SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gattex

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 5 mg of teduglutide*.

*A glucagon-like peptide-2 (GLP-2) analogue produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
The powder is white.

Patient safety information card

The marketing of Gattex is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gattex is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a medical professional with experience in the treatment of Short Bowel Syndrome (SBS).

Treatment should not be initiated until it is reasonable to assume that a patient is stable following a period of intestinal adaptation. Optimisation and stabilisation of intravenous fluid and nutrition support should be performed before initiation of treatment.

Clinical assessment by the physician should consider individual treatment objectives and patient preferences. Treatment should be stopped if no overall improvement of the patient condition is achieved. Efficacy and safety in all patients should be closely monitored on an ongoing basis according to clinical treatment guidelines.

Posology

Adults

The recommended dose of Gattex is 0.05 mg/kg body weight once daily. The injection volume per body weight is provided below in Table 1. Due to the heterogeneity of the SBS population, a carefully

monitored down-titration of the daily dose may be considered for some patients to optimise tolerability of the treatment. If a dose is missed, that dose should be injected as soon as possible on that day.

Treatment effect should be evaluated after 6 months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered.

Continued treatment is recommended for patients who have weaned off parenteral nutrition.

Table 1: Injection volume per body weight for adults

Body weight	Volume to be injected
38-41 kg	0.20 ml
42-45 kg	0.22 ml
46-49 kg	0.24 ml
50-53 kg	0.26 ml
54-57 kg	0.28 ml
58-61 kg	0.30 ml
62-65 kg	0.32 ml
66-69 kg	0.34 ml
70-73 kg	0.36 ml
74-77 kg	0.38 ml
78-81 kg	0.40 ml
82-85 kg	0.42 ml
86-89 kg	0.44 ml
90-93 kg	0.46 ml

Paediatric population (≥ 1 year)

Treatment should be initiated under the supervision of a medical professional with experience in the treatment of paediatric SBS.

The recommended dose of Gattex in children and adolescents (aged 1 to 17 years) is the same as for adults (0.05 mg/kg body weight once daily). The injection volume per body weight is provided in Table 2 below.

If a dose is missed, that dose should be injected as soon as possible on that day. A treatment period of 12 weeks is recommended after which treatment effect should be evaluated. There are no data available in paediatric patients after 12 weeks.

Table 2: Injection volume per body weight for paediatric population (≥ 1 year)

Body weight	Volume to be injected
10-11 kg	0.05 ml
12-13 kg	0.06 ml
14-17 kg	0.08 ml
18-21 kg	0.10 ml
22-25 kg	0.12 ml
26-29 kg	0.14 ml
30-33 kg	0.16 ml
34-37 kg	0.18 ml
38-41 kg	0.20 ml

Body weight	Volume to be injected
42-45 kg	0.22 ml
46-49 kg	0.24 ml
≥ 50 kg	See Table 1 under "Adults" section.

Special populations

Elderly
No dose adjustment is necessary in patients above the age of 65 years.

Renal impairment
No dose adjustment is necessary for adult or paediatric patients with mild renal impairment. In adult or paediatric patients with moderate and severe renal impairment (creatinine clearance less than 50 ml/min), and end-stage renal disease, the daily dose should be reduced by 50% (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. Gattex has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The product is not indicated for children under 1 year of age.

Method of administration

The reconstituted solution should be administered by subcutaneous injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Gattex should not be administered intravenously or intramuscularly.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or trace residues of tetracycline.

Active or suspected malignancy.

Patients with a history of malignancies in the gastrointestinal tract, including the hepatobiliary system and pancreas within the last five years.

4.4 Special warnings and precautions for use

It is strongly recommended that every time Gattex is administered to a patient, the name and lot number of the product are recorded in order to maintain a link between the patient and the lot of the product.

Adults

Colo-rectal polyps

A colonoscopy with removal of polyps should be performed at the time of starting treatment with Gattex. Once yearly follow-up colonoscopies (or alternate imaging) are recommended during the first 2 years of Gattex treatment. Subsequent colonoscopies are recommended at a minimum of five year intervals. An individual assessment whether increased frequency of surveillance is necessary should be performed based on the patient characteristics (e.g., age, underlying disease). See also section 5.1.

If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, Gattex therapy must be discontinued (see section 4.3).

Gastrointestinal neoplasia including hepatobiliary tract

In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. Development of small intestinal polyps has also been observed in human SBS patients within several months after start of teduglutide treatment. Because of this, upper gastro-intestinal endoscopy or other imaging is recommended before and during the treatment with teduglutide. If a neoplasia is detected, it should be removed. In case of malignancy, teduglutide treatment must be discontinued (see sections 4.3 and 5.3).

Gallbladder and bile ducts

Cases of cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, the need for continued Gattex treatment should be reassessed.

Pancreatic diseases

Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies. In case of pancreatic adverse events, the need for continued Gattex treatment should be reassessed.

Monitoring of small bowel, gallbladder and bile ducts, and pancreas

SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of small bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques.

Intestinal obstruction

Cases of intestinal obstruction have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued Gattex treatment should be reassessed.

Fluid overload and Electrolyte Balance

To avoid fluid overload or dehydration, careful adjustment of parenteral support is required in patients taking Gattex. Electrolyte balance and fluid status should be carefully monitored throughout treatment, especially during initial therapeutic response and discontinuation of Gattex treatment.

Fluid overload

Fluid overload has been observed in clinical trials. Fluid overload adverse events occurred most frequently during the first 4 weeks of therapy and decreased over time.

Due to increased fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during initiation of therapy. Patients should be advised to contact their physician in case of sudden weight gain, face swelling, swollen ankles and/or dyspnoea. In general, fluid overload can be prevented by appropriate and timely assessment of parenteral nutrition needs. This assessment should be conducted more frequently within the first months of treatment.

Congestive heart failure has been observed in clinical trials. In case of a significant deterioration of the cardiovascular disease, the need for continued treatment with Gattex should be reassessed.

Dehydration

Patients with SBS are susceptible to dehydration that may lead to acute renal failure.
In patients receiving Gattex, parenteral support should be reduced carefully and should not be discontinued abruptly. The patient's fluid status should be evaluated following parenteral support reduction and corresponding adjustment performed, as needed.

Concomitant medicinal products

Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption (see section 4.5).

Special clinical conditions

Gattex has not been studied in patients with severe, clinically unstable concomitant diseases, (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS), or in patients with malignancies within the last five years (see section 4.3). Caution should be exercised when prescribing Gattex.

Hepatic impairment

Gattex has not been studied in patients with severe hepatic impairment. The data from use in subjects with moderate hepatic impairment do not suggest a need for restricted use.

Discontinuation of treatment

Due to the risk of dehydration, discontinuation of treatment with Gattex should be managed carefully.

Paediatric population

See also general precautions for adults under this section.

Colo-rectal polyps/Neoplasia

Prior to initiating treatment with Gattex, faecal occult blood testing should be done for all children and adolescents. Colonoscopy/sigmoidoscopy is required if there is evidence of unexplained blood in the stool. Subsequent faecal occult blood testing should be done annually in children and adolescents while they are receiving Gattex.

Colonoscopy/sigmoidoscopy is recommended for all children and adolescents after one year of treatment, every 5 years thereafter while on continuous treatment with Gattex, and if they have new or unexplained gastrointestinal bleeding.

Excipients

Gattex contains less than 1 mmol sodium (23 mg) per dose. This means that it is essentially 'sodium-free'.

Caution is needed when administering Gattex to persons with a known hypersensitivity to tetracycline (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

No clinical pharmacokinetic drug-drug interaction studies have been performed. An *in vitro* study indicates that teduglutide does not inhibit cytochrome P450 drug metabolising enzymes. Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Gattex in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Gattex during pregnancy.

Breast-feeding

It is unknown whether teduglutide is excreted in human milk. In rats, mean teduglutide concentration in milk was less than 3% of the maternal plasma concentration following a single subcutaneous injection of 25 mg/kg. A risk to the breast-fed newborn/infant cannot be excluded. As a precautionary measure it is preferable to avoid the use of Gattex during breast-feeding.

Fertility

There are no data on the effects of teduglutide on human fertility. Animal data do not indicate any impairment of fertility.

4.7 Effects on ability to drive and use machines

Gattex has minor influence on the ability to drive and use machines. However, cases of syncope have been reported in clinical studies (see section 4.8). Such events might impact the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions were retrieved from 2 placebo-controlled clinical studies with teduglutide in 109 patients with SBS treated with doses of 0.05 mg/kg/day and 0.10 mg/kg/day for up to 24 weeks. Approximately 52% of the patients treated with teduglutide experienced adverse reactions (*versus* 36% of the patients given placebo). The most commonly reported adverse reactions were abdominal pain and distension (45%), respiratory tract infections (28%) (including nasopharyngitis, influenza, upper respiratory tract infection, and lower respiratory tract infection), nausea (26%), injection site reactions (26%), headache (16%), and vomiting (14%). Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complications. The majority of these reactions were mild or moderate.

No new safety signals have been identified in patients exposed to 0.05 mg/kg/day of teduglutide for up to 30 months in a long-term open-label extension study.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
All adverse reactions identified in post-marketing experience are *italicised.*

Frequency **System organ class**	**Very common**	**Common**	**Uncommon**	**Not known**
Infections and infestations	Respiratory tract infection*	*Influenza-like illness*		
Immune system disorders				*Hypersensitivity*

Frequency System organ class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders		Decreased appetite Fluid overload		
Psychiatric disorders		Anxiety Insomnia		
Nervous system disorders	Headache			
Cardiac disorders		Congestive heart failure		
Vascular disorders			Syncope	
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea		
Gastrointestinal disorders	Abdominal distension Abdominal pain Nausea Vomiting	Colorectal polyp Colonic stenosis Flatulence Intestinal obstruction Pancreatic duct stenosis Pancreatitis[†] Small intestinal stenosis	*Small intestinal polyp*[‡]	*Gastric polyp*
Hepatobiliary disorders		Cholecystitis Cholecystitis acute		
General disorders and administration site conditions	Injection site reaction[§]	Oedema peripheral		*Fluid retention*
Injury, poisoning and procedural complications	Gastrointestinal stoma complication			

*Includes the following preferred terms: Nasopharyngitis, Influenza, Upper respiratory tract infection, and Lower respiratory tract infection.
[†]Includes the following preferred terms: Pancreatitis, *Pancreatitis acute*, and Pancreatitis chronic.
[‡]Locations include duodenum, jejunum, and ileum.
[§]Includes the following preferred terms: Injection site haematoma, Injection site erythema, Injection site pain, Injection site swelling and Injection site haemorrhage.

Description of selected adverse reactions

Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Gattex may potentially trigger the development of antibodies. Based on integrated data from two trials in adults with SBS (a 6-month randomised placebo-controlled trial, followed by a 24-month open-label trial), the development of anti-teduglutide antibodies in subjects who received subcutaneous administration of 0.05 mg/kg teduglutide once daily was 3% (2/60) at Month 3, 17% (13/77) at Month 6, 24% (16/67) at Month 12, 33% (11/33) at Month 24, and 48% (14/29) at Month 30. In phase 3 studies with SBS patients who received teduglutide for ≥ 2 years, 28% of patients developed antibodies against *E. coli* protein (residual host cell protein from the manufacture). The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed pharmacokinetics of Gattex.

Injection site reactions

Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, injection site swelling and injection site haemorrhage (see also section 5.3). The majority of reactions were moderate in severity and no occurrences led to drug discontinuation.

C-reactive protein

Modest increases of C-reactive protein of approximately 25 mg/l have been observed within the first seven days of teduglutide treatment, which decreased continuously under ongoing daily injections. After 24 weeks of teduglutide treatment, patients showed small overall increase in C-reactive protein of approximately 1.5 mg/l on average. These changes were neither associated with any changes in other laboratory parameters nor with any reported clinical symptoms. There were no clinically relevant mean increases of C-reactive protein from baseline following long-term treatment with teduglutide for up to 30 months.

Paediatric population
In two completed clinical trials, there were 87 paediatric subjects (aged 1 to 17 years) enrolled and exposed to teduglutide for a duration of up to 6 months. No subject discontinued the studies due to an adverse event. Overall, the safety profile of teduglutide (including type and frequency of adverse reactions, and immunogenicity) in children and adolescents (ages 1-17 years) was similar to that in adults.

In three completed clinical studies in paediatric subjects (aged 4 to < 12 months corrected gestational age), the safety profile reported in these studies was consistent with the safety profile seen in the previous paediatric studies and no new safety issues were identified.

Limited long-term safety data is available for the paediatric population. No data are available for children under 4 months of age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

The maximum dose of teduglutide studied during clinical development was 86 mg/day for 8 days. No unexpected systemic adverse reactions were seen (see section 4.8).

In the event of an overdose, the patient should be carefully monitored by the medical professional.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX08.

Mechanism of action

The naturally occurring human glucagon-like peptide-2 (GLP-2) is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. Teduglutide is an analogue of GLP-2. In several nonclinical studies, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth.

Pharmacodynamic effects

Similar to GLP-2, teduglutide is 33 amino acids in length with an amino acid substitution of alanine by glycine at the second position of the N-terminus. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to *in vivo* degradation by the enzyme dipeptidyl

peptidase-IV (DPP-IV), resulting in an extended half-life. Teduglutide increases villus height and crypt depth of the intestinal epithelium.

Based on the findings derived from pre-clinical studies (see sections 4.4 and 5.3) and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appears to be a risk for the promotion of small intestinal and/or colonic neoplasia. The clinical studies conducted could neither exclude nor confirm such an increased risk. Several cases of benign colorectal polyps occurred during the course of the trials, however, the frequency was not increased compared to placebo-treated patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment (see section 4.4.), every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g., age and underlying disease, previous occurrence of polyps etc.).

Clinical efficacy

Adults

Teduglutide was studied in 17 patients with SBS allocated to five treatment groups using doses of 0.03, 0.10 or 0.15 mg/kg teduglutide once daily, or 0.05 or 0.075 mg/kg bid in a 21-day open-label, multicenter, dose-ranging study. Treatment resulted in enhanced gastrointestinal fluid absorption of approximately 750-1,000 ml/day with improvements in the absorption of macronutrients and electrolytes, decreased stomal or faecal fluid and macronutrients excretion, and enhanced key structural and functional adaptations in the intestinal mucosa. Structural adaptations were transient in nature and returned to baseline levels within three weeks of discontinuing the treatment.

In the pivotal phase 3 double-blind, placebo-controlled study in patients with SBS, who required parenteral nutrition, 43 patients were randomised to a 0.05 mg/kg/day dose of teduglutide and 43 patients to placebo for up to 24 weeks.

The proportion of teduglutide-treated subjects achieving a 20% to 100% reduction of parenteral nutrition at Week 20 and 24 was statistically significantly different from placebo (27 out of 43 subjects, 62.8% *versus* 13 out of 43 patients, 30.2%, p=0.002). Treatment with teduglutide resulted in a 4.4 l/week reduction in parenteral nutrition requirements (from a pre-treatment baseline of 12.9 litres) *versus* 2.3 l/week (from a pre-treatment baseline of 13.2 litres) for placebo at 24 weeks. Twenty-one (21) patients treated with teduglutide (48.8%) *versus* 9 on placebo (20.9%) achieved at least a one day reduction in parenteral nutrition administration (p=0.008).

Ninety-seven percent (97%) of patients (37 out of 39 patients treated with teduglutide) that completed the placebo-controlled study entered a long-term extension study where all patients received 0.05 mg/kg of teduglutide daily for up to an additional 2 years. In total 88 patients participated in this extension study, thereof 39 treated with placebo and 12 enrolled, but not randomised, in the previous study; 65 of 88 patients completed the extension study. There continued to be evidence of increased response to treatment for up 2.5 years in all groups exposed to teduglutide in terms of parenteral nutrition volume reduction, gaining additional days off parenteral nutrition per week, and achieving weaning of parenteral support.

Thirty (30) of the 43 teduglutide-treated patients from the pivotal study who entered the extension study completed a total of 30 months of treatment. Of these, 28 patients (93%) achieved a 20% or greater reduction of parenteral support. Of responders in the pivotal study who completed the extension study, 21 out of 22 (96%) sustained their response to teduglutide after an additional 2 years of continuous treatment.

The mean reduction in parenteral nutrition (n=30) was 7.55 l/week (a 65.6% reduction from baseline). Ten (10) subjects were weaned off their parenteral support while on teduglutide treatment for 30 months. Subjects were maintained on teduglutide even if no longer requiring parenteral nutrition. These 10 subjects had required parenteral nutrition support for 1.2 to 15.5 years, and prior to treatment with teduglutide had required between 3.5 l/week and 13.4 l/week of parenteral nutrition support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in parenteral support, respectively.

Of the 39 placebo subjects, 29 completed 24 months of treatment with teduglutide. The mean reduction in parenteral nutrition was 3.11 l/week (an additional 28.3% reduction). Sixteen (16, 55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral nutrition. At the end of study, 14 (48.3%), 7 (24.1%) and 5 (17.2%) patients achieved a reduction of 1, 2, or 3 days per week in parenteral nutrition, respectively. Two (2) subjects were weaned off their parenteral support while on teduglutide.

Of the 12 subjects not randomised in the pivotal study, 6 completed 24 months of treatment with teduglutide. The mean reduction in parenteral nutrition was 4.0 l/week (39.4% reduction from baseline – the start of the extension study) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction in parenteral support. At the end of study, 3 (50%), 2 (33%) and 2 (33%) achieved a reduction of 1, 2, or 3 days per week in parenteral nutrition, respectively. One subject was weaned off their parenteral support while on teduglutide.

In another phase 3 double-blind, placebo-controlled study in patients with SBS, who required parenteral nutrition, patients received a 0.05 mg/kg/day dose (n=35), a 0.10 mg/kg/day dose (n=32) of teduglutide or placebo (n=16) for up to 24 weeks.

The primary efficacy analysis of the study results showed no statistically significant difference between the group on teduglutide 0.10 mg/kg/day and the placebo group, while the proportion of subjects receiving the recommended teduglutide dose of 0.05 mg/kg/day achieving at least a 20% reduction of parenteral nutrition at Week 20 and 24 was statistically significantly different *versus* placebo (46% *versus* 6.3%, $p< 0.01$). Treatment with teduglutide resulted in a 2.5 l/week reduction in parenteral nutrition requirements (from a pre-treatment baseline of 9.6 litres) *versus* 0.9 l/week (from a pre-treatment baseline of 10.7 litres) for placebo at 24 weeks.

Teduglutide treatment induced expansion of the absorptive epithelium by significantly increasing villus height in the small intestine.

Sixty-five (65) patients entered a follow-up SBS study for up to an additional 28 weeks of treatment. Patients on teduglutide maintained their previous dose assignment throughout the extension phase, while placebo patients were randomised to active treatment, either 0.05 or 0.10 mg/kg/day.

Of the patients who achieved at least a 20% reduction of parenteral nutrition at Weeks 20 and 24 in the initial study, 75% sustained this response on teduglutide after up to 1 year of continuous treatment.

The mean reduction of weekly parenteral nutrition volume was 4.9 l/week (52% reduction from baseline) after one year of continuous teduglutide treatment.

Two (2) patients on the recommended teduglutide dose were weaned off parenteral nutrition by Week 24. One additional patient in the follow-up study was weaned off parenteral nutrition.

Paediatric population

Paediatric population between 1 and 17 years of age

The efficacy data presented are derived from 2 controlled studies in paediatric patients up to 24 weeks duration. These studies included 101 patients in the following age groups: 5 patients 1-2 years, 56 patients 2 to < 6 years, 32 patients 6 to < 12 years, 7 patients 12 to < 17 years, and 1 patient 17 to < 18 years. Despite the limited sample size, which did not allow meaningful statistical comparisons, clinically meaningful, numerical reductions in the requirement for parenteral support were observed across all age groups.

Teduglutide was studied in a 12-week, open-label, clinical study in 42 paediatric subjects aged 1 year through 14 years with SBS who were dependent on parenteral nutrition. The objectives of the study were to evaluate safety, tolerability, and efficacy of teduglutide compared to standard of care. Three (3) doses of teduglutide, 0.0125 mg/kg/day (n=8), 0.025 mg/kg/day (n=14), and 0.05 mg/kg/day (n=15), were investigated for 12 weeks. Five (5) subjects were enrolled in a standard of care cohort.

Complete weaning

Three subjects (3/15, 20%) on the recommended teduglutide dose were weaned off parenteral nutrition by Week 12. After a 4-week washout period, two of these patients had reinitiated parenteral nutrition support.

Reduction in parenteral nutrition volume

The mean change in parenteral nutrition volume from baseline at Week 12 in the ITT population, based on physician-prescribed data, was -2.57 (±3.56) l/week, correlating to a -39.11% (±40.79) mean decrease, compared to 0.43 (±0.75) l/week, correlating to a 7.38% (±12.76) increase in the standard of care cohort. At Week 16 (4 weeks following the end of treatment) parenteral nutrition volume reductions were still evident but less than observed at Week 12 when subjects were still on teduglutide (mean decrease of -31.80% (±39.26) compared to a 3.92% (±16.62) increase in the standard of care group).

Reduction in parenteral nutrition calories

At Week 12, there was a -35.11% (±53.04) mean change from baseline in parenteral nutrition calorie consumption in the ITT population based on physician-prescribed data. The corresponding change in the standard of care cohort was 4.31% (±5.36). At Week 16, the parenteral nutrition calories consumption continued to decrease with percentage mean changes from baseline of -39.15% (±39.08) compared to -0.87% (±9.25) for the standard of care cohort.

Increase in enteral nutrition volume and enteral calories

Based on prescribed data, the mean percentage change from baseline at Week 12 in enteral volume, in the ITT population, was 25.82% (±41.59) compared to 53.65% (±57.01) in the standard of care cohort. The corresponding increase in enteral calories was 58.80% (±64.20), compared to 57.02% (±55.25) in the standard of care cohort.

Reduction in infusion time

The mean decrease from baseline at Week 12 in the number of days/week on parenteral nutrition, in the ITT population based on physician-prescribed data, was -1.36 (±2.37) days/week corresponding to a percentage decrease of -24.49% (±42.46). There was no change from baseline in the standard of care cohort. Four subjects (26.7%) on the recommended teduglutide dose achieved at least a three-day reduction in parenteral nutrition needs.

At Week 12, based on subject diary data, subjects showed mean percentage reductions of 35.55% (±35.23) hours per day compared to baseline, which corresponded to reductions in the hours/day of parenteral nutrition usage of -4.18 (±4.08), while subjects in the standard of care cohort showed minimal change in this parameter at the same time point.

An additional 24-week, randomised, double-blind, multicentre study was conducted in 59 paediatric subjects aged 1 year through 17 years who were dependent on parenteral support. The objective was to evaluate safety/tolerability, pharmacokinetics and efficacy of teduglutide. Two doses of teduglutide were studied: 0.025 mg/kg/day (n=24) and 0.05 mg/kg/day (n=26); 9 subjects were enrolled in a standard of care (SOC) arm. Randomisation was stratified by age across dose groups. Results below correspond to the ITT population at the recommended dose of 0.05 mg/kg/day.

Complete weaning

Three (3) paediatric subjects in the 0.05 mg/kg group achieved the additional endpoint of enteral autonomy by week 24.

Reduction in parenteral nutrition volume

Based on subject diary data, 18 (69.2%) subjects in the 0.05 mg/kg/day group achieved the primary endpoint of ≥ 20% reduction in PN/IV volume at end of treatment, compared to baseline; in the SOC arm, 1 (11.1%) subject achieved this endpoint.

The mean change in parenteral nutrition volume from baseline at Week 24, based on subject diary data, was -23.30 (±17.50) ml/kg/day, corresponding to -41.57% (±28.90); the mean change in the SOC arm was -6.03 (±4.5) ml/kg/day (corresponding to a -10.21% [±13.59]).

Reduction in infusion time

At week 24, there was a decrease in the infusion time of -3.03 (±3.84) hours/day in the 0.05 mg/kg/day arm, corresponding to a percentage change of -26.09% (±36.14). The change from baseline in the SOC cohort was -0.21 (±0.69) hours/day (-1.75% [±5.89]).

The mean decrease from baseline at Week 24 in the number of days/week on parenteral nutrition, based on subject diary data, was -1.34 (±2.24) days/week corresponding to a percentage decrease of -21.33% (±34.09). There was no reduction in PN/IV infusion days per week in the SOC arm.

5.2 Pharmacokinetic properties

Absorption

Teduglutide was rapidly absorbed from subcutaneous injection sites with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absolute bioavailability of subcutaneous teduglutide is high (88%). No accumulation of teduglutide was observed following repeated subcutaneous administration.

Distribution

Following subcutaneous administration, teduglutide has an apparent volume of distribution of 26 litres in patients with SBS.

Biotransformation

The metabolism of teduglutide is not fully known. Since teduglutide is a peptide it is likely that it follows the principal mechanism for peptide metabolism.

Elimination

Teduglutide has a terminal elimination half-life of approximately 2 hours. Following intravenous administration teduglutide plasma clearance was approximately 127 ml/hr/kg which is equivalent to the glomerular filtration rate (GFR). Renal elimination was confirmed in a study investigating pharmacokinetics in subjects with renal impairment. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

Dose linearity

The rate and extent of absorption of teduglutide is dose-proportional at single and repeated subcutaneous doses up to 20 mg.

Pharmacokinetics in subpopulations

Paediatric population

Following subcutaneous administration, similar C_{max} of teduglutide driving the efficacy responses, across age groups (4 months corrected by gestational age to 17 years) was demonstrated by population pharmacokinetics modelling based on PK samples collected in the population following SC

0.05 mg/kg daily dose. However, lower exposure (AUC) and shorter half-life were seen in paediatric patients 4 months to 17 years of age, as compared with adults. The pharmacokinetic profile of teduglutide in this paediatric population, as evaluated by clearance and volume of distribution, was different from that observed in adults after correcting for body weights. Specifically, clearance decreases with increasing age from 4 months to adults. No data are available for paediatric patients with moderate to severe renal impairment and end-stage renal disease (ESRD).

Gender

No clinically relevant gender differences were observed in clinical studies.

Elderly

In a phase 1 study no difference in pharmacokinetics of teduglutide could be detected between healthy subjects younger than 65 years *versus* older than 65 years. Experience in subjects 75 years and above is limited.

Hepatic impairment

In a phase 1 study the effect of hepatic impairment on the pharmacokinetics of teduglutide following subcutaneous administration of 20 mg teduglutide was investigated. The maximum exposure and the overall extent of exposure to teduglutide following single 20 mg subcutaneous doses were lower (10-15%) in subjects with moderate hepatic impairment relative to those in healthy matched controls.

Renal impairment

In a phase 1 study, the effect of renal impairment on the pharmacokinetics of teduglutide following subcutaneous administration of 10 mg teduglutide was investigated. With progressive renal impairment up to and including end-stage renal disease the primary pharmacokinetic parameters of teduglutide increased up to a factor of 2.6 (AUC_{inf}) and 2.1 (C_{max}) compared to healthy subjects.

5.3 Preclinical safety data

Hyperplasia in the gall bladder, hepatic biliary ducts, and pancreatic ducts were observed in subchronic and chronic toxicology studies. These observations were potentially associated with the expected intended pharmacology of teduglutide and were to a varying degree reversible within an 8-13 week recovery period following chronic administration.

Injection site reactions

In pre-clinical studies, severe granulomatous inflammations were found associated with the injection sites.

Carcinogenicity / mutagenicity

Teduglutide was negative when tested in the standard battery of tests for genotoxicity.

In a rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium in males exposed to teduglutide plasma levels approximately 32- and 155-fold higher than obtained in patients administered the recommended daily dose (incidence of 1 out of 44 and 4 out of 48, respectively). Adenomas of the jejunal mucosa were observed in 1 out of 50 males and 5 out of 50 males exposed to teduglutide plasma levels approximately 10- and 155-fold higher than obtained in patients administered the recommended daily dose. In addition, a jejunal adenocarcinoma was observed in a male rat administered the lowest dose tested (animal:human plasma exposure margin of approximately 10-fold).

Reproductive and developmental toxicity

Reproductive and developmental toxicity studies evaluating teduglutide have been carried out in rats and rabbits at doses of 0, 2, 10 and 50 mg/kg/day subcutaneously. Teduglutide was not associated with effects on reproductive performance, *in utero* or developmental parameters measured in studies to investigate fertility, embryo-foetal development and pre- and post-natal development. Pharmacokinetic data demonstrated that the teduglutide exposure of foetal rabbits and suckling rat pups was very low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, L-Histidine, Dibasic sodium phosphate heptahydrate, Monobasic sodium phosphate monohydrate.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution, the solution should be used immediately.

6.4 Special precautions for storage

Store refrigerated at 2°C to 8°C.

Do not freeze.
The product may be stored for up to 3 months below 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

GATTEX (teduglutide) is supplied in a sterile, single-use 3 ml glass vial with rubber stopper (bromobutyl) containing 5 mg of teduglutide as a white, lyophilized powder to be reconstituted with 0.5 ml Sterile Water for Injection.

Each package contains 1,5,6,10,30 or 60 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Determination of the number of vials needed for administration of one dose must be based on the individual patient's weight and the recommended dose of 0.05 mg/kg/day. The physician should at each visit weigh the patient, determine the daily dose to be administered until next visit and inform the patient accordingly.

Tables with the injection volumes based on the recommended dose per body weight for both adults and paediatric patients are provided in section 4.2.

Syringe with the diluent Water for Injection must be assembled with a plunger and a reconstitution needle.

The powder in the vial must then be dissolved by adding all the solvent from the syringe.
After reconstitution, each vial contains 5 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 10 mg/ml

The vial should not be shaken, but can be rolled between the palms and gently turned upside-down once. Once a clear colourless solution is formed in the vial, the solution should be sucked up into a 1 ml injection syringe (or 0.5 ml or smaller injection syringe for paediatric use) with scale intervals of 0.02 ml or smaller (not included in the pack).

If two vials are needed, the procedure for the second vial must be repeated and the additional solution sucked up into the injection syringe containing the solution from the first vial. Any volume exceeding the prescribed dose in ml must be expelled and discarded.

The solution must be injected subcutaneously into a cleaned area on the abdomen, or if this is not possible, on the thigh (see section 4.2 Method of administration) using a thin needle for subcutaneous injection.

Detailed instructions on the preparation and injection of Gattex are provided in the package leaflet.

The solution must not be used if it is cloudy or contains particulate matter.

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

All needles and syringes should be disposed of in a sharps disposal container.

7. MANUFACTURER

Shire-NPS Pharmaceuticals inc.
300 Shire Way, Lexington, MA 02421, USA

8. REGISTRATION AUTHORISATION HOLDER

Neopharm LTD
Hashiloach 6, POB 7641, Petach Tiqva 49170, Israel

9. REGISTRATION NUMBER

152-48-33962-00

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Gattex pow for sol for inj SPC vs 02A