009, a total of 10 patients remain in the ongoing study at the time of this communication (January 2010). The sponsor has revised the ongoing TKT029 study to increase the total number of patients to a total of 25 by enrolling an additional 14 treatment naive patients (Cohort 2) into the study and to evaluate them for safety including immunogenicity. Cohort 2 will be treated with agalAF1 Replagal only, and safety data will be collected for at least 52 weeks. The first patient in Cohort 2 is anticipated to be enrolled in March 2010.

The available antibody data presented in this response cover the period from the first dose of RB Replagal received in TKT029 through to treatment with agalAF1 Replagal until the data cutoff date on 28 October 2009 in TKT029 Cohort 1. The results are summarised below.

During treatment with RB Replagal:

- *No treatment-related SAEs were reported*
- *No patient was IgE positive*
- *Three patients developed antibody positive responses:*

  - One patient (X) developed low IgG titres against RB Replagal on Week 55 of treatment and titres remained positive throughout treatment.

  - One patient (Y) developed low IgM and IgA titres against RB Replagal only on Week 13 of treatment. Subsequently the patient tested negative for all 4 antibodies responses until week 211 of RB Replagal treatment, the week prior to receiving first dose of agalAF1 Replagal. At week 211 of treatment, the patient tested positive for IgM antibody.

- One patient (Z) developed low IgM titres against RB Replagal only on Week 185 of treatment. Subsequently, this patient tested negative for all antibodies during RB Replagal treatment.

After the transition to the agalAF1 Replagal (as of the data cutoff date 28 October 2009)

- *No treatment-related SAEs were reported*
- *No patient was IgE positive*
- *No additional patient seroconverted after agalAF1 transition:*

- Patient X continued to be IgG positive after the transition to agalAF1 Replagal and maintained the antibody response seen before transition.

- Patient Y tested positive for IgM antibody on weeks 12 and 26 of agalAF1 Replagal treatment.

- Patient Z tested positive for IgM antibody only on Week 62 of agalAF1 Replagal treatment.

In summary, very few patients have seroconverted since the start of TKT023. No patients have seroconverted following transition from RB to agalAF1 Replagal.

As requested by the Delegate, Shire Australia will submit a Category 1 application of the interim report after 52 weeks of exposure in the initial 11 patients in the ongoing TKT029 study who transitioned from RB to agalAF1 product and subsequently a Category 1 application will be submitted for the final report after 52 weeks of exposure in the planned 25 patients in study TKT029.

Postmarketing Surveillance

Approximately 500 patients have received treatment with agalAF1 Replagal since it has been commercially available from July 2009. Available information does not show any concerns about safety, efficacy or immunogenicity and no serious adverse drug reactions have been reported since commercial supply of agalAF1 Replagal has commenced. In the EU, Shire committed to follow up the change to agalAF1 Replagal product in the regular Periodic Safety Update Reports (PSURs) including batch traceability. The July 2009 start date allowed the supply chain to be depleted in the preceding months in order to minimise the amount of RB stock held at customer sites within Europe. In clinical studies, samples for antibody testing are obtained at baseline and at protocol-specified time points. Specimens are analysed by Shire for presence of IgG, IgA, IgM and IgE. Antibody testing was carried out for 67 patients reported in the latest PSUR (PSUR No 10, covering 4 August 2008 to 3 August 2009) which follows on from the previous PSUR (PSUR No 9, covering 4 August 2007 to 3 August 2008) where 39 patients were tested. Although patients were not taking (sic) agalAF1 Replagal at the time, the sponsor expected some antibody data on this product in the next PSUR period. Shire is on schedule to fulfilling the EU post-approval commitments for the approval of agalAF1 Replagal variation, including providing a TKT029 study interim report of 52 weeks of agalAF1 Replagal exposure of the current 11 patients in January 2010, a subsequent final report after all 25 patients complete 52 weeks of therapy with Replagal AgalAF1, and continuing safety monitoring of agalAF1 Replagal with updates provided in the routine PSURs.

Pharmacodynamic Comparability

The Delegate has noted that only one time point was used in the pharmacodynamic study in mice which demonstrated pharmacodynamic comparability of the two products. The pharmacodynamic comparability between agalsidase alfa derived from both agalAF1 and RB processes utilised the murine knockout (Glatm1Kul) disease model. This is the most relevant model of Fabry disease but it has inherent limitations. In the experience of the sponsor, there is considerable heterogeneity in the initial tissue accumulation and subsequent reaccumulation of Gb3. As a consequence of this

heterogeneity, the sensitivity of the assay to distinguish subtle differences in substrate catabolism by the enzyme is less than would be preferred. In spite of the sensitivity limitations, the data obtained from intravenous agalsidase alfa administration, 3 times a week for 2 weeks, clearly demonstrates that considerable Gb3 clearance is obtained regardless of the manufacturing processes. The two week time point was chosen to be consistent with previous nonclinical development studies and is the ideal time frame to assess maximal Gb3 reduction. As the study was not intended to measure the rate of Gb3 re-accumulation, no additional time points were included.

Analytical Techniques

Characterisation of complex glycoproteins such as agalsidase alfa necessitates multiple analytical methods, each providing a different perspective of the protein and influenced by the sample preparation technique, the detection technology, and assay variability. The sponsor acknowledged that it could have clearer in the original application in providing a comparative analysis of the different assays used for comparability studies, specifically with regards to cellular uptake and its relationship with the enzyme's M6P content, both of which are critical quality attributes required for the total biological activity of agalsidase alfa along with the enzyme activity to remove the sulfate group. The sponsor provided a summary of the analytical techniques used.

From the sponsor's collective knowledge of the assay capability and the batches evaluated to date, there are minor differences in the amount of M6P containing glycans with the agalAF1 material being higher than the RB material. The extent of this difference varies with the assay used.

Since M6P containing glycans are required for the enzyme to be taken up and internalised by cells, the sponsor evaluated potential impact of the observed M6P differences on the in vitro and in vivo potency. Two cellular uptake assays were used for evaluating the potency attribute:

• The single dose internalisation assay which is the validated lot release assay, determines the level of internalised enzyme at a single concentration of enzyme added to the cells. This assay has much higher analytical variability than a subsequently introduced dose-response cellular uptake bioassay. The apparent lower internalisation observed for the agalAF1 lots by the initial internalisation lot release assay was due to this analytical variability. This is made more apparent when much higher internalisation results were obtained for the agalAF1 lots when tested in a subsequent assay.

• The dose-response assay analyses the amount of internalised enzyme as a function of enzyme concentration added to the cells, and compares the dose response curve of sample with that of a reference standard. This assay demonstrated a slightly higher level of cellular uptake for agalAF1 materials which appropriately correlates with the slightly higher level of M6P containing glycans.

The differences in these quality attributes triggered the nonclinical comparability studies. Pharmacokinetic, biodistribution, and pharmacodynamic studies were conducted in relevant animal models. As concluded by the nonclinical evaluator, the in vitro differences in the level of M6P containing glycans and cellular uptake, did not ultimately have biological in vivo significance.

Should this submission be eventually approved, the Delegate recommended the imposition of the following conditions of registration:

1. the submission as evaluable data, that is, lodged as a category 1 application, of the interim report after 52 weeks of exposure in the 11 patients in the ongoing study TKT029
2. the submission as evaluable data, that is, lodged as a category 1 application, of the final report after 52 weeks of exposure in the planned 25 patients in the ongoing study TKT029; in the event of incomplete recruitment to this study and its termination earlier than anticipated, the lodgement of the final study report will be required as a category 1 application

3. the provision to the TGA of a summary of efficacy, adverse event and immunogenicity data after each of 0, 3, 6, 9 and 12 months of therapy as proposed under the Sponsor Proposal Immunogenicity Plan outlined in the relevant EMEA type II variation assessment report.

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission and in making this recommendation, the ACPM noted that Fabry disease is a rare X – linked recessive disease which can lead to premature death, and the treatment options are limited. The Committee viewed the provision of clinical immunogenicity data as essential in such applications as the glycosylation pattern of the active ingredient has changed. Therefore the ACPM endorsed the conditions of registration proposed by the Delegate. In addition, the Committee had no objections to a home-based infusion programme for patients, providing they have been well stabilized on the therapy in a controlled, hospital setting beforehand.

The specific conditions of registration should include:

- submission of immunogenicity, efficacy and safety data from the ongoing study in the USA, TKT029 including comparisons of whatever immunogenicity results are available for weeks 0, 13, 25 and 51/52.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Replagal (containing agalsidase alfa ghu) for the indication:

long-term enzyme replacement therapy of patients with Fabry Disease (α-galactosidase A deficiency).

Specific conditions of registration included:

- The submission as evaluable data, that is, lodged as a category 1 application, of the interim report after 52 weeks of exposure in the 11 patients in the ongoing study TKT029
- The submission as evaluable data, that is, lodged as a category 1 application, of the final report after 52 weeks of exposure in the planned 25 patients in the ongoing study TKT029; in the event of incomplete recruitment to this study and its termination earlier than anticipated, the lodgement of the final study report will be required as a category 1 application
- The provision to the TGA of a summary of efficacy, adverse event and immunogenicity data after each of 0, 3, 6, 9 and 12 months of therapy as proposed under the Sponsor Proposal Immunogenicity Plan outlined in the relevant EMEA type II variation assessment report.
- The first five batches of Replagal (agalsidase alfa ghu) manufactured by the new process imported into Australia are not released for sale until: (1) samples of each batch have been tested and approved by the TGA Office of Laboratories and Scientific Services (OLSS), and/or (2) the manufacturer's release data have been evaluated and approved by OLSS.

Attachment 1. Product Information

PRODUCT INFORMATION

REPLAGAL® (agalsidase alfa ghu)

NAME OF THE DRUG

Replagal 3.5 mg/3.5 mL concentrated injection vial

Active Ingredient: agalsidase alfa ghu.

DESCRIPTION

Agalsidase alfa ghu is a human α-galactosidase A produced by genetic engineering technology. Agalsidase alfa ghu is a homodimer comprised of 2 approximately 50,000 dalton subunits, with each subunit containing 398 amino acid residues. The product is synthesised by a human cell line and has the identical amino acid sequence as that of α-galactosidase A produced in human tissues. Replagal is now manufactured using a serum-free bioreactor process.

Each 3.5 mL vial of Replagal contains 3.5 mg of agalsidase alfa ghu, monobasic sodium phosphate, polysorbate 20, sodium chloride, sodium hydroxide and water for injections. Replagal is provided as a sterile solution intended for intravenous administration. The drug product is supplied in a single-dose vial.

PHARMACOLOGY

General

Fabry Disease is a glycosphingolipid storage disorder that is caused by deficient activity of the lysosomal enzyme α-galactosidase A. Globotriaosylceramide (Gb3, also known as ceramide trihexoside, CTH), which is the glycosphingolipid substrate for this enzyme, progressively accumulates within vulnerable cells and tissues of affected patients. Endothelial, perithelial, and smooth muscle cells of the vascular system, renal epithelial cells, myocardial cells, dorsal root ganglia, and cells of the autonomic nervous system are selectively damaged by Gb3. The disease typically is characterised by recurrent episodes of severe pain in the extremities, heat intolerance, gastrointestinal distress and associated malabsorption, hypohydrosis, characteristic cutaneous lesions known as angiokeratomas, and a distinctive but asymptomatic corneal dystrophy. Vital organs are affected, and renal failure, myocardial infarctions, and cerebrovascular events are common clinical sequelae, commonly resulting in life expectancy to the fourth or fifth decade.

Replagal catalyses the hydrolysis of Gb3, cleaving a terminal galactose residue from the molecule. Agalsidase alfa ghu has been produced in a human cell line to provide for a human glycosylation profile that determines biodistribution to allow preferential uptake by target cells. The hydrolysis of Gb3 in affected individuals causes a reduction in the amount of Gb3 in many cell types in the body, including cells of the liver, heart, kidney, and blood vessels, and in the plasma. As a result, Replagal causes an improvement in or stabilisation of renal function and structure, a reduction in pain, a decrease in pain medication usage, an improvement in pain-related quality of life, and a decrease in cardiac mass with an associated improvement in cardiac function.

Pharmacokinetics

The pharmacokinetic properties of Replagal produced through the original roller bottle process have been studied in both adult males and females with Fabry Disease. Six dosages (ranging from 0.01 to 0.2 mg enzyme/kg body weight) were administered to male patients as 20 to 40 minute intravenous (IV) infusions while female patients received 0.2 mg enzyme per kg body weight as 40 minute infusions. The pharmacokinetic properties were essentially unaffected by the dose of the enzyme. Peak plasma concentrations were noted immediately after the completion of the infusions, and the absolute bioavailability of Replagal was estimated to be 100%. Following a single IV dose, Replagal had a biphasic distribution and elimination profile from the circulation. Pharmacokinetic parameters were not significantly different between male and female patients. At 0.2 mg/mL the elimination half-life of the protein from the blood was approximately 108 minutes in males (n=10) and 89 minutes in females. Plasma clearance after IV infusion was approximately 193 mL/minute in males compared with 140 mL/min in females and volume of distribution was approximately 17% of body weight in both sexes. Based on the similarity of pharmacokinetic properties in both males and females, tissue distribution in major tissues and organs is expected to be comparable in male and female patients.

In 24 children (aged 7-18 years), Replagal administered at 0.2 mg/kg was cleared faster from the circulation than in adults. Mean clearance of Replagal in children (aged 7-11 years), in adolescents (aged 12-18 years), and adults was 4.2 mL/min/kg, 3.1 mL/min/kg, and 2.3 mL/min/kg, respectively. Pharmacodynamic data suggest that at a dose of 0.2 mg/kg Replagal, the reductions in plasma Gb3 are more or less comparable between adolescents and young children (see CLINICAL TRIALS).

Following 6 months of treatment with Replagal male patients showed altered pharmacokinetics with reduced plasma half-life and more rapid elimination from the blood. These changes were associated with the development of low titre antibodies to agalsidase alfa ghu, and did not appear to be of clinical consequence. Most patients with low titre antibodies to agalsidase alfa ghu develop immunologic tolerance to the molecule.

Finally, based on the analysis of pre- and post-dose liver biopsies in adults with Fabry Disease, the tissue half-life has been estimated to be in excess of 24 hours.

Distribution

Studies in mice and rats with radio-iodinated agalsidase alfa showed that agalsidase alfa ghu was concentrated into the liver (up to 36% of the administered dose at 4h). Tissue uptake was 2 – 10 fold lower for the kidney and spleen and 10 – 20 fold lower for the heart based on tissue radioactivity concentrations. In humans, it is not possible to fully quantitate uptake, but a combination of histological and biochemical studies indicate that Replagal is taken up by the liver (estimated to be 10% of administered dose), kidney, heart, and blood vessels.

CLINICAL TRIALS

The safety and efficacy of Replagal (original roller bottle process) has been assessed in two pivotal studies in a total of 40 symptomatic adult male patients and a number of open-label studies in adult male as well as female and paediatric patients with Fabry Disease. Treatment was for up to 3 years at a dose of 0.2 mg/kg every other week.

Alternative dosing regimens were investigated in one small open-label study in 21 adult males which suggested similar efficacy and safety outcomes with different doses.

In the first pivotal study, 26 patients received infusions of either 0.2 mg/kg of Replagal or placebo every 2 weeks for 6 months. Twenty-five patients completed the study and entered a maintenance study. The outcome assessments included change in serious, debilitating pain as assessed by the Brief Pain Inventory (a validated pain measurement scale), measurements of renal structure and function, biochemical markers and other measures of pain including pain medication usage and pain related quality of life.

Compared with placebo, treatment with Replagal effected comprehensive and statistically significant changes in pain in patients with Fabry Disease. Patients generally began to show significant decreases in their level of pain by 8 to 16 weeks of therapy. Pain at its worst scores were reduced in 9/14 patients on agalsidase alfa ghu and 5/12 patients on placebo. Mean pain at its worst scores while off pain medication were 6.2 at baseline and 4.3 at week 24 for patients given agalsidase alfa ghu vs 7.3 at baseline and 6.8 at week 24 for patients on placebo. The difference in change in mean pain scores was statistically significant using Repeat Measure and ANCOVA analyses, p=0.021 and p=0.047 respectively. Pain severity and pain interference scores were not significantly different comparing week 24 to baseline by ANCOVA, but were significantly different using Repeat Measure analysis. There were statistically significant differences in days off pain medication (74.5 days agalsidase alfa ghu vs 12.9 placebo; p=0.013) and mean time to permanent discontinuation (30.5 days agalsidase alfa vs no placebo patient permanently discontinuing pain medication p=0.013). In subsequent paediatric studies, 17 male patients experienced a reduction in pain reaching statistical significance after 9 and 12 months of Replagal therapy compared to pre-treatment baseline. The mean pain score for female paediatric patients at baseline was lower and therefore the lower magnitude of improvement is not unexpected.

Twelve to 18 months of treatment with Replagal resulted in improvement in quality of life (QoL), as measured by validated instruments. The improvement was statistically significant in patients who had impaired QoL at the start of treatment.

After 6 months of therapy Replagal stabilised renal function compared with a decline in placebo treated patients. Kidney biopsy specimens revealed a significant increase in the fraction of normal glomeruli and a significant decrease in the fraction of glomeruli with mesangial widening in patients treated with Replagal in contrast to the patients treated with placebo. After 12 to 18 months of maintenance therapy, Replagal improved renal function as measured by inulin based glomerular filtration rate by 8.7 ± 3.7 mL/min. (p=0.030). Longer term therapy (48-54 months) resulted in stabilisation of GFR in male patients with normal baseline GFR > 90 mL/min/1.73 m^2) and with mild to moderate renal dysfunction (GFR 60 to < 90 mL/min/1.73 m^2), and in slowing of the rate of decline in renal function and progression to end-stage renal disease in male Fabry patients with more severe renal dysfunction (GFR 30 to < 60 mL/min/1.73 m^2).

In male paediatric Fabry patients, hyperfiltration can be the earliest manifestation of renal involvement in the disease. Reduction in their hypernormal eGFRs was observed within 6 months of initiating Replagal therapy in one paediatric study. While most of the24 patients had normal renal function at baseline, 7 males were observed to have hyperfilitration. Following Replagal therapy, mean GFR decreased from 149.4 ± 7.5 mL/min/1.73m^3 to 127.8 ± 7.6 mL/min/1.73m^3, which neared statistical significance (p=0.078).

In the second pivotal study, 15 patients with left ventricular hypertrophy completed a 6 month placebo controlled study and entered an open label extension study. The

outcome assessments included measurements of cardiac mass, renal function and biochemical markers, including cardiac Gb3. Treatment with Replagal for 6 months resulted in an 11.5 g decrease in left ventricular mass as measured by magnetic resonance imaging (MRI), while patients receiving placebo exhibited an increase in left ventricular mass of 21.8 g (p=0.041). Treatment with Replagal showed a trend in reducing cardiac Gb3 whilst other measures of effects on cardiac function were not associated with statistically significant changes. In addition, in the first study involving 25 patients, Replagal effected a significant reduction in cardiac mass after 12 to 18 months of maintenance therapy (p<0.001). Replagal was also associated with a decrease in mean QRS duration and a concomitant decrease in septal thickness on echocardiography. Two patients with right bundle branch block in the studies conducted reverted to normal following therapy with Replagal. Subsequent open label studies demonstrated significant reduction from baseline in left ventricular mass by echocardiography in both male and female Fabry patients over 24 to 36 months of Replagal treatment. The reductions in LV mass observed by echocardiography in both male and female Fabry patients over 24 to 36 months of Replagal treatment were associated with a meaningful symptom improvement. The functional assessments for symptoms of cardiovascular disease were conducted with the New York Heart Association (NYHA) classes for heart failure and the Canadian Cardiovascular Society (CCS) classes for angina. In a pooled, post hoc analysis of open-label studies, 21 patients (10 males and 11 females) improved to a better NYHA class, 16 patients (7 males and 9 females) had no change and no patient worsened. Twenty-three patients (12 males and 11 females) improved to a better CCS class, 13 patients had no change (5 males, 8 females) and two patients (2 females) worsened. The results, being based on a pooled, post hoc analysis of open-label studies, should be interpreted with caution.

Mean Gb3 decreases in plasma, urine sediment and liver, kidney and heart biopsy samples revealed a range of approximately 20 to 50 % decline. These decreases may represent a reasonable estimate of the total body burden of stored Gb3 mobilised by 6 months treatment with agalsidase alfa ghu.

There are limited data on the effects of Replagal on sentinel clinical events such as transient ischaemic attack, stroke, myocardial infarction, heart failure and initiation of renal dialysis. There are limited pharmacokinetic and long-term data on the use of Replagal in females and children with Fabry disease. Data in adult males indicate that generally, Replagal is safe to use as continuation therapy at home after adequate trials of administration in the hospital setting.

INDICATIONS

Replagal (agalsidase alfa ghu) is indicated for long-term enzyme replacement therapy of patients with Fabry Disease (α–galactosidase A deficiency).

CONTRAINDICATIONS

Life-threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients.

PRECAUTIONS

General

The diagnosis, assessment and management of Fabry Disease should only be undertaken by physicians with experience and training in the treatment of inherited diseases of metabolism. Replagal therapy should only be initiated or continued under the ongoing supervision of a physician with such expertise in the treatment of Fabry Disease.

Infusion reactions

In 13.7% of patients, Replagal has been associated with mild, acute idiosyncratic infusion reactions. Overall the percentage of infusion related reactions was lower in females than males. The most common symptoms have been rigors, headache, nausea, pyrexia, flushing and fatigue. Serious infusion reactions have been reported uncommonly; symptoms reported include pyrexia, rigors, tachycardia, urticaria, nausea/vomiting, angioneurotic oedema with throat tightness, stridor and swollen tongue. Other infusion-related symptoms may include dizziness and hyperhidrosis. The onset of infusion related reactions has generally occurred within the first 2-4 months after initiation of treatment with Replagal although later onset (after 1 year) has been reported as well. If mild or moderate acute infusion reactions occur, medical attention must be sought immediately and appropriate actions instituted. The infusion can be temporarily interrupted (5 to 10 minutes) until symptoms subside and the infusion may then be restarted. Mild and transient effects may not require medical treatment or discontinuation of the infusion. In addition, oral or intravenous pre-treatment, with antihistamines and/or corticosteroids, from 1 to 24 hours prior to infusion may prevent subsequent reactions in those cases where prophylaxis was felt to be indicated.

As with any intravenous protein product, allergic-type hypersensitivity reactions are possible. A severe infusion reaction has been reported in a clinical trial post-approval. Symptoms reported were pyrexia, rigors, tachycardia, nausea and vomiting. If severe allergic or anaphylactic-type reactions occur, the administration of Replagal should be discontinued immediately and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed.

Development of antibodies

As with all protein pharmaceutical products, patients may develop IgG antibodies to the protein. A low titre IgG antibody response has been observed in approximately 24% of the male patients treated with Replagal. Based on limited data this percentage has been found to be lower (7%) in the male paediatric population (2 out of 28 patients). These IgG antibodies appeared to develop following approximately 3-12 months of treatment. After 12 to 54 months of therapy, 17% of Replagal treated patients were still antibody positive whereas 7% showed evidence for the development of immunologic tolerance, based on the disappearance of IgG antibodies over time. The remaining 76% remained antibody negative throughout. No IgE antibodies have been detected in patients receiving Replagal.

Effects on fertility

Male and female fertility was not affected in rats at up to 1 mg/kg IV, corresponding to approximately 2 times the expected human exposure, based on AUC. No clinical studies have investigated the effects of agalsidase alfa ghu on fertility in humans.

Use in pregnancy – (Category B2)

Studies with agalsidase alfa ghu in pregnant rats and rabbits showed no evidence of embryonic or foetal damage at IV doses up to 1 mg/kg, with exposures approximately 2

times the expected human exposure, based on AUC. The effects of agalsidase alfa ghu on parturition and post-natal development have not been studied in animals.

Because animal reproduction studies are not always predictive of the human response, Replagal should be used during pregnancy only if clearly needed. There are no adequate and well-controlled clinical studies in pregnant women. Very limited clinical data on pregnancies exposed to Replagal (n=4) have shown no adverse effects on the mother and newborn child.

Use in lactation

There were no studies in lactating animals. It is not known whether Replagal is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Replagal is administered to a nursing mother.

Paediatric use

The experience in children is limited. Studies in children (0-6 years) have not been performed and no dosage regimen can presently be recommended in these patients as safety and efficacy have not yet been established. Limited clinical data in children (6.5-18 years) do not permit the recommendation of an optimal dosage regimen presently (see PHARMACOLOGY - Pharmacokinetics). Because no unexpected safety issues were encountered in the 6 month study with Replagal administered at 0.2 mg/kg in this population, this dose regimen is suggested for children between 6.5-18 years of age (see DOSAGE AND ADMINISTRATION).

Use in the elderly

Patients with Fabry Disease in the elderly age group were not available for clinical studies.

Carcinogenicity

Based on its mechanism of action Replagal is unlikely to be carcinogenic. Carcinogenicity studies have not been conducted with Replagal.

Genotoxicity

Based on its mechanism of action Replagal is unlikely to be mutagenic. Mutagenicity studies have not been conducted with Replagal.

Interactions with other medicines

No formal drug interaction studies have been conducted with Replagal. As α-galactosidase A is itself an enzyme, it would be an unlikely candidate for cytochrome P450 mediated drug-drug interactions. In the placebo-controlled studies, neuropathic pain medications were administered concurrently to most patients. No unexpected adverse events were associated with these concomitant therapies.

Impaired renal or hepatic function

Renal elimination of Replagal is considered to be a minor pathway for Replagal clearance. As metabolism is expected to occur by peptide hydrolysis, an impaired liver function is not expected to affect the pharmacokinetics of Replagal in a clinically significant way.

The presence of extensive renal damage may limit the renal response to enzyme replacement therapy, possibly due to underlying irreversible pathological changes. In

such cases, the loss of renal function remains within the expected range of the natural progression of disease.

Effects on ability to drive and use machines

Replagal has no influence on the ability to drive or use machines.

ADVERSE EFFECTS

The most commonly reported undesirable effects were infusion reactions which occurred in 13.7% of patients treated with Replagal in clinical trials. Most undesirable effects were mild to moderate in severity.

Table 1 lists adverse drug reactions (ADRs) reported for the 153 patients treated with Replagal in clinical trials, including 21 patients with history of end stage renal disease and 17 female patients. Information is presented by system organ class and frequency (very common >1/10; common >1/100, <1/10; uncommon >1/1000, <1/100). The occurrence of an event in a single patient is defined as uncommon in view of the number of patients treated. A single patient could be affected by several ADRs.

Table 1

Metabolism and nutrition disorders Common:	peripheral oedema
Nervous system disorders Very Common:	headache
Common:	dizziness,dysgeusia, neuropathic pain, tremor, hypersomnia, hypoesthesia, paraesthesia
Uncommon:	parosmia
Eye disorders Common:	lacrimation increased
Ear and labyrinth disorders Common:	tinnitus, tinnitus aggravated
Cardiac disorders	
Common:	tachycardia, palpitations
Vascular disorders Very Common: Common:	flushing hypertension
Respiratory thoracic and mediastinal disorders Common:	cough, hoarseness, throat tightness, dyspnoea, nasopharyngitis, pharyngitis, throat secretion increased, rhinorrhoea
Gastrointestinal disorders Very Common:	nausea
Common:	diarrhoea, vomiting, abdominal pain/discomfort
Skin and subcutaneous tissue disorders Common:	acne, erythema, pruritus, rash, livedo reticularis
Uncommon:	angioneurotic oedema, urticaria
Musculoskeletal system, connective tissue and bone disorders Common:	musculoskeletal discomfort, myalgia, back pain,

	limb pain, peripheral swelling, anthralgia, joint swelling
Uncommon:	sensation of heaviness
General disorders and administration site conditions Very Common:	rigors, pyrexia, pain and discomfort, fatigue
Common:	fatigue aggravated, feeling hot, feeling cold, asthenia, chest pain, chest tightness, influenza like illness, injection site rash, malaise
Investigations Common:	corneal reflex decreased
Uncommon:	oxygen saturation decreased

In clinical trials 13.7% of Replagal treated patients have experienced idiosyncratic infusion-reactions. The percentage of patients affected was lower in females than males. These effects have decreased with time, the majority of them being reported within the first 6 months of treatment. Symptoms have included predominantly rigors (chills), headache, nausea, pyrexia, flushing and fatigue with patients commonly experiencing pain/discomfort including exacerbated neuropathic pain, vomiting and chest or throat tightness. Other infusion-related symptoms may include dizziness and hyperhidrosis. All symptoms resolved with appropriate intervention, such as, stopping the infusion prior to restarting or medical therapy with antihistamines and/or corticosteroids. Serious infusion reactions have been reported uncommonly; symptoms reported include pyrexia, rigors, tachycardia, urticaria, nausea/vomiting, angioneurotic oedema with throat tightness, stridor and swollen tongue (see PRECAUTIONS – Infusion Reactions).

Adverse drug reactions reported in patients with history of end stage renal disease were similar to those reported in the general population.

Adverse drug reactions reported in the paediatric population (children and adolescents) were, in general, similar to those reported in adults. However, infusion related reactions and pain exacerbation occurred more frequently; being observed in 10/55 patients (18.2%). The most frequent were mild infusion-related reactions that mainly included rigors, pyrexia, flushing, headache, nausea, and dyspnoea.

DOSAGE AND ADMINISTRATION

In adults and children 6.5 years of age and older, Replagal is administered at a dose of 0.2 mg/kg body weight every 2 weeks by intravenous infusion over a period of 40 minutes. Therapy with Replagal should only be initiated or continued by a physician with expertise in the treatment of Fabry Disease (see PRECAUTIONS). Infusion of Replagal at home may be considered for patients who have been stabilised in a controlled hospital setting and are tolerating their infusions well. Replagal is not recommended in children below 6.5 years of age.

Instruction for use / handling

Replagal for patient administration should be prepared by slowly mixing the appropriate amount of Replagal into 100 mL of normal saline (0.9% sodium chloride) suitable for IV administration. Once diluted into normal saline, the solution should be rocked gently to mix, but not shaken. To reduce potential microbiological hazard, Replagal diluted into normal saline should be used as soon as practicable after preparation as the product does not contain any bacteriostatic preservatives. However, when prepared under

aseptic conditions, the diluted product may be stored for 24 hours at 2 - 8°C. The diluted solution must be administered via an IV line, which contains a standard 0.2 micron filter. Do not mix Replagal with or administer in conjunction with other drug solutions.

The chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 25°C.

OVERDOSAGE

There is no experience with overdosage of Replagal.

For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Presentation

Replagal is provided as a sterile, clear and colourless solution intended for intravenous administration. A minute amount of fine particulate matter, causing the solution to appear slightly hazy, may be present.

Each vial (3.5 mL) of Replagal contains 3.5 mg of agalsidase alfa ghu, 12 mg monobasic sodium phosphate as a buffering agent, 0.8 mg polysorbate 20 as a stabilising agent, 31 mg sodium chloride as an isotonic agent and sodium hydroxide for pH adjustment to produce a solution at a pH of 5.4-6.6. Replagal contains no antimicrobial agent.

Replagal is supplied in a single-dose vial closed with a butyl rubber stopper and sealed with an alumin*i*um overseal with a flip-off plastic cap.
Pack size: x 1 vial (3.5 mL) of Replagal (agalsidase alfa ghu) concentrated injection vial.

Storage

Replagal vials should be stored at 2-8°C. Do not use beyond the expiration date stamped on the vial. DO NOT SHAKE VIALS.

Replagal is supplied in single-use vials and contains no antimicrobial agent. The product is for treatment of one patient only on one occasion. Discard any remaining contents.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE

S4

Date of TGA approval: 7 May 2010