CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

MEDICAL REVIEW(S)

Summary Safety Review for Regulatory Action

Date	(Stamped date)
From	Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products ODE III, CDER FDA
Subject	Division Safety Director Summary Review
NDA #	203441
Applicant Name	NPS Pharmaceuticals
Date of Submission	November 30, 2011
PDUFA Goal Date	September 30, 2012, major amendment - extended to December 31, 2012
Proprietary Name / Established (USAN) Name	Gattex (teduglutide [rDNA origin])
Dosage Forms / Strength	Lyophilized Powder for Injection, 5 mg
Orphan Drug Designation	6-29-2000
Route of Administration	Subcutaneous
Review Classification	Standard
Proposed Indication(s)	GATTEX® (teduglutide [rDNA origin]) powder for subcutaneous injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS). Gattex is used to improve intestinal absorption of fluid and nutrients.
Action/Recommended Action for NME:	Approval: Indication as per approved labeling (see approval letter)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	John Troiani
Statistical Review	Behrang Vali
Pharmacology Toxicology Review	Tamal Chakraborti
CMC Review.	Yichun Sun
Quality Microbiology Review (sterile products)	Brian Riley
Clinical Pharmacology Review	Lucy Fang
Clinical Pharmacometrics Review	Anshu Marathe
QT IRT Review	Moh Jee Ng
Immunogenicity Review	Joao Pedras-Vasconselos
Facilities Review/Inspection	Zhong Li
DCDP of OPDP	Kendra Jones/Eunice Chung-Davies
DSI - Division of Bioequivalence and GLP Compliance Office of Scientific Investigations	Young Moon Choi Khairy Malek
CDTL Review	Ruyi He
OSE/DMEPA	Manizheh Siahpoushan
OSE/DRM	Carolyn Yancey

OND=Office of New Drugs
DCDP of OPDP=Division of Consumer Drug Promotion in the Office of Prescription Drug Promontion
Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DMPP=Division of Medical Policy Programs
DRM=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Safety Deputy Director Review

1. Introduction

The purpose of this review is to highlight the risks and benefits associated with the use of Gattex (teduglutide [rDNA origin]) for injection to be used in patients with Short Bowel Syndrome (SBS), as well as, commenting on the Risk Evaluation and Mitigation Strategy (REMS), the post-marketing required studies (REMS) and the professional labeling including the Medication Guide (MG).

2. Background

Small Bowel Syndrome (SBS) results from surgical resection of some or all of the small or large intestine. If extensive, it can lead to malabsorption of protein, fluid, electrolytes and micronutrients. Following surgery, compensatory increases in bowel absorptive capacity can take up to two years to occur. If after two years the SBS patient still requires total parenteral nutritional support, it is unlikely that that patient will be completely weaned from such support[1].

Teduglutide has been shown to increase villus height and crypt depth of the intestinal epithelium resulting in enhanced absorptive capacity of the intestine.

Teduglutide is a 33 amino acid peptide that differs from its natural analog, glucagon-like peptide-2 (GLP-2) receptor agonist in the substitution of alanine (in native GLP-2) for glycine at the second position at the N-terminus. This single amino acid substitution provides resistance to in vivo degradation of teduglutide by dipeptidyl protease-IV (DPP-IV) resulting in an extended half-life. Teduglutide is manufactured using a recombinant strain of Escherichia coli.

The European Commission granted marketing authorization for "Revestive-teduglutide" on August 30, 2012. There is limited post-marketing experience in countries outside of the United States at the time of this review.

Regulatory History:
20 October 1998: Pre-IND meeting
26 April 1999: IND 58,213 submission for teduglutide in SBS
29 June 2000: US Orphan Drug designation granted
06 October 2003: End of Phase 2 meeting on clinical (Study 004) and nonclinical topics. Key items discussed were:

- Dosing: 0.05 and 0.10 mg/kg/day
- Standard outpatient care re: PN and concomitant medications
- Though study population would exclude SBS patients with unstable PN regimens, the results of the trial could potentially be extrapolated to such patients
- Proposed PN optimization/stabilization procedures, performance of colonoscopy in patients with a colon, mucosal biopsies of small intestine
- Primary efficacy endpoint is percent responders (reduction of at least 20% from baseline in weekly PN/IV volume at Week-24).

[1] Buchman AL. The clinical management of short bowel syndrome: steps to avoid parenteral nutrition. 1997. Nutrition. 13(10): 907-13.

- Conduct of two (replicative) trials was strongly recommended based on NME status

06 June 2006: Type C Meeting. FDA gives PK advice for special populations of hepatic and renal impairment. No formal drug-drug interaction studies are required, unless evidence arises for interactions. (Applicant later submitted hepatic impairment and multi-dose PK studies on 30-Jun-2010; and renal impairment study on 13-Sep-2011).
23 January 2007: Type C Meeting. Primary endpoint change discussed. By this time, Study 004 had randomized 84 patients and 55 patients had completed 24 weeks of treatment. Sponsor stated this change was not based on an interim analysis. FDA suggested performing a second clinical trial using the new primary endpoint. Note: Protocol amendment #4 (13-Feb-2007) incorporates primary endpoint change.
18 January 2008: Type C Meeting. Results of Study 004 are known. Need for and design of confirmatory Phase 3 study (CL0600-020) for at least 24 weeks collecting safety and efficacy data. FDA notes lack of a clear dose-response relationship for efficacy in Study **004.**
14 July 2008: Meeting to further discuss the results of Study CL0600-004, the planned Phase 3 Study (CL0600-020) and the acceptability of the same PN/I.V. reduction volume endpoint of the development program for filing a marketing application. "FDA notes that the study does show some clinical benefit however dose response has not been demonstrated. Study 004 has not shown which is the best dose for phase 3 studies. FDA indicates that the NPSP is free to select its dose. It would accept a 0.05 mg/kg/day to support an NDA; however it is not convinced that 0.05 mg/kg/day is the best dose." FDA confirms that "one additional study is needed" and "that a 2 arm design (0.05 mg/kg/day vs. placebo) would be acceptable to support an NDA". FDA encourages collection of neutralizing antibody data.
30 November 2011: NDA submitted to the FDA
10 August 2012: NDA amendment submission extends review date to 30 December 2012.
30 August 2012: European Commission adopted the CHMP decision granting marketing authorization for "Revestive-teduglutide", and an orphan medicinal product for human use.
3 August 2012: FDA received major amendment within 3 months of the user fee goal date, therefore the review clock was extended and a new user-fee-goal date of December 30, 2012 was established.
16 October 2012: FDA held Gastrointestinal Drug Advisory Committee (GIDAC)

Highlights of Review Issues:
1. **New Molecular Entity:** first in its class; glucagon-like peptide-2 (GLP-2)
2. **Efficacy:** demonstrated by two randomized controlled studies both with extensions. The primary efficacy endpoint was amended in one of these during the conduct of the study.
3. **Primary Endpoint:** evaluation of clinical meaningfulness, advice sought from the Advisory Committee
4. **Safety:** potential safety concerns based upon mechanism of action of Gattex.
5. **Risk Mitigation and Evaluation Strategies (REMS):** discussion at the GIDAC Meeting.

3. CMC/Device

The Chemistry and Manufacturing review concludes that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

The Amended CMC review concludes that:
"The updated drug substance specification now includes limits for the Class I metals (b) (4) , in conformance with USP <232> recommendations. NPS Pharmaceuticals also makes a Post Marketing Commitment to add limits to the drug substance specification for the remaining metals listed in the USP monograph. This will be done as soon as the method for determining the metals is appropriately validated, but no later than March 31, 2013. This approach is considered acceptable since

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