

**CENTER FOR DRUG EVALUATION AND
RESEARCH AND CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**

APPLICATION NUMBER:
125151/0

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Biotechnology Products, Division of Therapeutic Proteins

Cover Page

FROM: Harold Dickensheets, Ph.D. *H. Dickensheets 7/18/06*
Drug Product CMC Reviewer, DTP

SUBJECT: BLA 125151

Through: Barry Cherney, Ph.D., Deputy Director, DTP *Barry Cherney*
7-18-06

DATE: July 18, 2006

Product: Idursulfase

Sponsor: Shire Human Genetic Therapies (formerly Transkaryotic Therapies, Inc.
(TKT))

Cc: Serge Beaucage, Ph.D., DTP

Drug Product Review Summary and Reviewer Recommendation

The materials submitted by the sponsor regarding Idursulfase drug product and its manufacturing process have been reviewed and deemed acceptable, provided that the following post-marketing commitments are agreed upon;

- An action limit for any new _____ will be added to the _____ assay. The method will be validated and the revised Drug Product specifications will be submitted to FDA by January 2007.
- Upon qualification and validation, an _____ assay will be added to the Drug Product release specifications. A validation report will be completed by September 2006, and the revised Drug Product specifications will be submitted to FDA by September 2006.
- A qualification study will be conducted to assess the sensitivity of the currently employed _____ test method for _____ against the _____ test. The data generated by the study will demonstrate that the employed _____ method provides assurances of the safety and purity of idursulfase equal to or greater than the assurances provided by the _____ test. The qualification report will be submitted to FDA by June 2007.

Based upon the information reviewed regarding the drug product, **I recommend approval** of the biologics license application.

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**APPEARS THIS WAY
ON ORIGINAL**

I. Drug Product Review Summary and Reviewer Recommendation

The materials submitted by the sponsor regarding Idursulfase drug product and its manufacturing process have been reviewed and deemed acceptable, provided that the following post-marketing commitments are agreed upon;

- An action limit for any new _____ will be added to the _____ assay. The method will be validated and the revised Drug Product specifications will be submitted to FDA by January 2007.
- Upon qualification and validation, an _____ assay will be added to the Drug Product release specifications. A validation report will be completed by September 2006, and the revised Drug Product specifications will be submitted to FDA by September 2006.
- A qualification study will be conducted to assess the sensitivity of the currently employed _____ test method for _____ against the _____ test. The data generated by the study will demonstrate that the employed _____ method provides assurances of the safety and purity of idursulfase equal to or greater than the assurances provided by the _____ test. The qualification report will be submitted to FDA by June 2007.

Based upon the information reviewed regarding the drug product, I **recommend approval** of the biologics license application.

II. Additional Significant Review Items

A number of additional items arose during the review of the application, including revisions/information requested by the Agency [HD] concerning;

1. Labeling

Based upon the sponsor's photostability data, the phrase "Protect from light" will be added to the package and vial labels, as well as to the package insert.

2. Process

- a. Information regarding comparison of the sensitivity of the sponsor's current _____ method for detection of _____ technique. The results were comparable.
- b. Drug Product manufacturing in-process hold time limits were revised to bring these hold times into agreement with validated times and to provide missing limits.

3. _____ Specification Revision

4. Additional Stability Data Review:

The stability data originally submitted included; _____ of real-time storage for the _____ Commercial scale validation lots, up to _____ of stability data for _____ other drug product lots produced from Commercial scale drug substance, and data from _____ additional Phase II/III clinical drug product lots (up to 24 months stability on one of these) at the labeled temperature of $5\pm 3^{\circ}\text{C}$. These data are supportive of the proposed Commercial scale Idursulfase drug product expiry dating period of 24 months; although additional stability data from other lots with ≥ 24 months of data were requested to strengthen the argument for the full 24 month dating period.

With respect to the submission of the major clinical amendment and extension of the review clock, it was possible for the company to submit updated stability data on both the Phase II/III lots and the Validation Lots. They were also requested to present trending analyses for those stability parameters showing change over time, with confidence intervals about the linear regression line. This information was requested from the sponsor during the June 7, 2006 teleconference.

The sponsor has provided the requested stability update, which per review (see attached teleconference call response titled "Review of Shire's Responses (submitted 06-15-06) to discussions held during 06-07-06 CMC Teleconference", was deemed acceptable and supportive of the requested drug product expiry dating period of 24 months at 2-8°C.

5. Addition of a drug product stability limit for the impurity _____

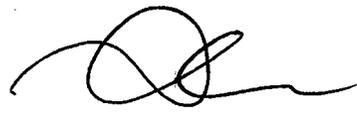
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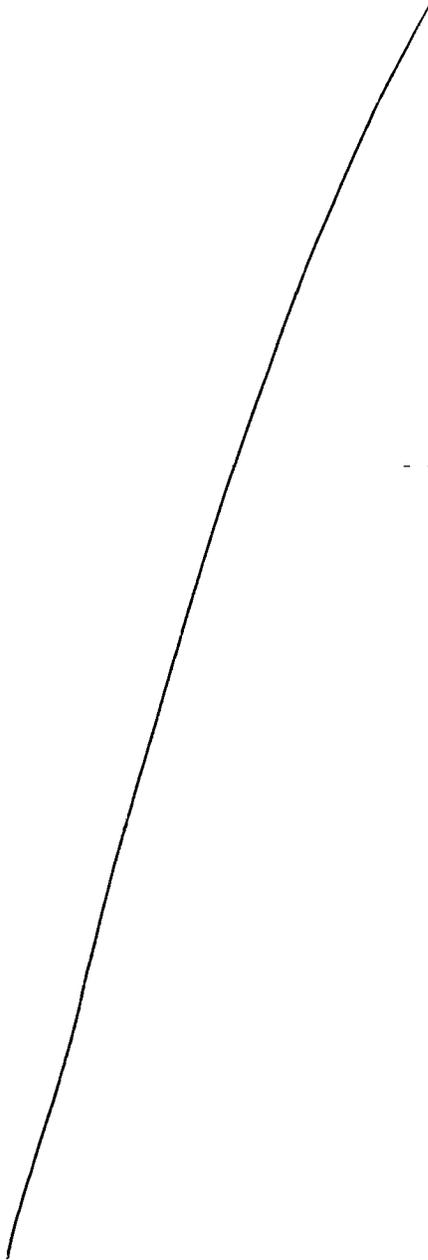
§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

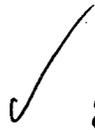
§ 552(b)(4) Draft Labeling

 7-18-06

From: Lai Xu, M.D./Ph.D. *RALPH M. BERNSTEIN, PH.D., ADA 2/7/06*
To: Barry Cherney, Ph.D, Deputy Director, DTP, OBP, OPS, CDER
Through: Serge Beaucage, Ph.D. *Barry Cherney 7-18-06*
Product: Idursulfase, "human iduronate-2-sulfatase"
Sponsor: Transkaryotic Therapies, Inc
Subject: Review memo for



12 Page(s) Withheld



§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

REVIEW REPORT

Date: July 17, 2006

From: Ying-Xin Fan, Ph.D

Ying-Xin Fan 7-18-06

Through: Gibbes Johnson, Ph.D, Barry Cherney, Ph.D

Gibbes Johnson 7-18-06

Barry Cherney 7-18-06

To: BLA 125151 File

Subject: Review of potency assays (enzyme activity and — for comparability and release testing in BLA 125151. This review file contains the reviews for original submission and amendments (125151/0/7, 125151/0/14, and DATS Log Number 60003218).

Sponsor: Shire HGT

Product Name: Idursulfase (Iduronate-2-sulfatase, I2S, DRX006A)
ELAPRASE (Proposed proprietary name)

Indication: — treatment of Mucopolysaccharidosis II (Hunter syndrome; MPS II)

Content

Part I: Introduction

Part II: Enzyme activity assays

Part III: — assay

Part IV: — Assay

Part V: Drug substance and product release testing potency specifications

**Part VI: Comparability of phase II/III and commercial process drug
substances**

Part VII: Summary

Part VIII. Recommendation and postmarketing commitments

Part I: Introduction:

Iduronate-2-sulfatase (I2S) belongs to the evolutionarily conserved family of mammalian sulfatases in lysosomes and hydrolyzes the C2-sulfate ester bonds of the nonreducing iduronic acid residue in both dermatan sulfate and heparan sulfate. The in vivo potency of I2S is dependent on several factors including

of idursulfase; therefore the potency assays are very important for control of the manufacture of this therapeutic enzyme.

The sponsor assessed the product potency by the following methods: enzyme specific activity,

In addition, content were measured. Of these assays assay was not included in the release testing. Here, I review the assays for enzyme activity and and related issues in comparability studies and drug substance and product release testing.

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

From: Ennan Guan, M.D./Ph.D. *Ennan Guan 5/17/06*
To: BLA: 125151/0, Original Submission
Through: Barry Cherney, Ph.D. Deputy Director, CDER/OPS/OBP/DTP, HFM541 *Barry Cherney*
Product: Idursulfase *5-17-06*
Sponsor: Transkaryotic Therapies (TKT) Inc.
Final Date: May 27, 2006

I. Characterization of the _____ for Idursulfase Production



F. Adventitious Agent Testing during Routine Manufacture

II. _____ Studies



III. Test Methods and Validation Data for J _____

- A. Review of Test Methods
- B. Validation of _____ Assay

IV. Summary and Conclusion

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Memorandum

Date: May 8, 2006

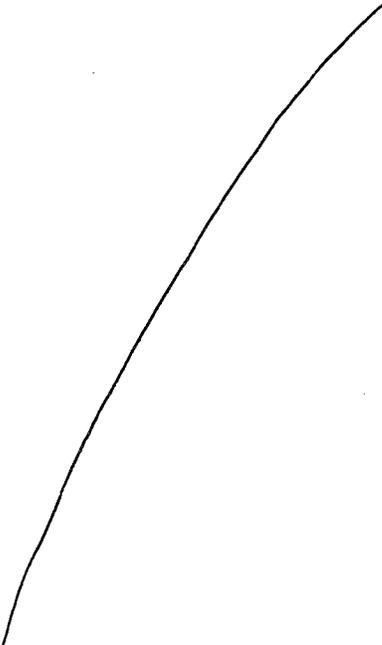
From: Serge L. Beaucage, Ph. D., DTP, OBP, OPS, CDER. *Serge Beaucage 7-18-06*

To: Barry Cherney, Ph. D, Deputy Director, DTP, OBP, OPS, CDER *Barry Cherney 7-18-06*
Gibbes Johnson, Ph. D., DTP, OBP, OPS, CDER.

Subject: BL 125151
Product: Iduronate-2-sulfatase (ELAPRASE™, idursulfase)
Manufacturer: Shire Human Genetic Therapies.
Proposed Use: Enzyme replacement therapy for mucopolysaccharidosis II (Hunter Syndrome).

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



CMC Review Data Sheet

1. **BLA#** STN 125151/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** December 5, 2005
4. **REVIEWERS:** Serge Beaucage, Ph.D.
Harold Dickensheets, Ph.D.
Gibbes Johnson, Ph.D.
Ying-Xin Fan, Ph.D.
Ennan Guan, Ph.D.
Jin Hai Wang, Ph.D.
Ralph Bernstein, Ph.D.
Lai Xu, Ph.D.

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS:**

6. **SUBMISSION(S) BEING REVIEWED AS FOLLOW UP TO PREVIOUS COMMUNICATIONS**

<u>Submission(s) Reviewed</u>	<u>Document Date to EDR</u>
STN 125151/0 Original Submission	December 5, 2005
STN 125151/0/0007 Response 74 day letter	April 10, 2006
STN 125151/0/0008 IR	April 20, 2006
STN 125151/0/0009 IR	April 24, 2006
STN 125151/0/0010 IR	April 27, 2006
STN 125151/0/0013 IR	May 8, 2006
STN 125151/0/0014 IR	May 10, 2006
STN 125151/0/0015 IR	May 15, 2006
STN 125151/0/0016 IR	May 18, 2006
STN 125151/0/0017 IR	June 1, 2006
STN 125151/0/0018 IR	June 5, 2006
STN 125151/0/0020 IR	July 12, 2006
STN 125151/0/0021 IR	July 17, 2006

7. **NAME & ADDRESS OF APPLICANT:**

Name: Shire Human Genetic Therapies, Inc..
Address: 700 Main Street
Cambridge, MA 02139
Representative: Robert Corcoran
Telephone: (617) 349-0200

8. DRUG PRODUCT NAME/CODE/TYPE:

- (i) Proprietary Name: Elaprase™
- (ii) Non-Proprietary Name: Idursulfase
- (iii) Code name: DRX006A
- (iv) Chemical Name: Iduronate-2-sulfatase
- (v) Drug Review Status: Fast Track, Orphan Product

9. DOSAGE FORM: Concentrated solution (2.0 mg/mL).

10. STRENGTH/POTENCY:

- (i) The product contains 6.0 mg/vial of ELAPRASE™ (idursulfase).
- (ii) Potency is based on enzyme specific activity and _____
_____ Mass units are used for dosing.
- (iii) Dating period for vial product is 24 months when stored at 2°C to 8°C. Following dilution into saline, the diluted drug product is stable for 48 hours post-dilution when stored at 2°C to 8°C.

11. ROUTE OF ADMINISTRATION: The product is for intravenous infusion when added to 100 mL of 0.9% Sodium Chloride for Injection, USP

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13. **CMC Inspectional Activities involving product reviewers**

The inspection covered the manufacturing operations for the Biological License Application (BLA), STN 125151/0 for the drug, Idursulfase (iduronate-2-sulfatase), at Shire Human Genetic Therapies in Cambridge, MA 02139. The inspection was conducted on March 20-24, 2006 and covered buildings — The inspection team consisted of Patricia F. Hughes, Ph.D., OC/DMPQ/TFRB, Serge Beaucage, Ph.D., OPS/OBP/DTP, and Kathy Lee, M.S., OPS/OBP/ DTP. At the time of the inspection three products were produced at the drug substance manufacturing facilities. These were, Idursulfase (subject of the PLI inspection),

The inspection covered five systems: Quality, Facilities and Equipment, Materials, Production Processes, and Laboratory Controls. A 6-item FDA Form 483 was issued to the firm. Adequate responses to the 483 items were received by the agency. The facility was found to be in compliance with cGMPs and capable of manufacturing idursulfase drug substance in a consistent manner.

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125151 for Elaprased (idursulfase) manufactured by Shire Human Genetic Therapies, Inc. Adequate documentation of this recombinant form of the human lysosomal enzyme, iduronate 2-sulfatase has been presented in regard to manufacturing controls, methods and process validation, product characterization, consistency of manufacture (comparability of clinical and commercial conformance lots of idursulfase), release and stability specifications, and real time and accelerated stability data. The information submitted in this application supports the conclusion that the manufacture of idursulfase is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents and in compliance with the safety parameters recommended by the FDA. It is recommended that this product be approved for human use under the conditions specified in the package insert. However, there are a number of additional studies that will improve the overall quality assessment of the product and will be implemented by the sponsor as described in section B.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We propose the following post-marketing commitments:

1. Shire commits to develop and implement an improved _____ assay for drug product release and stability testing. Results and proposed specifications will be submitted to CDER by May 31, 2007.
2. Shire commits to develop and implement an improved enzyme potency assay which _____
— The assay will be used for drug substance and product release and stability testing. Results and proposed specifications will be submitted by January 31, 2008.
3. Shire commits to perform a laboratory scale study to support the maximum cumulative hold time for all in-process intermediates in the commercial purification process of the drug substance. Results from this study will be submitted by January 31, 2007.



4. Shire commits to establish an action limit to be added to the _____ assay for the appearance of any _____. The revised drug product specification will be submitted by January 31, 2006.
5. Shire commits to develop an _____ that will be added to the drug product release specifications. The revised specifications will be submitted by September 30, 2006.
6. Shire commits to perform a qualification study, which will be conducted to assess the sensitivity of the currently employed _____ test method for _____ against the _____ test. The report will be submitted by June 30, 2007.
7. Shire commits to re-evaluate the analytical methods for the qualification and release of future reference standards, and to revise and tighten the acceptance criteria. The revised protocol will be submitted as a supplement by June 30, 2009.
8. Shire commits to evaluate and revise as necessary all acceptance criteria for release of idursulfase drug substance and product manufactured at commercial scale. The results together with any revisions to the specifications for drug substance and product will be submitted by September 30, 2008.
9. Shire commits to test and provide data from studies TKT024 and TKT024EXT using patient samples that are positive in the screening assay, in the inhibition-of-entry neutralization assay, to assess whether patient antibodies block entry of enzyme into cells. The information will be submitted to FDA by September 30, 2007.
10. Shire commits to track binding and neutralizing antibodies using sensitive and validated assays over an extended time period to assess the potential loss of antibodies (immunologic tolerance) to ELAPRASE. Individual patient data should be provided as a function of time and a correlation of antibody status with clinical efficacy and GAG levels provided. This information will be submitted to FDA by December 31, 2008.
11. Shire commits to develop, describe, and provide validation data for a neutralizing assay that can detect the presence of antibodies that inhibit the entry of idursulfase into cells. This information will be submitted to FDA by May 31, 2007.
12. Shire commits to provide complete validation data for the Conformation Specific Assay (CSA), particularly with regard to sensitivity (ng/mL) and specificity of detection of the assay. This information will be submitted to FDA by December 31, 2006.

13. Shire commits to fully validate an IgE assay for detection of anti-idursulfase IgE antibodies. This information will be submitted to FDA by June 30, 2007.

14. Shire commits to investigate and provide data on the nature of the genetic mutations of iduronate-2-sulfatase in patients in study TKT024, titled "A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Clinical Study Evaluating the Safety and Efficacy of Weekly and Every Other Week Dosing Regimens of Iduronate-2-Sulfatase Enzyme Replacement Therapy in Patients with MPS II," and to correlate findings with the level of endogenous enzyme (via protein, not enzyme activity assessment), the antibody response (binding, neutralizing and IgE), and clinical outcome in TKT024 and TKT024EXT, titled "An Open Label Extension study of TKT024 Evaluating Long-term Safety and Clinical Outcomes of MPS II Patients Receiving I2S Enzyme Replacement Therapy". This information will be submitted to FDA by January 31, 2008.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Product(s)

General Characteristics. Idursulfase is the USAN name for Shire's highly purified recombinant form of the naturally occurring human lysosomal enzyme iduronate-2-sulfatase. The glycoprotein is expressed in a human cell line as a single polypeptide chain

The amino acid sequence of idursulfase, predicted from the cDNA sequence is confirmed by

The enzyme contains 8 occupied *N*-linked glycosylation sites composed of complex, oligosaccharide chains. The *N*-linked glycosylation sites were determined by to occur at asparagines

The presence of mannose-6-phosphate (M6P) residues on the oligosaccharide chains facilitates internalization of the enzyme via the M6P receptors present on the cell surface and subsequent delivery of the enzyme to the lysosomes.

Biological activity. Idursulfase is a lysosomal enzyme involved in the catabolic breakdown of the glycosaminoglycans (GAG), dermatan sulfate and heparan sulfate. It is an exosulfatase and hydrolyzes 2-sulfate esters from the non-reducing end of iduronate 2-sulfate. Since glycosaminoglycans are degraded in a well-ordered sequential fashion, deficiency of the natural enzyme results in the accumulation of dermatan and heparan sulfate chains in the lysosomes of a variety of cell types, leading to the clinical disorder Hunter syndrome (Mucopolysaccharidosis II). Similar to other human sulfatases, the



enzymatic activity of idursulfase is dependent on _____

Activity and potency assays. The potency of idursulfase, *in vivo*, is dependent on several factors including _____ Shire's

methodology for measuring potency includes (i) an enzymatic specific activity assay; (ii) _____ the

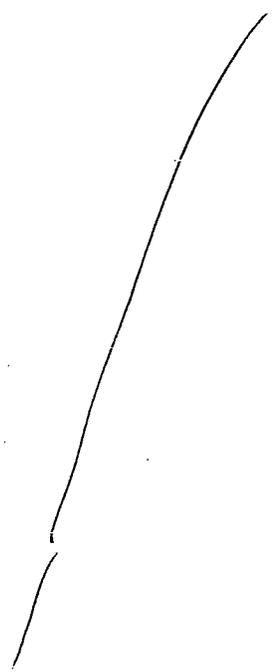
substrate used in the enzymatic specific activity assay is heparin disaccharide, which is not a physiologically relevant substrate, and has a relatively _____

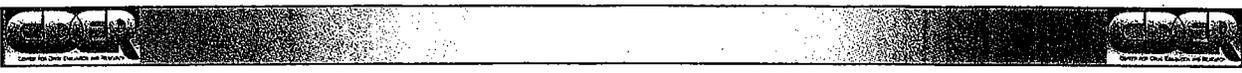
_____ Shire has agreed to post-marketing commitments aimed at developing a new enzyme activity assay that would use a physiologically relevant substrate and a new _____ assay that

The _____ assay _____

_____ Shire has qualified this assay and has agreed to perform the _____ potency assay as an interim lot release test for idursulfase drug product until the new enzyme activity assay and the new _____ assay formats are implemented. The comparability of phase II/III and commercial drug substance lots has been demonstrated with regard to the original potency measurements as described above.

Manufacture of Drug Substance. Idursulfase is expressed in a human cell line _____





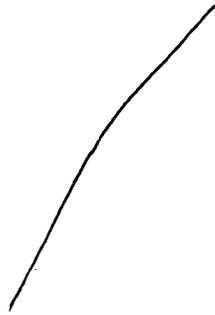
Release testing of idursulfase Drug Substance include: _____

Some of the potency tests must be refined through PMCs and Shire has committed to evaluate and revise as necessary all the release test specifications (see PMC section).

Overall, the manufacturing process for Idursulfase drug substance is well controlled through defined operating and performance parameters. The process appears to have been appropriately validated and produces a consistent product that meets its expected quality attributes.

Development and Comparability. The original cell culture and purification process used for generating idursulfase for the non-clinical development studies and Phase I/II clinical trials was scaled-up and improved in order to obtain higher yield, purity, and potency of idursulfase prior to initiation of the Phase II/III clinical study. The approach to assess comparability of idursulfase manufactured by the Phase I/II and Phase II/III processes included comprehensive physico-chemical characterization, using methodologies capable of detecting differences in _____ and other quality criteria that may impact functional enzyme activity, together with non-clinical studies to assess pharmacodynamic activity and biodistribution. Comparability of the Phase II/III manufacturing process with the Phase I/II process as it relates to safety and efficacy of the preparations was established. Idursulfase from the Phase II/III process had similar structural characteristics to that produced by the Phase I/II process but exhibited an increased _____ resulting in essentially a 2-fold increase in enzyme specific activity. The increased *in vitro* activity and the observed _____ did not affect the *in vivo* tissue biodistribution or pharmacodynamic properties of idursulfase. The Phase II/III material had an improved purity profile, reflecting the reduction in the use of _____ during the cell culture process and improvements made to the purification process.

Following completion of the manufacture of idursulfase for the Phase II/III study, the manufacturing process was scaled up to the intended commercial scale of _____, and additional specific process improvements related to process robustness and efficiency were introduced. Specifically, _____



When taken altogether, the data submitted by Shire adequately supports the comparability of idursulfase manufactured by both the commercial and Phase II/III processes.

Manufacture of Drug Product. The drug product is manufactured _____ filled into glass vials. ELAPRASE™ is intended for intravenous infusion and is supplied as a sterile, nonpyrogenic clear to slightly opalescent colorless solution in a 5 mL Type I glass vial. Each vial contains an extractable volume of 3.0 mL with an idursulfase concentration of 2.0 mg/mL at a pH of approximately 6, providing 6.0 mg idursulfase, 24.0 mg sodium chloride, 6.75 mg sodium phosphate monobasic monohydrate, 2.97 mg sodium phosphate dibasic heptahydrate, and 0.66 mg polysorbate 20. The vials are closed with a butyl rubber stopper with fluororesin coating and an aluminum overseal with a blue flip-off plastic cap. ELAPRASE™ does not contain preservatives and must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP.

Degradation and Stability. Forced degradation studies show that idursulfase is structurally and biologically quite stable if not exposed to heat or _____ were the primary degradation products observed under all stress conditions. If exposed to low levels of _____ occurred as elucidated by _____ A decrease in specific activity was also noted under these conditions and may be the result of _____

Exposure to _____ conditions led to _____, with loss of all enzymatic activity. No appreciable amount of _____ was observed. _____



However, real-time stability data under the recommended storage conditions indicate that idursulfase drug substance and drug product have a robust stability profile. Stability data supports an expiration dating period of _____ for idurdulfase drug substance stored



at and 24 months for idursulfase drug product stored at 2 °C to 8 °C. In use stability studies support the labeled recommendations for preparation and administration of the product. The stability protocols for the purpose of extending the dating period and for annual stability studies of drug substance and drug product are appropriate and should be approved.

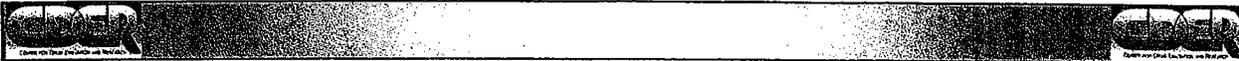
Immunogenicity. Mucopolysaccharidosis II (Hunter's syndrome) is a mucopolysaccharidosis caused by deficiency of iduronate-2-sulfatase and the only X-linked recessive traits (all other MPS are inherited as autosomal recessive traits). MPS II is a progressive disorder and characterized by involvement of multiple organs and excretion of unmodified dermatan sulfate and heparan sulfate in the urine.

Immunogenicity is determined by multiple product and host factors. The nature of the assay, assay validation and the time of serum sample collection also have significant impacts on the reported incidence of immunogenicity. For this trial, dosing was performed either on weekly or every other week (EOW) basis. It was reported by sponsor that blood samples were taken just prior to the next infusion. In TKT024, no I2S was detectable in serum 24 hours after infusion of clinical dose of I2S. Therefore, it is unlikely that there was significant interference from on-board product (see review).

The sponsor initially validated a classic ELISA assay where they confirmed results with a validated radio-immuno-assay (RIP). Although the assay appeared sensitive (135 ng/ml), subsequently it was found that it failed to detect the majority of positive samples. During the BLA review process the sponsor submitted a new non-validated binding assay, the conformation specific assay (CSA) that detected anti-I2S antibodies in a large number of samples confirmed to be positive by RIP. Consequently, the determination of the incidence of antibody positive patients was based on a positive result in either the classic ELISA or the CSA ELISA with confirmation by the RIP assay. When these results were combined, the immune response rate was determined to be 50% (47/94) in TKT024 and TKT024EXT. Because of the withdrawal of the Every Other Week treatment part of the study (EOW), the immune response rate for weekly I2S is 50.79% (32/63). Enzymatic-activity neutralizing antibody was detected in 7 patients in TKT024 and TKT024EXT. An assay to measure antibody mediated blockade of enzyme uptake into cells has not been developed. When this is developed patient samples positive in the screening assay will need to be tested.

Regarding efficacy, in the TKT024 weekly study, an improvement in 6 Minute Walk Test (6MWT), and reduction in urinary GAG and liver volume were observed. In several patients, antibodies to the product appeared to interfere with improvement in the 6MWT. Antibodies were also associated with impaired clearance of urinary GAG. There appeared to be no association between the development of antibodies and liver volume and spleen volume reduction. The effects of antibody on I2S tissue distribution were not reported.

Regarding safety, there were more infusion associated adverse events (IAEs, total 241 events) in antibody positive patient undergoing weekly treatment in TKT024 and



TKT034EXT than in antibody negative patients (104 events). There were more cardiac disorders in antibody positive patients (14 events) than antibody negative patients (1 event). Events such as arrhythmia, cyanosis and hypotension were only found in antibody positive patients. Isolated respiratory disorders were found uniquely in antibody positive patients who experienced dyspnoea, bronchospasm and throat tightness. Skin disorders contributed significantly to the increased IAEs in antibody positive patients. The high rate of infections was not changed after I2S treatment and antibodies did not seem to impact that finding. No renal problems were reported in antibody positive patients.

The incidence of reported allergic reactions was 38% (24/63) in TKT024 weekly and TKT024EXT placebo. It is higher in IgG + patients (56%, 18/32) and less in IgG negative patients (19%, 6/31). All test samples were negative for IgE (IgE ELISA was not validated yet). Sponsor submitted their new analysis regarding anaphylactic/anaphylactoid reactions according to the requirement of at least two system involvement (skin, cardiac, or respiratory) in BLA125151-0-0013 on May 15, 2006. 11 patients were listed with hypersensitivity reactions [11%, or 11/(94+12) (without EOW group it is 13%, 10/(64+12)]. Of note, patients with hypersensitivity reactions were all positive for IgG antibody except patient 018-013-0002. Therefore, there were more hypersensitivity reactions in IgG positive patients, although it is not clear whether such patients also have IgE antibodies.

The sponsor reported that total treatment emergent AEs in antibody positive patients were not more than that in antibody negative patients in TKT weekly and TKT024EXT placebo. However, there were more cardiac and skin disorders in antibody positive patients than in antibody negative patients. No correlation was found between the death of four patients during the studies and the antibody status.

B. Description of How the Drug Product is Intended to be Used.

ELAPRASE™ is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. ELAPRASE provides exogenous enzyme for uptake into cellular lysosomes and has been shown to improve walking capacity and pulmonary function in these patients. The recommended dosage regimen of ELAPRASE is 0.5 mg/kg of body weight administered every week as an intravenous infusion.

ELAPRASE™ is a concentrated solution and must be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each vial of ELAPRASE™ contains a 2.0 mg/mL solution of idursulfase protein (6.0 mg) in an extractable volume of 3.0 mL, and is for single use only. ELAPRASE™ contains no preservatives. The diluted solution should be used immediately. If immediate use is not possible, the diluted solution can be stored refrigerated at 2°C to 8°C for up to 48 hours, or must be administered within 8 hours if held at room temperature. The total volume of infusion



should be administered over a period of 1 to 3 hours.

ELAPRASE™ vials should be stored under refrigeration at 2°C to 8°C and protected from light. ELAPRASE™ should not be frozen or shaken and should not be use after the expiration date on the vial. The recommended expiration dating period for ELAPRASE™ is 24 months at 2°C to 8°C.

C. Basis for Approval or Not-Approval Recommendation

Approval is based on the submission of adequate Manufacturing and Control documentation for idursulfase Drug Substance and Drug Product. This documentation includes comprehensive information and data on manufacturing controls, methods and process validation, product characterization, consistency of manufacture (comparability of clinical and commercial lots of idursulfase), and stability. Idursulfase is a highly purified and well characterized product with release specifications that will ensure lot-to-lot consistency. ELAPRASE™ Drug Product has a high degree of stability in solution and will remain within specifications if stored as recommended (2°C to 8°C) during the assigned shelf-life of 24 months. Given that ELAPRASE™ is manufactured through a robust and consistent process resulting in a safe and effective product, it should be approved for the proposed indication. Post-marketing commitments, described in the recommendations section above, will provide additional assurance for the continued purity, potency, efficacy, and safety of the product.

III. Administrative

A. Reviewers' Signature

Product Reviewer/CMC Team Lead: Gibbes Johnson, Ph.D.

Gibbes Johnson 7/21/06

Product Reviewer: Serge Beaucage, Ph.D.

Serge Beaucage 7/21/06

Product Reviewer: Harold Dickensheets, Ph.D.

Harold Dickensheets 7/21/06

Product Reviewer: Ying-Xin Fan, Ph.D.

Ying-Xin Fan 7/21/06

Product Reviewer: Ennan Guan, Ph.D.

Ennan Guan 7/21/06

Product Reviewer: Ralph Bernstein, Ph.D.

Ralph Bernstein 7/21/06

Product Reviewer: Lai Xu, Ph.D.

Lai Xu 7/21/06

Product Reviewer: Jin Hai Wang, Ph.D.

Jin Hai Wang 7/21/06

Product Reviewer: Elizabeth Shores, Ph.D.

Elizabeth Shores 7/21/06

B. Endorsement Block

Product Team Leader: Gibbes Johnson, Ph.D.

Gibbes Johnson 7-21-06

Product Deputy Director: Barry Cherney, Ph.D.

Barry Cherney 7-21-06

Product Division Director: Amy Rosenberg, M.D.

Amy Rosenberg 7-21-06

C. CC Block

Office Director: Steven Kozlowski, M.D.

Division of Therapeutic Proteins File/BLA STN 125151/0

CMC Assessment

**APPEARS THIS WAY
ON ORIGINAL**