

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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

and enhanced epithelial barrier function. Teduglutide also increased the absorptive function of the intestinal mucosa in rats and monkeys. In a rat model of SBS, teduglutide increased the rate or magnitude of the intestinal adaptive response to intestinal resection at a dose of 0.2 mg/kg/day. In neonatal piglets with jejuno-ileal resection, teduglutide showed significant improvements in crypt-villus architecture in the small intestine, as well as in duodenal, jejunal and ileal glucose transport and jejunal glutamine transport.

In pivotal toxicology studies, major treatment-related effects (hypertrophy/hyperplasia) were related to the pharmacological activity of teduglutide. In the 26-week toxicity study in mice at 2, 10 and 50 mg/kg/day, major treatment-related histopathological changes were seen in the small and large intestines (epithelial and villus hypertrophy and hyperplasia), gall bladder (epithelial hypertrophy and hyperplasia accompanied by subacute inflammation), and sternal bone marrow (myeloid hyperplasia). In the 1-year toxicity study in cynomolgus monkeys at 1, 5 and 25 mg/kg/day, major treatment-related histopathological changes were seen in the small and large intestines (mucosal hyperplasia), stomach (mucosal hyperplasia), pancreas (hypertrophy/hyperplasia of the pancreatic duct epithelium), liver and gall bladder (epithelial hypertrophy and hyperplasia of the bile duct in the liver and mucosal hypertrophy/hyperplasia of the gall bladder). In juvenile minipigs, similar treatment-related histopathological changes were observed in the small intestine (minimal/slight villous hypertrophy), gall bladder (cystic mucosal hyperplasia), and extrahepatic bile duct (cystic mucosal hyperplasia).

In the subcutaneous fertility and early embryonic study in rats, teduglutide did not show any adverse effects on early embryonic development or fertility parameters at doses up to 1000 times the recommended daily human dose. In the subcutaneous embryofetal development in rats and rabbits, teduglutide was not teratogenic at doses up to 1000 times the recommended daily human dose. Likewise in the subcutaneous pre and postnatal development study in rats, teduglutide did not show significant adverse effects on pre or postnatal development at doses up to 1000 times the recommended daily human dose.

Teduglutide was not genotoxic in the Ames test, *in vitro* chromosomal aberration test in Chinese hamster ovary (CHO) cells, and *in vivo* mouse micronucleus test. In a 2-year carcinogenicity study by the subcutaneous route in rats at 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct (0/50, 0/50, 1/50 and 4/50 at 0, 3, 10 and 35 mg/kg/day, respectively; $p=0.0037$, trend test) and jejunum (0/50, 1/50, 0/50 and 5/50 at 0, 3, 10 and 35 mg/kg/day, respectively; $p=0.0031$, trend test) of male rats. There were no drug related tumor findings in females.

Gattex will be labeled as a pregnancy category B, as there are no adequate and well controlled studies in pregnant women.

Due to its growth promoting pharmacological effects, teduglutide has a potential to cause hyperplastic changes, including tumor formation, and this potential will be included in the product labeling.

CLINICAL PHARMACOLOGY

The pharmacokinetics of Gattex were evaluated in both healthy subjects and subjects with SBS. Subjects with SBS had a lower drug exposure than healthy subjects.

Absorption: With the to-be-marketed formulation, Gattex reached peak plasma concentration 3-5 hours after SC administration in the abdomen, thigh or arm. A formal relative bioavailability study evaluating the relative bioavailability of Gattex after administration in these 3 sites indicated that exposure was similar. The maximal plasma concentration and exposure (C_{max} and AUC) of Gattex was dose proportional over the dose range of 0.05-0.4 mg/kg. The C_{max} in subjects with SBS following SC administration was 36.8 ng/mL at the 0.05 mg/kg/day SC dose and the AUC was 0.15 µg·hr /ml. No accumulation of Gattex was observed following repeated daily SC administration.

Distribution: Following intravenous administration in healthy subjects, Gattex had a mean volume of distribution at steady state of approximately 103 (±23) mL/kg, similar to blood volume.

Metabolism: The metabolic pathway of Gattex was not investigated in humans; however, as an analog to native GLP-2, Gattex 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 Gattex plasma clearance was 127 mL/kg/hr which is roughly equivalent to the GFR, suggesting that Gattex is primarily cleared by the kidney. Gattex was rapidly cleared with a mean terminal half life (t_{1/2}) of approximately 2 hours in healthy subjects and 1.3 hours in subjects with SBS.

Special Populations:

Age and Gender: Plasma concentration time profiles and pharmacokinetics of Gattex were similar in healthy elderly subjects and younger subjects, and in men and women.

Renal Impairment: Following a single 10 mg SC dose in subjects with moderate to severe renal impairment, C_{max} and AUC increased with increasing degree of renal impairment. The primary pharmacokinetic parameters of Gattex increased up to a factor of 2.6 (AUC) and 2.1 (C_{max}) in subjects with end stage renal disease (ESRD) compared to healthy subjects. In subjects with moderate to severe renal impairment and ESRD, dosage reduction by 50% is recommended, because of decreased renal clearance.

Hepatic Impairment: In subjects with moderate hepatic impairment, the C_{max} and AUC of Gattex were only slightly lower (~10% to 15%) after a single 10 mg SC dose compared to healthy matched control subjects, therefore no dosage adjustment is necessary in subjects with moderate hepatic impairment. The pharmacokinetics of Gattex was not assessed in subjects with severe hepatic impairment.

Drug-Drug Interaction(s) (DDI):

No *in vivo* DDI studies were conducted based on results from *in vitro* studies in which significant inhibition or induction of cytochrome P450 isozymes was not observed at doses of Gattex up to 2000 ng/mL, a concentration significantly greater (55-fold) than that of the C_{max} observed at the clinical dose of 0.05 mg/kg. As Gattex is not a pro-inflammatory cytokine or cytokine modulator, DDI studies are not required even though the relevance of *in vitro* studies to the *in vivo* setting is unclear. Additionally, Gattex was neither a substrate nor an inhibitor of P-gp at concentrations above 2000 ng/mL.

It is important to note that the potential for pharmacodynamic (PD) mediated drug-drug interactions exists because Gattex has demonstrated the PD effect of increasing intestinal absorption. This effect should be considered when Gattex is co-administered with drugs requiring titration or having a narrow therapeutic index. This information will be included in the product labeling.

Thorough QT Study:

No significant QTc prolongation was detected with SC administration of 5 mg of Gattex or at a supra-therapeutic dose of 20 mg in the Thorough QT (TQT) study. This study was a randomized, partially blinded, single dose, four-way cross over, active and placebo controlled study. 70 healthy subjects received Gattex 5 mg SC, Gattex 20 mg SC, placebo and moxifloxacin 400 mg. The 20 mg SC supratherapeutic dose produced mean C_{max} concentrations 3.8 fold above the C_{max} for the 5 mg SC dose. At these concentrations there was no detectable prolongation of the QT interval. Of note, the C_{max} at the 20 mg SC dose produced concentrations above those expected in subjects with ESRD.

Immunogenicity:

Overall, the immunogenicity incidence (anti-drug antibody) rate increased with the duration of treatment (18% at 6 months, 27% at 12 months and 38% at 18 months) and the majority of subjects had the first occurrence of anti-drug antibody (ADA+) finding at 6 months after treatment initiation. Among 34 subjects who were treated with Gattex in both the pivotal study and the extension study, 6 subjects tested ADA+ at baseline (of which 5 continued to be ADA+ in the extension study) and 8 additional subjects became ADA+ post-baseline. The incidence rate was 38% (13/34) for subjects who received

Gattex treatment for the duration of 18 months. Among 51 subjects who initiated Gattex treatment in the extension study, 14 subjects were ADA+ (14/51, 27%) during the extension study after 12 months of Gattex treatment.

Anti-teduglutide specific antibodies showed evidence of cross reactivity against the native GLP-2 protein in 5 out of 6 ADA+ subjects at 6 months post treatment in the pivotal study. It has not been established if these antibodies are neutralizing. The average weekly response for these six subjects trended toward improvement during the 6 months of the trial and appeared to stabilize in the extension study. This response was similar to the mean response in the subjects who did not have an ADA positive status at week 24.

The impact of ADA on PK is unknown and has not been adequately assessed. All ADA+ subjects were responders during the controlled treatment period up to 1.5 years and 26 of the 27 subjects who developed antibodies post baseline had reduced PN/IV volume at the time of last dosing; however, the long term impact of the presence of ADA is unknown. This information will be included in the product labeling.

EFFICACY:

Efficacy of Gattex in SBS was assessed in two randomized, double blind, placebo-controlled, parallel group, multinational, multicenter trials (Study 004 and Study 020). Each of these trials had a non-randomized open-label extension study (Study 005 and Study 021, respectively). Study 020 demonstrated a statistically significant ($p=0.002$) difference between Gattex and placebo for the primary endpoint which is percent responders in each study group who achieved at least a 20% reduction in weekly PN/IV volume at weeks 20 and 24: (63% [27/43] versus 30% [13/43] Gattex and placebo respectively). Study 004 did not meet the protocol specified primary endpoint (the difference between Gattex 0.10 mg/kg/day and placebo in percent responders who achieved at least a 20% reduction in weekly PN/IV volume at weeks 20 and 24 as a graded response analysis) but did demonstrate benefit for the key secondary endpoint of difference between Gattex 0.05 mg/kg/day and placebo in percent responders (46% Gattex, 6% placebo). The pre-specified graded categorical response analysis did not allow for statistical testing beyond the primary endpoint which involved the 0.10 mg/kg/day dose, but nevertheless, the 0.05 mg/kg/day dose demonstrated a clear benefit compared to placebo and provides robust support for study 020.

Study 004 enrolled 83 subjects with SBS who required PN/IV at least 3 times weekly and randomized them to Gattex 0.10 mg/kg/day (N=32), Gattex 0.05 mg/kg/day (N=35) or placebo (N=16) for up to 24 weeks. Subjects' PN/IV status was optimized during a maximal 8 week baseline period. At weeks 4, 8, 12, 16, and 20, investigators adjusted each subject's PN/IV volume based upon percent change in urine output. For increases in urine output < 2 liters a day, PN/IV could be decreased by no more than 10% while for urine outputs > 2 liters a day PN/IV could be decreased based upon the investigator's clinical judgment. The proportion of subjects achieving at least a 20% reduction of PN/IV volume both at week 20 and week 24 (responders) was statistically significantly different from placebo (46% vs. 6.3%, $p < 0.01$) for those subjects receiving the recommended

Gattex dose of 0.05 mg/kg/day. The difference in responders compared to placebo for the Gattex 0.10 mg/kg/day group was not statistically significant. Two subjects on the Gattex 0.05 mg/kg/day dose were able to be totally weaned from parenteral support by week 24. Treatment with Gattex resulted in a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week reduction for placebo at 24 weeks. As per protocol, after 6 months of treatment, 77 subjects underwent small and large intestine biopsy resulting in 390 individual pathology specimens. No features of dysplasia were seen in any biopsy. Gattex treatment resulted in expansion of the absorptive epithelium by significantly increasing villus height in the small intestine.

Sixty-five subjects from study 004 entered a long term Trial (005) for up to an additional 28 weeks of treatment. Subjects on Gattex retained their original dose assignment (Gattex 0.10 or 0.05 mg/kg/day), while patients originally assigned to placebo were randomized to active treatment (Gattex 0.10 or 0.05 mg/kg/day). Of the responders in the original trial who entered the extension phase, 75% sustained response on Gattex after up to 1 year of continuous treatment. In the recommended dose group (0.05 mg/kg/day) 68% of subjects achieved at least a 20% reduction in parenteral support after an additional 28 weeks of treatment (17/25 subjects). The mean reduction of weekly parenteral support volume was 4.9 L/week (a 52% reduction from baseline) after 1 year of continuous treatment. One additional subject in the extension phase of the study was weaned from parenteral support, with a total of 3 subjects on the 0.05 mg/kg/day dose able to discontinue parenteral support.

Study 020 sequentially followed Study 004. Results from Study 004 were used to inform the design of 020. In Study 020, only the 0.05 mg/kg/day dose was evaluated. Study 020, added an earlier time point for fluid adjustment at week 2 (performing adjustments at weeks 2, 4, 8, 16 and 20), allowed up to a 30% reduction in fluid at each adjustment time point, and used the difference in percent responders between groups (responders defined as those who had a reduction of 20% to 100% in PN/IV volume at weeks 20 and 24 compared to baseline) as the primary endpoint.

Study 020 was a two stage trial, with the first stage requiring optimization of the subject's PN/IV for a maximum of 8 weeks followed by an 8 week PN/PV stabilization period where PN/IV remained the same. During optimization, PN/IV could be adjusted up to a 30% decrease based upon urine output and oral intake. Following stabilization, 86 subjects were randomized to Gattex 0.05/mg/kg/day SC (n=43, of which 42 received Gattex) or placebo (N=42) daily for 24 weeks of treatment. The primary efficacy endpoint was the difference between groups in the number of responders defined on a per subject basis as achievement of a 20%-100% reduction from baseline in weekly PN/IV volume.

The mean age of the patients enrolled was 50.3 years. The average length of time of PN/IV dependency was 6.25 years (range 1-25.8 years). The most common reasons for intestinal resection were: vascular disease, 34%; Crohn's disease, 21%; and other 21%. A stoma was present in 45% with the most common type being a jejunostomy/ileostomy (82%). The mean length of the remaining small intestine was 77.3 ± 64.4 cm (range 5-

343 cm). The colon was not in continuity in 44% of subjects. The baseline mean number of prescribed PN/IV perfusion days was 5.73 with a standard deviation of ± 1.59 days.

The results of the trial showed that 63% (27/43) of Gattex treated subjects responded to treatment as opposed to 30% (13/43) of placebo treated subjects ($p = 0.002$). At week 24, the mean reduction in PN/IV volume was 4.4 L/week from a baseline of 12.9 L/week for Gattex treated subjects versus a mean reduction of 2.3 L/week from a baseline of 13.2 L/week for placebo treated subjects ($p < 0.001$). Twenty-one subjects on Gattex (53.8% as compared to 9 (23.1%) on placebo achieved at least a one day reduction in PNIV administration ($p=0.005$).

Subjects that were enrolled in Study 020 could elect to continue treatment in the ongoing open label extension, Study 021. 97% of subjects (76/78) continued into the extension where all subjects receive 0.05 mg/kg/day SC for up to an additional 2 years. By trial design, subjects continue to take Gattex even if they no longer require PN/IV support. The trial is ongoing. An interim assessment of this trial (021) was performed on patients who had completed one year of therapy on Gattex: 6 months in Study 020 and 6 months in Study 021 (N=34). 91.2% of these patients (31/34) showed continued response in reduction of PN/IV volume. 3 Subjects were completely weaned from PN/IV therapy at the time of the interim report. 52.9% (18/34) subjects have achieved at least a 1 day per week reduction; 13 (38.2%) at least a 2 day reduction and 8 (23.5%) at least a 3 day reduction in PN/IV requirement.

SAFETY

Overall, 566 (safety population) subjects were exposed to Gattex and 198 to placebo across 15 clinical trials as follows:

- 299 subjects in the clinical pharmacology studies
 - 89 (16% of 566) for less than 6 months
 - 135 (24% of 566) for at least 6 months but no more than 12 months
 - 75 (13% of 566) for at least 12 months
- 173 subjects in the SBS Efficacy and Safety trials
- 94 subjects in other studies (Crohn's Disease)

The incidence of adverse events in subjects with SBS was evaluated in two randomized, double blind, placebo controlled trials (Study 004 and Study 020), in which a total of 77 subjects received Gattex 0.05 mg/kg/day SC and 59 subjects received placebo. Overall 68/77 (88.3%) of subjects receiving Gattex had an adverse event as compared to 49/59 (83.1%) taking placebo. In general the events were mild or moderate. The overall high rate of adverse events in this population (both Gattex and placebo treated) reflects both the underlying disease and the necessity for parenteral support and its associated complications.

Adverse reactions reported in $\geq 5\%$ of Gattex treated subjects (0.05 mg/kg/day SC) and at a rate greater than placebo were as follows: Abdominal pain: 37.7% Gattex, 27.1% placebo; Upper Respiratory Tract Infection: 26.0% Gattex, 13.6% placebo; Nausea: 24.7% Gattex, 20.3% placebo; Abdominal Distention: 19.5% Gattex, 1.7% placebo; Vomiting: 11.7% Gattex, 10.2% placebo; Fluid Overload: 11.7% Gattex, 10.2% placebo; Flatulence: 9.1% Gattex, 6.8% placebo; Hypersensitivity: 7.8% Gattex, 5.1% placebo; Appetite Disorders: 6.5% Gattex, 3.4% placebo; Sleep Disturbance 5.2% Gattex, 0% placebo; Coughing: 5.2% Gattex, 0% placebo; Skin Hemorrhage: 5.2% Gattex, 1.7% placebo; Stoma Complication: 13/31 (41.9%) Gattex, 3/22 (13.6%) placebo. (53 subjects total had a stoma in controlled trials; 22 in the placebo group, 0 in the Gattex 0.10 mg/kg/day, and 31 in the Gattex 0.05 mg/kg/day group. The stomas were of differing surgical types, they supported different types of anatomical anastomoses and they had variable histories with regard to obstruction prior to study initiation. The subject numbers are too small to draw a conclusion with regard to association of treatment with Gattex and stomal obstruction).

Injection site reactions were observed at a similar incidence in Gattex and placebo treated subjects.

The most commonly reported ($\geq 5\%$) adverse reactions across all studies including long term open label safety studies (N=566 Gattex treated subjects) were: abdominal pain (30.0%); injection site reaction (22.4%); nausea (18.2%); headache (15.9%); abdominal distention (13.8%); upper respiratory tract infection (11.8%); asthenic conditions (9.5%); vomiting (8.8%); musculoskeletal pain (8.5%); catheter sepsis (7.8%); cognition and attention disorders and disturbances (7.8%); constipation (7.4%); fluid overload (6.9%); diarrhea (6.9%); stoma complication (6.5%); hypersensitivity (6.4%); flatulence (6.2%); urinary tract infection (6.2%); febrile disorder (6.0%); and increased hepatic enzymes (5.5%).

In the pooled Gattex treated group in the SBS placebo-controlled study data (N=109 Gattex, 0.05 or 0.10 mg/kg/day SC; N=59 placebo) 12% of subjects discontinued. The most common reason for discontinuation was adverse events (8%) of which the most common were constipation and abdominal distension, for which there were no discontinuations in the placebo group. In the pooled placebo group (N=59), the most common reason for discontinuation was adverse event (7%) which included catheter sepsis, increased stool (frequency, volume), intestinal polyp, and transplantation, none of which except for catheter sepsis occurred in the Gattex group.

In the long term extension trial (Study 005), 7 of 8 discontinuations for adverse events were in patients previously treated with Gattex in Study 004. The reasons for discontinuation in these 7 patients included abdominal pain, hyperplastic colon polyp, irritable bowel disease, vomiting, nausea, cough, and cerebrovascular accident (CVA). The case of CVA occurred in a 64 year old white female (005-0145-0005) with history of stroke, who had been on Gattex for 59 days.

There were 3 deaths reported during the drug development program: two subjects were receiving Gattex 0.05 mg/kg/day SC during extension studies and one subject died during the screening period. One patient on Gattex died of metastatic adenocarcinoma, origin presumed to be gastrointestinal (GI), and one died of small cell lung cancer. The patient who died in screening suffered a massive upper GI bleed.

Potential Safety Concerns with Gattex:

The safety profile of Gattex was evaluated with regard to specific concerns based on mechanism of action, nonclinical safety data, adverse events in clinical trials, clinical laboratory data and literature review. The following areas of concern were identified:

- Potentiation of neoplastic growth including intestinal polyps
- GI stenosis and intestinal obstruction
- Cholecystitis
- Pancreatic disease
- Increased absorption of fluid absorption and risk of hypervolemia
- Hypersensitivity reactions

Potentiation of Neoplastic Growth Including Intestinal Polyps:

No treatment-emergent malignancies were reported in placebo-controlled trials with Gattex. Three patients in the ongoing extension Study 021 were reported with neoplasms of the GI tract and lung.

The subject with GI tract malignancy was a 47 year old male with Hodgkin's disease, diagnosed in 1988, for which he was treated with both radiation and chemotherapy. Both his disease and therapy contributed to an increased risk for developing secondary malignancies, particularly those of gastrointestinal origin. Autopsy revealed adenocarcinoma with extensive metastases to liver, bone, lung, and regional nodes, with a primary site that was difficult to localize. Expert radiology consultants agreed that a 2 cm left lobe liver lesion was present on the CT scan performed prior to trial entry. This subject received placebo in the controlled portion of the trial (Study 020) for 6 months, and Gattex 0.05 mg/kg/day SC therapy for 11 months during the ongoing extension (Study 201).

A 73 year old male subject with a history of cigarette smoking was diagnosed with squamous cell carcinoma of the right lung on Day (b)(6) of treatment with Gattex 0.05/0.05 mg/kg/day SC.

A 64 year old male subject with a 30 year history of smoking 30 cigarettes a day was diagnosed with non-small cell carcinoma of the left lung after (b)(6) days of therapy with Gattex 0.05 mg/kg/day SC.

Based on available data, a relationship between malignancy and therapy with Gattex cannot be determined.

Intestinal Polyps:

In the pooled SBS placebo controlled trial with Gattex, no subjects were diagnosed with polyps in the Gattex 0.10 mg/kg/day SC group. In the Gattex 0.05 mg/kg/day SC group, 2 subjects were diagnosed with polyps and in the placebo group, polyps were detected in 1 subject. In the long term extension trials, 4 subjects were diagnosed with polyps, at days 87, 189, 190, and 230.

From the 3 polyp cases (2 in the Gattex treated group and 1 in the placebo treated group) in the SBS placebo controlled studies, it is difficult to conclude a relationship between Gattex and the development of GI epithelial polyps. GI polyps, especially at stomal sites, are not uncommon in patients who have undergone bowel resection. On the other hand, a finding of polyps is not inconsistent with the mechanism of action of Gattex and the nonclinical findings. As for the cases in the long-term studies, the absence of a concurrent control group makes it difficult to determine the role of Gattex in polyp formation and growth. Although a biologically plausible mechanism for a relationship exists, a definitive statement regarding the relationship of polyps and treatment with Gattex cannot be made based on available data.

GI Stenosis and Intestinal Obstruction:

In the SBS placebo-controlled trials (Study 004, Study 020), no cases of GI obstruction were reported in the placebo group. In the Gattex treated groups 6/109 (5.5%) cases of GI obstruction were reported: 3 (3.9%) in the Gattex 0.05 mg/kg/day SC group and 3 (9.4%) in the Gattex 0.10 mg/kg/day SC group, none of which required surgical intervention.

In the SBS extension trials (Study 005 and Study 021), 6 new patients experienced GI stenosis/obstruction, one of whom required procedural intervention (endoscopic dilation).

These cases of GI obstruction were all associated with a prior history of recurrent obstruction and stricture/adhesions from previous surgery.

Although prior bowel surgery increases the risk for intestinal obstruction, these data suggest the possibility of a dose-response relationship with use of Gattex. An obstructive clinical presentation (obstruction or pseudo-obstruction) is not inconsistent with the mechanism of action of Gattex with increased luminal fluid reabsorption leading to stool dessication and bowel wall thickening potentially causing slower transit.

Acute Cholecystitis:

In the SBS placebo controlled studies the incidence of cholecystitis was as follows: 0 placebo treated subjects, 3 (3.9%) subjects on Gattex 0.05 mg/kg/day SC, and 1 (3%) subject on Gattex 0.10 mg/kg/day SC. Of these, 3 had a prior history of cholestasis/cholecystitis. In the extension trials, 5 subjects on Gattex 0.05 mg/kg/day SC and 2 subjects on Gattex 0.01 mg/kg/day SC developed acute cholecystitis. Of these, 3 subjects had a prior history of cholecystitis/cholestasis.

While no cases of biliary disease were seen in the placebo treated group, the number of cases observed is small and gallbladder/liver/pancreatic disease is very common in PN/IV dependent SBS patients.

Pancreatic Disease:

In the SBS placebo controlled trials, 4 subjects experienced signs or symptoms of pancreatic abnormality. 2 subjects, one on Gattex 0.05 mg/kg/day SC and one on Gattex 0.10 mg/kg/day SC, experienced abdominal pain associated with amylase/lipase elevations. Both had a prior history of such elevations. One patient was subsequently determined to have small bowel obstruction and the other to have cholecystitis, both with associated pancreatitis. Two additional patients, one on Gattex and one on placebo experienced asymptomatic elevations of pancreatic enzymes. Both had a prior history of such elevations. In the extension trials, a single case of chronic pancreatitis was seen in the Gattex 0.10 mg/kg/day SC group on day 153.

All patients who developed signs or symptoms of pancreatic disease had a prior history of such disease and all had co-morbidities that do not allow a clear assessment to be made regarding a possible association between use of Gattex and pancreatic disease.

Increased Absorption of Fluid and Risk of Hypervolemia:

In the SBS placebo controlled trials, fluid overload associated symptoms were reported in 4/59 (6.8%) of placebo treated subjects and 9/77 (11.7%) of Gattex 0.05 mg/kg/day SC treated subjects.

The possibility of fluid overload should be considered when administering Gattex. The mechanism of action of Gattex promotes fluid absorption as part of its clinical benefit, however, this increase is potentially harmful to patients with congestive heart failure or renal disease. The incidence of fluid overload in controlled trials was nearly double that placebo in the Gattex treated group. The applicant will address this issue in labeling.

Hypersensitivity Reactions:

In the SBS placebo-controlled trials, hypersensitivity was reported in 3/59 (5.1%) of placebo treated subjects, 3/32 (9.4%) of Gattex 0.10 mg/kg/day SC treated subjects and 6/77 (7.8%) of Gattex 0.05 mg/kg/day treated subjects. None of these patients was ADA positive.

No instances of possible anaphylactic reactions to Gattex were found in the safety data base.

ADVISORY COMMITTEE:

A meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) was held on October 16, 2012, to consider the following: The adequacy of the available safety and efficacy data; the overall adequacy of the Applicant's proposed labeling (including a Medication Guide) with regard to the safety issues described above; the adequacy of the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMs); the adequacy of the additional long term post-marketing safety assessment proposed by the Applicant (which consists of a voluntary patient registry with follow-up); and the overall risk/benefit balance of Gattex.

In discussing the adequacy of the efficacy data, GIDAC concluded that the primary efficacy endpoint of a $\geq 20\%$ reduction in the PN/IV requirement as was used in Trial 020 is clinically meaningful and that the combined results of Trials 004 and 020 demonstrated that Gattex is efficacious in adult patients with SBS. The Committee was unanimous in its conclusion.

With regard to safety, the Committee felt that the potential tumor promoting concerns with use of Gattex could be adequately handled by the Applicant's proposed labeling as could the other GI related concerns of potential increased incidence of biliary disease, pancreatic disease, and GI stenosis and obstruction. Labeling warning of the specific potential issues and recommending pre-use screening with relevant endoscopy, imaging and laboratory studies as well as interval post dosing follow-up studies would provide adequate safety monitoring. GIDAC felt that no additional monitoring was required for the potential for non-GI malignancies and that no specific monitoring or follow-up was required for potential immunogenicity related concerns given the lack of significant clinical findings and the lack of any phenotypic change with regard to interference with the GLP-2 pathway in animal studies.

With regard to the Applicant's proposed REMs, the Committee voted 10 to 1 (with one abstention) that the proposed REMs is adequate and that no further elements are necessary. The proposed REMs consists of a Communication Plan directed to prescribers including: a Dear Healthcare Provider Letter, (twice a year for 3 years with gastroenterologists and colorectal/gastrointestinal surgeons targeted); a Dear Professional Society Letter (directed to professional organizations for dissemination of safety risk information to the membership); a Prescriber Educational Slide Deck (for face to face presentation to prescribers); and Patient Educational Material (given to prescribers for use with individual patients for patient education).

In addition to the REMs, the Applicant proposes to include a medication guide (for patient information and education) as part of the labeling, and implement a voluntary Patient Registry. The intent of the Applicant is to enroll as many subjects with SBS using Gattex into the Registry as possible, as well as non-users with SBS. The Registry will follow patients long term (at least 10 years) with regard to the above mentioned safety issues. GIDAC expressed some concern over the details surrounding the Registry, emphasizing the need for as complete a patient enrollment as possible and the need for long term follow-up (10 years or more). The Committee did not recommend mandatory enrollment in the Registry as a prerequisite for use of the drug because they felt that this would be too restrictive. The Committee voted 10 to 1 with 1 abstention in support of the adequacy of the post-marketing safety follow-up plans including the Applicant's proposed REMs and the Registry.

With regard to the overall risk to benefit balance of Gattex, the Committee voted unanimously that the benefits outweighed the risks for use of Gattex in adult patients with SBS.

I concur with the opinions of GIDAC as outlined above.

PEDIATRIC CONSIDERATIONS:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosage regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless the requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, the Applicant is exempt from the PREA requirement.

POSTMARKETING REQUIREMENTS and COMMITMENTS:

PMR(s)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes the FDA to require holders of approved drug and biological product applications to conduct post marketing studies and clinical trials for certain purposes if FDA makes certain findings required by statute.

FDA has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to access a signal of a serious risk of possible acceleration of neoplastic growth and enhancement of colon

polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that the following study be conducted:

A prospective, multi-center, long-term, observational, registry study of short bowel syndrome patients treated with Gattex in a routine clinical setting, to assess the long-term safety of Gattex. The study should be designed around a testable hypothesis to rule out a clinically meaningful increase in colorectal cancer risk above an estimated background risk in a suitable comparator. The choice of an appropriate comparator population(s) and corresponding background rate(s) should be justified relative to the Gattex exposed patients. Sample sizes and effect sizes that can be ruled out under various enrollment target scenarios and loss to follow-up assumptions should be provided. The primary outcome should be colorectal cancer, and secondary outcomes should include other malignancies, colorectal polyps, bowel obstruction, pancreatic and biliary disease, heart failure, and long-term effectiveness. Patients should be enrolled over an initial 5-year period and then followed for a period of at least 10 years from the time of enrollment. Progress updates of registry patient accrual and a demographic summary should be provided annually. Registry safety data will be provided in periodic safety reports. The final protocol and statistical analysis plan should be submitted to the FDA for review and concurrence prior to study initiation.

Final Protocol Submission: 09/2013
Study Completion: 12/2029
Final Report Submission: 06/2031

PMC(s)

The Applicant agrees as a Post Marketing Commitment that elemental impurities specifications will be expanded to include limits and testing for all metals, as recommended in USP <232>. 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 the primary safety concern from trace metals that can be present comes from the Class I metals and the drug specifications for these metals have been set and found to be acceptable. Limits for the additional metals will further improve the quality of the drug substance, but these metals do not pose the safety hazard of the Class 1 metals.

RISK EVALUATION and MITIGATION STRATEGY (REMs):

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and

Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

The following REMs and Elements to Assure Safe Use will be required for Gattex:

A REMS is necessary to ensure the benefits of Gattex outweigh the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex.

A communication plan describing the risks as detailed above is necessary to support implementation of the REMs. Additionally, elements to assure safe use are also required. The elements to assure safe use will include training for health care providers who prescribe Gattex and appropriate risk information for patient education.

A REMs assessment plan will also be required and should include an evaluation of healthcare providers' understanding of the serious risks described above as well as an evaluation of patients' understanding of such risks.

Such assessments should be provided according to the timetable established in the approved REMs document.

TRADENAME REVIEW:

On February 21, 2012, The Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology concluded that the tradename "Gattex" is acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA KUSIAK
12/21/2012