CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**203441**
Original Submission Dates	**11/30/2011**
PDUFA Due Date	**12/30/2012**
Brand Name	**Gattex**
Generic Name	**Teduglutide**
Primary Reviewer	**Lanyan Fang, Ph.D.**
Team Leader	**Yow-Ming Wang, Ph.D.**
Primary PM Reviewer	**Justin Earp, Ph.D.**
Team PM Leader	**Nitin Mehrotra, Ph.D. (Acting)**
OCP Division	**DCP III**
OND Division	**DGIEP**
Sponsor	**NPS Pharmaceuticals**
Relevant IND(s)	**58,213**
Submission Type	**NME**
Formulation; Strength(s)	**Lyophilized powder; 5 mg/vial to be reconstituted with 0.5 mL sterile water for injection**
Proposed indication	**Treatment of Short Bowel Syndrome (SBS)**
Proposed Dosage and Administration	**0.05 mg/kg subcutaneous (SC) injection once daily, altering sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms.**

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

GATTEX® (teduglutide [rDNA origin], ALX-0600) is a 33–amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2), a peptide that is secreted primarily from the lower gastrointestinal tract. Teduglutide is being proposed to treat adult patients with Short Bowel Syndrome (SBS), who need parenteral support (parenteral nutrition/intravenous hydration, PN/IV) to supplement nutrition, through improving intestinal absorption of fluid and nutrients. This proposed indication was granted Orphan Designation (OD) on June 29, 2000.

For treating patients with SBS, the FDA approved Zorbtive™ [somatropin (rDNA origin) for injection, NDA 021597] in 2003. In 2004 the FDA approved NutreStore™ [L-glutamine for oral solution, NDA 021667] which should be administered as a cotherapy with Zorbtive™ together with optimal management of short bowel syndrome, such as a specialized oral diet.

The sponsor submitted an original New Drug Application for GATTEX® (teduglutide [rDNA origin], NDA 203441) on 11/30/2011. The submission contains a total of 14 completed clinical trials and an interim report of an ongoing open-label, extension study in SBS subjects (CL0600-021, Table 1). A total of 623 unique subjects received at least one dose of teduglutide and 198 subjects treated with placebo in the clinical program. Four *in vitro* drug-drug interaction study reports, six single-dose pharmacokinetic (PK) study reports, three multiple-dose pharmacokinetic/pharmacodynamic (PK/PD) study reports, PK/PD data and immunogenicity data from four Phase 3 studies with SBS subjects were reviewed in this clinical pharmacology review.

Data from four Phase 3 efficacy and safety studies form the basis to support the proposed indication. (1) The pivotal double blind, placebo-controlled study (CL0600-020) that compared one dose level, 0.05 mg/kg/day, of teduglutide to placebo and (2) its ongoing, open-label extension study (CL0600-021); and (3) a supportive double-blind, placebo-controlled study (CL0600-004) that compared two dose levels, 0.05 mg/kg/day and 0.10 mg/kg/day, of teduglutide to placebo and (4) its randomized, double-blind extension study CL0600-005 that studied the long term safety of 0.05 mg/kg/day and 0.10 mg/kg/day daily doses of teduglutide. Based on results from these studies, the sponsor proposed a daily teduglutide dose of 0.05 mg/kg for the proposed indication.

In this review, teduglutide and ALX-0600 were used interchangeable.

1.1 Recommendation

From a clinical pharmacology perspective, the information submitted to support this NDA is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post-Marketing Requirements

The Clinical Pharmacology review team recommends the following post marketing requirement (PMR) as a sub-study of long term post-marketing safety trial(s):

The sponsor should assess the long-term impact of anti-drug antibodies (ADA) on safety and efficacy to include *in vivo* determination of ADA levels.

1.3 Post-Marketing Commitments

There are no post-marketing commitments for this submission.

1.4 Summary of Clinical Pharmacology Findings

The pharmacokinetics (PK) of teduglutide was evaluated in both healthy subjects and subjects with SBS. Teduglutide formulation strength (and/or SC injection volume) appears to have an impact on teduglutide PK upon SC administration (Study CL0600-022); therefore, the summary of clinical pharmacology findings are primarily based on data obtained with the to-be-marketed formulation strength (10 mg/mL).

Teduglutide PK after SC administration of the to-be-marketed formulation at the proposed clinical dose was characterized in the target patient population during Phase 3 study CL0600-004. Subjects with SBS appeared to have a lower drug exposure than healthy subjects. The overall summary of clinical pharmacology is presented below.

Pharmacokinetics (PK)

Absorption

Teduglutide was absorbed with a peak concentration at 3-5 hours after subcutaneous (SC) administration at abdomen, thigh, or arm with the to-be-marketed concentration (10 mg/mL). The maximal plasma concentration and exposure (C_{max} and AUC) of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg. No accumulation of teduglutide was observed following repeated daily SC administration. In healthy subjects, teduglutide had an absolute bioavailability of 88% after abdominal SC administration (Study CL0600-006).

Following SC administration of 0.05 mg/kg/day dose of teduglutide to subjects with SBS, median peak teduglutide concentration (C_{max}) was 36.8 ng/mL and overall median area under the curve ($AUC_{0-\tau}$) was 0.15 µg•hr/mL (Study CL0600-004).

Relative Bioavailability – alternative injection sites

The relative bioavailability of teduglutide was 89% and 92% for SC injection at the thigh and the arm, respectively, relative to SC injection at the abdomen (based on ANCOVA analysis of $AUC_{0-\infty}$) in healthy subjects. The 90% confidence interval (CI) for AUC_{0-t} or $AUC_{0-\infty}$ was within the 80% to 125% range, indicating that exposure was similar after SC injection at these 3 sites (Study CL0600-015).

Distribution

Following IV administration in healthy subjects, teduglutide had a mean (±SD) volume of distribution at steady state (Vss) of about 103 (± 23) mL/kg (Study CL0600-006), similar to the blood volume.

Metabolism

The metabolic pathway of teduglutide was not investigated in humans. However, as an analog to native GLP-2, teduglutide is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as the endogenous GLP-2. It is not likely to be metabolized by common drug metabolizing enzymes such as CYP, glutathione-S-transferase, or uridine-diphosphate glucuronyltransferase.

Elimination
Following IV administration in healthy subjects, teduglutide plasma clearance was approximately 127 mL/hr/kg which is roughly equivalent to the GFR suggesting that teduglutide is primarily cleared by the kidney (CL0600-006). Teduglutide was rapidly eliminated with a mean terminal half life ($t_{1/2}$) of approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Special Population
Teduglutide PK was evaluated in healthy elderly subjects, subjects with renal impairment, and subjects with hepatic impairment. Plasma concentration-time profiles of teduglutide were similar for healthy non-elderly and elderly subjects (Study CL0600-018). Except for creatinine clearance (CLcr), none of the evaluated intrinsic factors including age, gender, and hepatic impairment) had a significant effect on the PK of teduglutide.

Hepatic Impairment
Following a single SC administration of 20 mg teduglutide to subjects with moderate hepatic impairment, teduglutide C_{max} and AUC were lower (10 ~15%) compared to those in healthy matched control subjects; no dose adjustment is needed when administered to individuals with moderate hepatic impairment (CL0600-017). Teduglutide was not assessed in subjects with severe hepatic impairment.

Renal Impairment
Following a single SC administration of 10 mg teduglutide to subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide C_{max} and $AUC_{0-\infty}$ increased with increasing degree of renal impairment. The primary PK parameters of teduglutide increased up to a factor of 2.6 ($AUC_{0-\infty}$) and 2.1 (C_{max}) in ESRD subjects compared to healthy subjects (Study CL0600-018).

Based on these results, SBS patients with renal impairment would be exposed to higher levels of teduglutide due to a decrease in the renal clearance of the drug. Therefore, a dose reduction by 50% is recommended in patients with moderate to severe renal impairment and ESRD

Comparability Assessment
The phase 3 studies used the to-be-marketed formulation. However, the formulation strength appears to have impact on the extent of exposure following SC injection based on data in one single study that evaluated the same dose of teduglutide administered in two different formulation strengths (Study CL0600-022).

Drug-Drug Interaction (DDI)
No *in vivo* DDI studies were conducted based on results from *in vitro* studies in which significant inhibition or induction on tested cytochrome P450 isozymes was not observed at 2000 ng/mL

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.