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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 21, 2012
TO: NDA 203441
Gattex (teduglutide [rDNA] powder for subcutaneous injection)
NPS Pharmaceuticals

FROM: Victoria Kusiak, M.D.
Deputy Director, Office of Drug Evaluation III

Subject: Approval Action

SUMMARY:

Gattex is a 33 amino acid recombinant analog of the human glucagon-like peptide-2 (GLP2), a peptide that is secreted primarily from the lower gastrointestinal tract and increases intestinal absorptive capacity. Gattex is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependant on parenteral support (parenteral nutrition/ intravenous hydration [PN/IV]). Gattex received Orphan Designation (OD) for this proposed indication on June 29, 2000.

Gattex differs from GLP-2 in the substitution of glycine for alanine at the second position of the N terminus. The glycine substitution results in resistance to degradation, extending the pharmacological activity of Gattex. Gattex binds to the GLP-2 receptors located in subpopulations of enteroendocrine cells, subepithelial myofibroblasts, and enteric neurons of the submucosal and myenteric plexus with receptor activation releasing intermediary growth factors locally, which act on epithelial cells. It has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine. Gattex increases villus height and crypt depth of the intestinal epithelium resulting in enhanced absorptive capacity of the intestine as demonstrated by greater absorption of fluids, electrolytes, and nutrients, reduced fecal fluid loss, and diminished diarrhea. In addition, Gattex has been shown to accelerate intestinal adaptation, increase nutrient transporter activity, enhance barrier function of the small intestine, and decrease intestinal inflammation. These effects form the rationale for use in patients with SBS.

SBS is caused by a reduction in intestinal surface area, leading to inadequate absorptive capacity and typically follows major surgical resection of the small intestine with or without complete or partial resection of the colon. SBS also occurs (rarely) secondary to congenital intestinal abnormality or underlying intestinal disease. Reduction in small intestine surface area leads directly to reduction of absorption of macro-nutrients, water and electrolytes, resulting in malnutrition, diarrhea, dehydration, and weight loss. The amount of nutritional and fluid impairment is dependant upon multiple factors including

the amount of residual intestine and colon, the presence or absence of an ileal segment, and the degree of spontaneous intestinal adaptation. For many patients SBS is a lifelong disease associated with significant increases in morbidity and mortality. PN/IV therapy itself is associated with increases in morbidity and mortality. Catheter related infections, central venous thrombosis and /or embolism and liver disease with eventual liver failure are known complications in SBS patients being treated with PN/IV. In the United States there are approximately 10,000 to 15,000 adult SBS patients requiring chronic PN/IV therapy which is typically given for 10 or more hours per day for 5-7 days a week.

The recommended dose of Gattex is 0.05mg/kg administered once daily by subcutaneous injection, alternating sites of injection between the four quadrants of the abdomen, or alternating thighs, or alternating arms.

This memorandum documents my concurrence with the Division of Gastroenterology and Inborn Errors of Metabolism Product's (DGIEP'S) approval recommendation for Gattex 0.05 mg/kg administered subcutaneously once daily for the treatment of adult patients with SBS who are dependant on parenteral support.

REGULATORY HISTORY

The following espouses the regulatory activity associated with the Gattex application:

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 to discuss clinical (Study 004) and nonclinical topics. Key items discussed were:

- Dosing: 0.05 and 0.10 mg/kg/day.
- Standard outpatient care with regard to PN and concomitant medications.
- Potential extrapolation of trial results to the excluded population of SBS patients with unstable PN regimens (allowed).
- Proposed PN optimization/stabilization procedures, performance of colonoscopy in patients with a colon, mucosal biopsies of small intestine.
- Primary efficacy endpoint as percent responders (reduction of at least 20% from baseline in weekly PN/IV volume at Week-24).
- Strong recommendation to conduct two replicate trials given the NME status of Gattex.

06 June 2006: Type C Meeting to discuss special populations and pharmacokinetic (PK) studies. Key items discussed were:

- PK advice for conduct of studies in special populations of hepatic and renal impairment. (The applicant later submitted hepatic impairment and multi-dose PK studies on 30-Jun-2010; and a renal impairment study on 13-Sep-2011).

- No requirement for formal drug-drug interaction studies, unless evidence arises for specific interactions

23 January 2007: Type C Meeting to discuss the primary efficacy analysis. Key items discussed were:

- Applicant's amended primary efficacy analysis for Study 004, which had randomized 84 patients with 55 having completed 24 weeks of therapy. The amendment of the primary endpoint analysis was not based upon an interim analysis.
- FDA recommendation to perform a second clinical trial using the new primary endpoint.

18 January 2008: Type C Meeting to discuss the results of Study 004. Key items discussed were:

- Need for and design of a confirmatory Phase 3 study (CL0600-020) of at least 24 weeks to collect safety and efficacy data.
- Lack of a clear dose-response relationship for efficacy in Study 004.
- Monitoring of Immunogenicity
- Need for a thorough QT study (Study 001).

14-July-2008 Meeting: Type C Meeting to discuss the results of Study 004 and the planned Phase 3 Study (CL0600-020) with regard to the acceptability of the same primary endpoint of reduction in volume of PN/I.V. used in study 004 as acceptable in Study CL0600-020. Key items discussed were:

- Lack of demonstration of dose response in Study 004
- Lack of dose justification for study CL0600-020. FDA indicates that NPS is free to select the dose used for the trial.
- FDA will accept a 0.05 mg/kg/day to support an NDA
- 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.

25 April 2011: Type B Pre-submission Meeting to discuss clinical data, nonclinical data, and submission logistics. Key items discussed were:

- FDA recommendation to delay submission until approximately 64 patients with at least 12 months of exposure are enrolled in the initial safety and efficacy databases.
- Applicant to characterize the impact of immunogenicity on PK, efficacy, safety.
- Inclusion of clinically meaningful measures of nutritional status. Analyses of these measures could be supportive of the primary endpoint and should be included in the NDA.
- A pediatric waiver is not required based on Orphan Designation.

30 November 2012: 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", an orphan medicinal product for human use.

CHEMISTRY MANUFACTURING and CONTROLS

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product for the requested dosage form.

The Applicant was requested to add a test method and acceptance criteria for (b) (4) to the drug substance specification and is currently developing a suitable procedure. The Applicant will implement this addition to the drug substance specification as a Post Approval Commitment (PMC).

CLINICAL MICROBIOLOGY

The drug product is sterile (b) (4) and lyophilized. There are no Clinical Microbiology issues.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The applicant has conducted adequate nonclinical studies with Gattex which included pharmacology, safety pharmacology, pharmacokinetic, and acute and chronic toxicology studies. In mice, acute toxicology studies were conducted as well as repeated dose toxicology studies (14 days to 26 week duration); in rats, repeated dose toxicology studies were conducted (14 days to 26 weeks duration); in cynomolgus monkeys, repeated dose toxicology studies were conducted (14 weeks to 1 year duration); and in juvenile mini-pigs, repeated dose toxicology studies were conducted (14 days to 90 days duration).

Genotoxicity studies (Ames, chromosome aberration test in Chinese hamster ovary cells, *in vivo* micronucleus test in mice), reproductive toxicology studies (fertility and early embryo-fetal development in rats, embryo-fetal development in rats and rabbits and pre and postnatal development in rats), and special toxicology studies (antigenicity and local tolerance studies) were conducted. All toxicology studies were conducted using the subcutaneous (SC) route of administration which is the intended clinical method of use.

Doses administered subcutaneously to mice and rats were up to 1000 times the recommended daily human dose (50/mg/kg/day), while cynomolgus monkeys received approximately 500 times the recommended human daily dose (25/mg/kg/day).

Pharmacology studies examined the intestinotrophic activity of teduglutide in several animal species. In mice, teduglutide increased weight and length of the small intestine

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